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Science and Social Context: The regulation of recombinant bovine growth hormone (rbGH) in the United States and Canada, 1982-1998

by

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A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy
Graduate Department of Political Science
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Abstract

Science and social context:
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Doctor of Philosophy 1999
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This dissertation explores the relationship between science and public policy in the case of recombinant bovine growth hormone (rbGH), a genetically-engineered drug which increases milk yield in cows. The product was approved by the United States Food and Drug Administration in 1993; it has not been approved in Canada. In both countries, the debate over the product's safety has been intensely controversial. The dissertation argues that problems in the relationship between science and policy arise at the point when judgements are made about the scientific evidence. Although there was agreement about the scientific evidence across institutions, the interpretation of that evidence diverged depending on the context from which it was viewed. The dissertation uses Helen Longino's concept of contextual empiricism to explain the varying outcomes in different settings. Scientists' conception of the kind of evidence required to make a judgement about product safety, and their interpretation of that evidence, was guided by the background assumptions they brought to it. These assumptions were context-dependent, however, with the result that policy responses differed between the U.S. and Canada, and the assumptions themselves were the subject of conflict in both countries. The difference in the U.S./Canadian response is the most obvious example of a contrast in the assessment of the drug's introduction. The dissertation also examines differing interpretations between the academic, corporate, and regulatory settings in order to elucidate the science and policy relationship. The dissertation contributes to the literature on science and public policy by examining the process by which scientists make sense of empirical evidence. It argues for the relevance of the concept of contextual empiricism for understanding the science-policy

relationship. It has attempted a theoretical synthesis, drawing on concepts from the history and philosophy of science and political economy to better understand this relationship. The concept of contextual empiricism accounts for both the degree of consensus about the evidence, and the degree of divergence in its interpretation, between institutions and jurisdictions.

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Acronyms

CAC - Codex Alimentarius Commission

CDC - Canadian Dairy Commission

BVD - Bureau of Veterinary Drugs (Canada)

CEPA - Canadian Environmental Protection Act

CMSMC - Canadian Milk Supply Management Committee

CVM - Center for Veterinary Medicine (U.S.)

FAO - United Nations Food and Agriculture Organization

FDA - Food and Drug Administration

FFDCA - Federal Food, Drug, and Cosmetic Act (U.S.)

FOI - Freedom of Information

GAO - General Accounting Office

INAD - Investigational New Animal Drug Application

JECFA - Joint WHO/FAO Expert Committee on Food Additives

NADA - New Animal Drug Application

NADE - Office of New Animal Drug Evaluations (US)

NBAC - National Biotechnology Advisory Committee (Canada)

NOC - Notice of Compliance (Canada)

OSTP - Office of Science and Technology Policy

PAMP - Post-Approval Monitoring Program

TFPC - Toronto Food Policy Council

VMAC - Veterinary Medicine Advisory Committee (U.S.)

WHO - World Health Organization

Chapter One

Introduction

1. Introduction

On January 14 1999, Health Canada rejected Monsanto's application to license recombinant bovine growth hormone (rbGH) in Canada. (The drug is also known as recombinant bovine somatotropin (rbST) or simply bovine somatotropin (bST)).[1] The product is developed using recombinant DNA (rDNA) technology, a form of biotechnology. When injected into lactating dairy cows, the product results in a 10-15% increase in milk production.[2] In the early 1980s, four multinational chemical and pharmaceutical companies competed to bring the product to market - Monsanto, a chemical corporation[3] based in St. Louis, Missouri; Elanco, the animal products division of Eli Lilly, a pharmaceutical corporation; Upjohn, also a pharmaceuticals producer; and American Cyanamid, a pesticides producer. By 1998, however, only Monsanto's application was active in Canada.

Health Canada's decision was made on the grounds that although the drug posed little risk to human health, animal health was jeopardized. It was announced after nine years

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[1] Even the name has been controversial. Early scientific reports refer to the naturally-derived hormone as bGH (see Bauman et al. 1982; Eppard et al. 1985). In later years, the product manufacturers, proponents, and regulators have referred to the natural version as "somatotropin," or bST (the dictionary definition of somatotropin is "growth hormone") and to the recombinant product as recombinant bovine somatotropin or rbST (although this is usually shortened to bST). Opponents, on the other hand, refer to it as recombinant bovine growth hormone, or rbGH. The drug's proponents believe that the term "growth hormone" associates the drug with steroid hormones and thus misrepresents the nature of the product, which is a protein. (Steroid hormones act directly on the cell, whereas protein hormones cause cellular responses by binding to the cell surface. Steroids survive digestion whereas proteins do not). Although some company representatives contend that only "somatotropin" is the correct scientific term, the pituitary hormone was called "growth hormone" and scientific reports refer to the recombinant product as growth hormone, including the FDA's summary of the human health data. (See Juskevich and Guyer 1990: also Burton et al. 1994) The use of the term "somatotropin" in preference to "growth hormone" seems to date from around 1986 - at the U.S. House of Representatives hearings in 1986, it was stated that the term "somatotropin" had been coined by industry to get away from the negative associations with the word hormone (U.S. House of Representatives 1987: 2). I use the terms rbGH and rbST interchangeably, but generally I use the term rbGH. I also use the terms "sometribove" and Posilac to refer to Monsanto's product formulation, the only product of its type approved for use in the U.S.

[2] Initial estimates were much higher - later reports indicate that this range is more likely.

[3] Monsanto spun off its chemical division in 1997, hence the term "chemical corporation" no longer accurately describes the company. This will be discussed in Chapter Two.

of review. The last six months of that review have been particularly turbulent, as Senate hearings probed the decision-making process, and scientists alleged that they had been pressured by the company, and senior management, to approve the drug in spite of their own misgivings. This case study, therefore, is a useful one for understanding the complexities of the science-policy relationship.

Health Canada's rejection of the drug stands in contrast to the U.S. Food and Drug Administration (FDA) approval in 1993. The difference between the U.S. and Canadian regulatory response is one of the puzzles which the thesis explores. However, this puzzle is intended to illustrate the nature of the relationship between science and policy. A different approach could have been taken. It would have been possible to focus on the difference between the two countries from an institutional perspective in order to analyze the impact of institutions on a particular policy outcome. However, my approach has been to examine the impact of institutions on the way that scientific evidence is produced and interpreted. It is the production and interpretation of evidence in the policy context that is the focus of the thesis.

I argue that although there was agreement among the various actors regarding what the evidence *showed*, the *interpretation* of that evidence diverged, depending on the context from which it was viewed. In making this argument, I rely on Helen Longino's (1990) concept of contextual empiricism. Longino suggests that judgements about empirical evidence are based on background assumptions we bring to its assessment; these assumptions are related to the context in which those judgements are formed. Therefore, I argue that in order to understand the relationship between science and policy, we must look at the expectations and assumptions which guide the interpretations made by scientists. Given this focus on scientists' perceptions, it is possible to argue that the outcome could be explained in terms of the individual personalities involved. However, I argue that these perceptions are shaped by context in two different senses. First, the goals and mandate of the institution in which the scientist operates exert a particular kind of pressure on him or

her, thereby promoting or constraining particular types of choices. Second, the broader political-economic context also affects scientists' interpretations. The two factors which were most significant here were the nature of the dairy system, and the significance of the biotechnology industry. In order to assess the likely effect of a product, scientists must have some knowledge of the social context into which the drug is to be introduced, and an implicit acceptance of the values inherent in that context.

Scientists in all contexts - regulatory, corporate, and academic - start from a base of existing scientific knowledge, what Kuhn (1970) terms "normal" science. The extent to which scientists question the assumptions from normal science is affected by the context in which they operate, however. Regulatory scientists' mandate precludes basic research. Their communication with those outside the regulatory body is restricted by the need to maintain the confidentiality of proprietary information. They are conscious of the time limitations that they work within, and the importance of timeliness to their career prospects. They are also conscious of corporate costs and competitive pressures. Regulatory scientists are expected to fulfill their mandate to protect public health, on the one hand, and to avoid imposing an undue regulatory burden on corporations, on the other. They are therefore caught in a juncture between the requirements of the regulatory body, and broader corporate and public pressures.

Under these circumstances, regulatory scientists decide what kind of evidence can "reasonably" be requested from the company. Reviewers' definition of safety was bounded by distinctions between what was reasonable and unreasonable, which in turn reflected distinctions made in conventional science. If the degree of risk can already be explained on the basis of existing knowledge, they are unlikely to ask for further data. In both Canada and the U.S., it was decided that long-term human health testing was unnecessary because the likelihood of risk was already known to be low. An additional two-week feeding study was conducted as a result of political pressure rather than scientific doubt. This decision was questioned by critics and, in Canada, by scientists within the Health Protection

Branch. The approach taken by regulatory scientists can be contrasted with that of scientists engaged in basic research, who are more likely to question the assumptions from conventional science and to require empirical support for them. Basic scientists are also more likely to acknowledge the limitations of their experimental method, rather than to make comparisons with the existing context in order to generalize from limited experimental data. Corporate scientists, on the other hand, are also likely to rely on conventional knowledge and to rely on contextual knowledge to downplay risk and ambiguity even further. In the rbGH case, corporate scientists claimed that not only was there no risk from increased levels of growth factor in milk, but there was no increase in growth factor. In the thesis, I examine the methodology and conclusions of corporate and academic science in order to contrast this with the regulatory review process, and in order to explore the development of positions which fed into the policy debate.

The relevance of the broader political-economic context can be seen in the decision on animal health. With regard to animal health, the difference between the U.S. and Canada becomes salient. Reviewers in both countries decided that the animal health data showed problems that were both statistically and biologically significant. The scientists differed in their assessment of the extent of the problem, however. In the U.S., animal health effects were also determined to be manageable, a judgement which depended on knowledge about existing dairy practices, and the implicit acceptance of their viability. All technologies require that we adapt our behaviour in some way. The adaptation of behaviour required by the introduction of rbGH reinforced a system of dairy production which is reliant on technologies such as antibiotics and reproductive drugs. Existing dairy practices were factored in to the studies themselves, in which reviewers required a balance between a "scientific" study and a "realistic" study which would reflect actual conditions on the farm. Actual conditions on the farm were taken to include the use of what are known as "extra-label" drugs, that is, drugs which have been used in ways which violate their conditions of approval. The data from these studies still showed that problems increased, but it was

concluded that a "successful" farmer, who was managing existing problems, could also manage these. A successful farmer, as a series of Office of Technology Assessment (OTA) reports pointed out, was located in the south or south-west of the country, producing on an industrial dairy of between 500 and 1500 cows. When you have more animals in larger units, the possibility of disease is higher, and so is the resultant use of antibiotics. Since the rbGH decision, the U.S. has also introduced legislation which has legitimized the use of extra-label drugs. The FDA's assessment placed the ultimate responsibility for managing animal health problems with the farmer, and the institutions for monitoring drug residues in the milk supply.

In Canada, on the other hand, animal health problems were regarded as "severe" rather than subtle, and it was the regulators, rather than the farmers, who were seen as responsible for protecting animal welfare and the viability of Canadian farms. The consequences of increased disease rates were viewed in terms of the supply management system; if antibiotic use resulted in milk disposal, the farmer would be unable to produce in accordance with quota requirements.

The political economy of agriculture literature is useful here in understanding agricultural production. Although valid criticisms of the literature have been made, there are important insights from the literature which are relevant here. One is that agricultural production needs to be considered in its relation to other forms of capitalist production. The other is that the form of domestic agriculture is related to the nature of the prevailing international regulatory regime. Domestically-based systems of agricultural production and protection are not merely the consequence of policy-making at the national level, but of international systems of regulation which permit or inhibit certain types of domestic policy. The post-world war two economic order encouraged the development of policies of national regulation, based on the U.S. model. However, this model paradoxically facilitated the rise of agribusiness corporations whose reach extended beyond national boundaries. The rbGH case can be seen as an example of a trend toward both the

industrialization and globalization of agricultural production, and varying national responses to it. The approval of rbGH in the U.S. implicitly recognized the acceptability of the industrial model and its further expansion. This model has not been universally accepted, however, and in Canada the shift of responsibility for the drug's consequences implied by this model was not regarded as acceptable.

The thesis research was motivated by an empirical puzzle. I was curious about the ferocity of the safety debate regarding bovine growth hormone. How had the debate about this issue been resolved, or why had it failed to be resolved? How did scientists in different contexts reason about this issue? Although the thesis is empirically focused, it makes a theoretical contribution to the literature on science and public policy in several ways. One, it argues for the relevance of the concept of contextual empiricism for understanding the science-policy relationship. Two, the thesis has attempted a theoretical synthesis, drawing on concepts from the history and philosophy of science and political economy to better understand this relationship. This adds to the insights from the science-policy literature and suggests that empirical findings from the case study may be used to re-think the findings from this literature.

For example, Liora Salter's (1988) and Sheila Jasanoff's (1986) work, distinguish "normal" science from science used for public policy purposes. The thesis concurs with the distinction between regulatory and "normal" science, but argues that paradoxically one of the factors which distinguishes it is precisely its dependence on normal science. Jasanoff's comparative-institutional perspective is also useful. Jasanoff emphasises the distribution of power among the three branches of government as a critical factor in determining the difference in scientific debate between different jurisdictions. The thesis suggests that the institutional structure in which decision-making takes place may influence the outcome, but in ways which are different than those suggested by this model. The U.S. model, Jasanoff notes, is more amenable to public participation and intervention, but this does not influence the decision-making process prior to public review. The recent Canadian

experience raises the question of whether Congressional and public pressure may in fact have served to discourage dissent within the FDA and foreclose the kind of diversity of response which was present in Canada.

The internal dissension at Health Canada highlights the deficiencies in the risk communication approach. (See for example Powell and Leiss, 1997) This approach locates the difficulty in the science-policy relationship in the communication of technical knowledge to a public which does not share the same expertise. The thesis suggests that there is not only a distinction in the perception between experts and the public, but between experts on this issue. One could perhaps explain internal dissension in terms of a lack of communication within the Department, but I believe it is an issue of differences in scientific judgement. The question of how these differences are resolved is not merely a question of communication.

The thesis also argues that the communication of risk during the review process is inherently problematic under the current system. The rbGH case shows that the complexity of scientific information is likely to be distorted in the political debate. It is also problematic when not all of the data can be discussed. The confidentiality of information creates problems both in relationship between regulators and the rest of the scientific community, and regulators and the public. Basic scientists' questions about the FDA's conclusions could not be answered with the limited information which was released. The public's concerns were aggravated when the release of information conflicted with the story presented by other actors in the debate, particularly university scientists and health professionals. University extension workers had promoted the product as "safe" prior to the completion of its review; when leaks of data, and subsequent official releases of information, appeared to contradict this finding, confidence in both the regulator and other public bodies was eroded.

Communicating the scientific debate in a way which was understandable, and yet which did justice to the complexities of the debate, was one of the challenges of the thesis.

Researching the thesis was also challenging because the controversial nature of the subject, and the confidential nature of the data made it particularly difficult to obtain interviews, and to obtain complete information once interviews were given. Interviewees often could not refer to specific details of the case, but spoke in generalities. The content and detail of discussions within and between organizations could not be divulged. The focus on rbGH alone, as in a focus on any single case study, places certain limitations on the generalizability of the conclusions that can be drawn here. However, the very uniqueness of the case, and the confidentiality of specific details, offers greater scope for generalization because interviewees spoke generally rather than specifically.

The other methodological limitation was that interviewees had the opportunity to scrutinize and veto questions before the interview took place, and to amend and delete from quotes and paraphrases from the interview. Most of the questions however were accepted. Most of the quotes were also accepted, but not all.

Sheila Jasanoff has said that "regulation...is a kind of social contract that specifies the terms under which state and society agree to accept the costs, risks and benefits of a given technological enterprise." (1995a: 311) The thesis explores the problematic nature of this contract and the difficulty for regulators of assessing the risks associated with a technology when there is no consensus about its benefits.

2. Literature review

As discussed above, the thesis draws on insights from the science and public policy, history and philosophy of science, and political economy of agriculture literature. The following section provides a brief overview of issues in these literatures and the concepts from them which are relevant for this study.

2.1. Science and public policy literature

Some analysts have located the problems in the science/policy relationship externally to that relationship; the literature on risk communication locates the problem in

the perception and transmission of information about risk. For example, in *Mad Cows and Mother's Milk*, Douglas Powell and William Leiss (1997) have argued that science itself is relatively unproblematic; it is the communication of risk, or more precisely, its mismanagement, which results in controversy. They define risk as "the probability of harm in any given situation," which is determined by "a) the nature of the hazard and b) the extent of anyone's exposure to the hazard." Risk communication "is the process of exchanges about how best to assess and manage risks among academics, regulatory practitioners, interest groups, and the general public" (33). When those responsible for risk assessment fail to communicate their findings to the public in a timely and effective manner, a risk information vacuum develops, in which fears are amplified and distorted by misinformation - " inadvertently misleading data" - and disinformation - "deliberately misleading data" (31).

Risk communication is difficult because members of the public, and the experts responsible for communicating risk to them, use two different languages to represent their understanding of risk. "Public assessment" is based on people's understanding of their everyday experiences, and does not necessarily incorporate expert findings. "Expert assessment," on the other hand, is probabilistic and based on technical knowledge. The divide between "public" and "expert" assessments and linguistic forms cannot be eliminated, but can be reduced by good communication practices.

Leiss and Powell explain the rbST controversy as the outcome of poor risk communication. They conclude that, in Canada, risk assessment assumptions were not made explicit; public concerns were not understood; and no agency took responsibility for transmitting accurate information and creating a consensus. In Canada, the information vacuum resulted in "damage done to the science-based risk-assessment process by the silence of some parties and the mischief of others, who so thoroughly intermixed peripheral issues with the health risk ones so that no reasonable risk discussion was possible" (213). In the U.S., on the other hand, third parties were engaged in the risk assessment process,

and regulators communicated frequently with the public, with the result that controversy died away after the drug was approved in 1994.

This interpretation cannot be sustained in the rbGH case. It is not only communication of the conclusions which has differed between the U.S. and Canada, but the conclusions themselves. Nor can the expert/public distinction be sustained in this case; the conclusions from the evidence have been controversial even within Canada's Health Protection Branch. The case cannot be categorized as a case of poor risk communication, because there was no consensus to communicate from Health Canada. Finally, risk communication by governments and corporations is problematic when the review is ongoing. Laws which protect the confidentiality of proprietary information prevent the release of data which are critical to the final decision. In the rbGH case, a simple statement on animal health, and its human health implications, could not be arrived at before all the data were submitted and analyzed. Statements were issued by the FDA regarding human health, which may have eased controversy in the U.S.; however, these statements may also have inflamed it by seeming to have compromised the Agency's objectivity when the animal health review was incomplete.

Other analysts, on the other hand, have not assumed that science in a public policy context is transparent, but suggest rather that scientific findings must be translated into public policy. For example, Liora Salter problematizes the concept of science in a public role and suggests that the nature of the scientific enterprise is altered by public policy involvement. Salter differentiates "mandated science" - science used for the purposes of making public policy - from conventional science (1988: 1). She states that a mandate to develop recommendations or decisions for public policy exerts a pressure on science that is reflected both in the activities of scientists and in their work or its interpretation (3).

According to Salter, mandated science is a type of activity with four characteristics. It is an *idealized* science - that is, it is required to serve purposes that only an ideal science could fulfill. It is supposed to be publicly intelligible, and to establish clear public choices

for decision makers; yet it is also required to produce results which are credible to the scientific community, to be value-free, and to be an open and public exercise. It is *imbued with legal considerations* - decisions made on the basis of scientific evidence have significant legal implications of which researchers are aware. The debates within mandated science are *unique* - mandated science tends to evaluate scientific investigations rather than to conduct them. Scientists in a public policy role often have to address scientists as well as regulators, and different conclusions may be drawn from their findings by different audiences. Finally, mandated science "makes explicit the moral dilemmas posed by science". Scientists' knowledge of social, moral and legal constraints affects their recommendations (5-8).

The very nature of mandated science, however, contradicts these idealized requirements. Since it has a public policy role, mandated science has a close relationship to values; because scientific evidence is conflicting and uncertain, its conclusions often cannot be neatly divided to represent two sides of a public policy debate; and because it is mostly not published nor peer-reviewed it is not as "public" as conventional science (5). Salter argues that science and policy issues are so closely intertwined in mandated science that they cannot be distinguished. Not all mandated science is controversial; however, once an issue in mandated science becomes controversial, Salter argues, it is difficult for a dispassionate assessment of it to be conducted. Once a risk issue becomes politicized, the environment in which it is assessed is fundamentally changed.

Salter's work is extremely useful for understanding the pressures under which policy-relevant science is conducted. It does not, however, explain the rbGH case, and the difference in outcome in the two jurisdictions. Mandated science, Salter argues, exists in every jurisdiction; we must therefore look to factors other than those she has identified in order to understand the science/policy relationship in the rbGH case. Also, in this case, scientific issues could be distinguished from judgements about the context into which the drug was to be introduced. The distinctions can be seen through the difference in the

position of corporate, academic, and regulatory scientists working on rbGH. The rbGH controversy exerted pressures on scientists in the policy debate, but did not transform the interpretation of the data. It was the assumptions underpinning the various interpretations which led to the controversy, and which motivated the rbGH debate.

Other analysts attribute the difficulties in the science and policy relationship to the nature of the policy process. From an examination of regulatory science in comparative perspective, analysts such as Sheila Jasanoff have argued that the nature and outcome of scientific debates are affected by the structure of the political system in which they take place: "a fundamental feature of political organization - the allocation of political authority among the three branches of government - heavily influences the form and intensity of scientific debates relating to risk" (1986: 5). In the United States, the fragmentation of political power means that the regulatory process is closely supervised by both Congress and the courts. Congressional committees may convene public hearings into regulatory matters, and Congressional representatives may request that the investigative arm, the General Accounting Office (GAO), inquire into the conduct of the regulatory process. For example:

> In 1978, the FDA took part in fifty-one hearings before twenty-four different Congressional committees and subcommittees, the GAO issued eight investigative reports on issues affected by the FDA, and the Agency responded to 4,463 written inquiries from Congress. (Brickmann, Jasanoff and Ilgen 1985: 45)

Congress also has sufficient resources to acquire external expertise on policy-relevant science.

Regulatory action also takes place under judicial oversight.[4] The Administrative Procedure Act of 1946 authorized the courts to overturn decisions not based on "substantial

[4] Jasanoff has noted that the capacity of the courts to affect policy has been circumscribed in the case of biotechnology by the 1986 Coordinated Framework for the Regulation of Biotechnology (see Jasanoff 1995b: 157). In the 1980s, the courts also followed a new doctrine with regard to their assessment of agencies' regulatory decisions - "the mere existence of scientific uncertainty did not justify the regulation of trivial risks." In Monsanto v. Kennedy, 1979, the DC circuit judged that although the governing statute granted agencies authority to regulate even trivial risks, the agency should not conform to this standard if the risk was insignificant (82).

evidence" (Jasanoff 1995: 69). As a result of "the extraordinary judicialization of the American administrative process," Jasanoff states that

> Agency rule-making has acquired many of the characteristics of a formal trial. As a result, individual citizens and citizen groups have unparalleled right to intervene in administrative proceedings, to question the expert judgements of government agencies, and ultimately to force changes in policy through litigation. (1986: 56)

In Parliamentary systems, in contrast, the judiciary is more reluctant to invalidate regulatory actions. There are also fewer mechanisms for opening up the regulatory process to public participation. The Freedom of Information Act in Canada, for example, is more restrictive than that in the United States, and there is no Canadian or European equivalent of the GAO. Although commissions of inquiry may investigate government action, these are rarely established, and in Parliamentary systems, the legislature is much less likely to challenge regulatory action than in the United States. Jasanoff therefore characterizes the U.S. as "formal, open, adversarial, and confrontational," in contrast to the Canadian and European approach which is "informal, confidential, consultative, and cooperative" (56).

She does not think that this degree of openness in the U.S. necessarily assists in the resolution of policy conflict, but rather prolongs the examination of evidence which cannot in itself solve a political dilemma. Habitual questioning by Congress also serves to undermine, rather than to bolster, public confidence in regulatory agencies (Brickmann, Jasanoff and Ilgen 1985: 96). Although this work sheds light on the policy process, it does not adequately explain the science and policy in the rbGH case. In this case, the nature of the political system in the U.S. enabled critics to use the investigative branch of Congress, as well as the investigative offices within the executive branch, to review and critique the decision-making process. Advisory committee meetings were also open for public comment. However, it is important to distinguish mechanisms for review from the decision-making process itself. Jasanoff suggests a pluralistic model of decision-making, in which a number of different actors may influence the policy process. In the rbGH case, however, public hearings served to communicate and legitimize the FDA's findings to the

public, but they did not influence the outcome. In order to understand the decision in this case, one needs to examine the assessment of the evidence *prior* to its public discussion. Scientists needed to come to some conclusions about the product before submitting those conclusions for review; it is this process which the thesis examines. The institutional differences in the policy process explain neither the outcome, nor the duration, of the controversy in the two countries; this would lead one to expect that a decision would have been reached in Canada before the U.S.

2.2. Philosophy of Science Literature

Since my primary concern is with the science/policy relationship, I do not explore the issues raised in the philosophy of science literature extensively; however, I draw on the work of two thinkers whose concepts are germane to the rbGH case.

In *The Structure of Scientific Revolutions*, Kuhn (1970) argued that although empirical evidence restricted the number of possible scientific accounts of a particular phenomenon, it could not fully explain the prevalence of any particular account. In order for observations to make any sense to the observer, they have to be assimilated into a paradigm - an overarching structure of established evidence and belief which defines natural entities and their interaction, and guides future research about them. "Normal" science is circumscribed by the boundaries of the paradigm; it is "firmly based upon one or more past scientific achievements, achievements that some particular scientific community acknowledges for a time as supplying the foundation for its further practice." (1970: 10) Observation, therefore, is theory-laden; scientists define the natural world in terms drawn from pre-existing theory. The use of terminology in one theory may therefore have a different meaning, and refer to different entities, than the same terminology in another theory. Consequently, theories are incommensurable with one another, because the phenomena they refer to are different.

The process of paradigm creation is social as well as "scientific." No paradigm can account for every instance of a phenomenon; counter-instances can always be found, and

can always be taken as evidence for an alternative viewpoint. In order to get on with the work of doing normal science, its practitioners cannot puzzle over every counter-instance. It is when these counter-instances conflict with scientists' fundamental theoretical commitments, or their attempts to solve a practical problem, that a new paradigm is likely to arise. New paradigms are created when anomalies become apparent; that is, when there are an increasing number of observations for which existing theories can no longer account. Anomalous observation coincides with conceptual construction; an unexpected occurrence cannot be recognized as posing a threat to the existing paradigm without the simultaneous development of concepts to account for it.

The awareness of anomaly is necessary, but not sufficient, for the establishment of an alternative framework. In order for the new paradigm to displace its predecessor, it must be accepted by the community of scientists, a process which depends as much on persuasive power as rational assessment. New explanations are initially resisted by adherents to conventional knowledge. They do not become paradigmatic until they are accepted by the majority of practitioners, a practice of persuasion and conversion which cannot be fully accounted for, Kuhn argues, by the advantages of the new theory. Once the new paradigm has been established, its principles are transmitted via the literature and scientific training. Normal science:

> Often suppresses fundamental novelties because they are necessarily subversive of its basic commitments. Nevertheless, so long as those commitments retain an element of the arbitrary, the very nature of normal research ensures that novelty shall not be suppressed for very long (5).

Although paradigm change is resisted, it is the existence of a paradigm which permits scientific progression; it allows for both the further explorations of the concepts and relationships posited by existing theory, and the radical re-conception of these as anomalies become apparent. Although the paradigm is a precursor of change, alternative theories will not usually be formulated by the adherents to the conventional view, but by those outside it.

Helen Longino (1990) departs from both the Kuhnian account of scientific practice, and the realist account, which holds that theories in the "mature" sciences, such as physics, are approximately true. In *Science as Social Knowledge*, Longino argues that scientific practice involves two types of values, constitutive and contextual. Constitutive values are the goals which science seeks to attain, such as truth, scope, accuracy, and fruitfulness. They are "the source of the rules determining what constitutes acceptable scientific practice or scientific method" (4). Since these goals are assumed to be the prerogative of science, they are often not regarded as "values." Contextual values, on the other hand, "belong to the social and cultural environment in which science is done"; they consist in "group or individual preferences about what ought to be" (4).

Longino argues that there is a necessary connection between the background assumptions that we bring to the reading of scientific - and everyday - evidence and the conclusions we draw from it. Consequently, she states that "evidential reasoning is always context dependent, that data are evidence for a hypothesis only in the light of background assumptions that assert a connection between the sorts of thing or event that the data are and the processes or states of affairs described by the hypothesis" (215). Background assumptions do not always encode social values, but do provide a means by which these values may enter the reasoning process.

Her approach differs from a Kuhnian one because this does not mean that the object of observation itself changes depending on the contextual framework through which it is viewed, but that different aspects of the object will become significant depending upon our background assumptions. A piece of evidence may be used to support a number of hypotheses. Which hypothesis it is used to support therefore is not dependent merely on the evidence itself but the background hypothesis used to connect the two. Scientists approaching the same piece of evidence from two different perspectives do not "see" two different things, but different aspects of the same thing; what is significant about the object for one, is not necessarily significant for the other. Also, "it is not always the case that the

same body of evidence supports different theories - different features may constitute evidence for a different hypothesis" (54). Longino rejects Kuhn's incommensurability thesis because:

> If theories are really incommensurable, we cannot make the initial judgement that they offer incompatible explanations of the same phenomena, for we have no way to justify judgements of compatibility and incompatibility, difference or sameness. (28)

Although what counts as "evidence" for a particular hypothesis will depend on background assumptions, these assumptions can still be differentiated from the evidence, and the hypothesis which it has been taken to support.

Longino argues that objectivity is a social property. She distinguishes between objectivity as a characteristic of the scientific method, and objectivity as a characteristic of individual practitioners. To say that something is objective means that it "reflects the critically achieved consensus of the scientific community" (74). If socially-produced objectivity is to be achieved, it must be capable of transforming both individual and communal scientific practice, which entails the existence of recognized fora for criticism, shared standards, and shared intellectual authority. The diversity of the community strengthens objectivity by increasing the number of perspectives brought to bear on scientific practice.

Longino refers to her approach as "contextual empiricism," which

> is empiricist in treating experience as the basis of knowledge claims in the sciences...[and] contextual in its insistence on the relevance of context - both the context of assumptions that supports reasoning and the social and cultural context that supports scientific inquiry - to the construction of knowledge. (219)

I use Longino's concept of contextual empiricism to analyze the rbGH case. The interpretation of the rbGH data depended on two kinds of assumptions; those based on Kuhnian "normal" science, and those based on judgements about the context into which the product was to be introduced. I will use the term contextual knowledge, rather than contextual values, in order to capture the nature of the latter kind of judgements. These

judgements depended on *knowledge* about practices within that context, as well as *implicit* values about their acceptability.

Longino's position can be distinguished from that of analysts from the social constructivist school, such as Latour and Woolgar (1979) and Knorr-Cetina (1981). These analysts suggest that science is as thoroughly imbued with value judgements, and as reflective of social relationships, as any other human activity. Latour and Woolgar have investigated "the socially available procedures for constructing an ordered account out of the apparent chaos of available perceptions" (33). They conclude that the acceptance of an account is not determined by its utility in explaining a particular state of affairs, but by social factors. The production of credible information occurs through a competitive rather than a communal process by which rival interpretations are eliminated. This process of elimination is dependent on the resources available to defeat alternative explanations. As one account becomes accepted, the economic costs of raising an objection to it increase, and the more difficult it becomes to raise the capital necessary to purchase the materials, equipment and labour time necessary in order to construct an alternative. Science is therefore not universal, but locally constructed. The local only becomes universal by virtue of the resources which enable the social process of elimination, and consequent acceptance, to proceed. Not only, therefore, does science not deserve special status, but the granting of such status to science blinds us to the way in which scientific facts are constructed. Latour and Woolgar note that "it is because the controversy settles that a statement splits into an entity and a statement about an entity; such a split never precedes the resolution of controversy" (180). I argue, however, that it is possible to isolate something deserving of the name science (putting aside the question of science's status) in the decision-making over rbGH, and that the object of investigation and the controversy can be distinguished.

2.3. Political economy of agriculture literature

Given that one of the world's largest agricultural biotechnology and seed companies, Monsanto, is the producer of rbGH, one might expect the science policy

relations in this case to be shaped most importantly by the political economy of agriculture. In Chapter Two of the thesis, a brief outline of the political economy of agricultural biotechnology will be given to provide background information to the study, and because its influence is important. Political economy does not determine the outcome in this case; rather I use the political economy of agriculture literature to understand this context.

In the 1980s, most commentators agreed that agriculture was in a period of crisis characterized by reduced farm numbers, falling incomes, and trade conflict. Analysts studying the political economy of agriculture have explained this crisis by tracing the historical development of the global food production system and its relation to broader economic structures. The central point is that prevailing industrial production practices also affect the food system. Kenney et al. (1991) have argued that:

> Historically, the effective integration of agriculture into the Fordist economy resulted in great part from political solutions to the overproduction crisis of the 1920s and 1930s, most specifically in response to the Great Depression. This crisis was partially solved by transforming farmers, traditionally self-reproductive producers, into consumers of mass-produced inputs ranging from petrochemical fertilizers to farm machinery (174).

The U.S. supported agriculture through price support, marketing, and supply management programs. Price support and credit policies enabled farmers to purchase industrial inputs such as agricultural chemicals and machinery, as well as processed food. Agriculture thereby became connected into the Fordist system of production, in which mass production and mass consumption were linked. The farm crisis of the 1980s is to be understood as part of a wider breakdown in the Fordist production system, in which the mass production/mass consumption dyad and its complementary forms of domestic regulation could no longer be sustained. Although these policies aimed to protect domestic agriculture, Harriet Friedmann (1991) has argued that their implementation facilitated the integration of food sectors across national lines.

The formation of a global food regime - which Harriet Friedmann defines as "a rule-governed structure of production and consumption of food on a world scale" - extended the U.S./ Fordist model internationally (1993: 30). The food regime is a global

system in which production and consumption may be nationally or internationally based. In a nationally-based food regime, production - at least in developed countries - is determined by agricultural policies which support local production and may involve protection measures and price supports. In a system organized along transnational lines, production is oriented toward a competitive global market.

From 1947 to 1972, Friedmann argues, the food system was governed by a "surplus regime" based around the U.S. system of food production. The U.S. surplus system was comprised of three food complexes: the wheat complex, the "durable food" complex, and the livestock complex. Each complex was characterized by different levels of state, and corporate, involvement in food production. In wheat, the U.S. protected its domestic markets and raised farm incomes through price supports. Government policy - and technological developments - created surpluses which were disposed of outside of markets, as food aid to the Third World, to avoid lowering prices. Under the "durable food" complex, corporations contracted with specialized farms for standard raw materials to be processed into packaged foods. The livestock complex was based around the increased production and consumption of meat, and the increased production of soy and maize as animal feed. Whereas European wheat production replicated U.S. national production, European livestock firms imported feed inputs from the U.S., creating an Atlantic agro-food sector around which the world food economy was reconfigured (1993: 37).

Several factors led to the demise of the surplus regime. Massive Soviet grain purchases in the early 1970s created shortages which the U.S. responded to by encouraging debt-financed production. The breakdown of the 1970s was not automatically expressed in declining farm incomes. However, the breakdown of the regime led to the creation of massive debt in the farm sector and, later, even greater surplus problems. The breakdown of the Bretton Woods monetary system also destabilized the financial and monetary relations around which the regime was based. In the 1980s, the European

Common Agricultural Policy (CAP) led to increased competition between European and subsidized U.S. grain markets (McMichael 1992: 349).

As the Fordist form of production/regulation disintegrates, another form will, the literature suggests, come to replace it. Philip McMichael has contended that the new regime emerging from the breakdown of the post-war system is based around the internationalization of food production and distribution (McMichael 1992: 345). This global system, known as the agro-industrial production chain, divides food production into four processes: the use of inputs e.g. seeds, pesticides, machinery; agricultural production; industrial processing; and international distribution (Ruivenkamp 1988: 288). It consists in the increasing importance of transnational companies in food production, processing, and distribution; the integration of diverse localities through agro-food corporations' global sourcing strategies; and the changing of diets to reflect Western tastes.

The internationalization of finance and other sectors of capital has had implications for global regulatory mechanisms. McMichael argues that international regulatory systems such as the Uruguay Round of GATT negotiations and the increasing power of the IMF and the World Bank have facilitated capital accumulation on a global scale. States' compliance with the requirements of these regimes has created the "transnationalisation of the state"; meaning that state structures and policies are more responsive to the requirements of global capital than to the promotion and protection of domestic welfare. Under these circumstances, domestic agricultural policy has been directed away from the development of a coherent national sector, and towards integration into global production circuits (McMichael 1991: 83).

This literature aims to provide a unifying context for thinking about agriculture. Recent critiques, however, have argued that in the quest for a unifying theory, insufficient attention has been paid to the empirical reality of agricultural production. Goodman (1997) argues that globalization is not a single phenomena, but is comprised of several "world scale" processes - "internationalization, multinationalization, transnationalization, and

globalization - that operate *concurrently*, yet differently, in the world economy." (665) Goodman points out that the ideology of competitiveness is likely to lead, not to global economic integration, but to greater regional integration within the triad of North America, Western Europe, and South-East Asia. World-scale processes transform states and regions unevenly, suggesting that there is greater room for variation among institutional structures and productive forms than the globalization literature suggests. Similarly, Robert Wade (1996) argues that two important measures of economic integration, trade and foreign direct investment, show a high degree of concentration among *developed* countries; where North-South integration does take place, it is highly regionalized. Wade also argues that resources, such as skill, capital, and technology, are relatively immobile. For example, not only are multinationals tied more closely to their home base than much of the literature suggests, but they are not entirely mobile with respect to the territories they invest in.

Evidence of the regionalization, and the unevenness of internationalization, is found in the rbGH case. Due to different political structures, the policy issue has been dealt with differently in Europe than in North America. With respect to dairy production, regional agreements and international agreements have conflicted; ironically, the primacy of the international agreement has protected the Canadian dairy industry from a U.S. challenge under the North American Free Trade Agreement (NAFTA). Although an ideology of global competitiveness has been extremely important to both government policy and corporate strategy in both the U.S. and Canada, this has played out differently in the two countries. The Canadian dairy industry is still protected from external competition, Canadian exports are minimal, and the supply management system is in place. In the U.S., on the other hand, the debate about rbGH was simultaneously a debate about the necessity for technological innovation in response to the increasing importance of market mechanisms.

3. Methodology

In order to explore the social and political background to the decision-making process regarding rbGH, as well as the process itself, I examined both U.S. and Canadian government documents pertaining to both the facilitation, and regulation, of biotechnology, including relevant statutes and administrative guidelines, and, in the U.S. case, Congressional hearings regarding particularly controversial decisions and trends, such as the patenting of animals and the commercialization of scientific research. In regard to the rbGH debate, I also researched the Congressional and Parliamentary hearings into the subject, and, for the U.S., the various advisory committee meetings regarding human health implications, labelling issues, and the post-approval monitoring program. I also covered the various General Accounting Office and Department of Health and Human Services Inspector-General's reports, and, for Canada, the House of Commons Agriculture and AgriFood Committee reports, government response, and rbST Task Force reports.

The political economy of biotechnology development was researched through documents from the Monsanto company, including annual reports and internal publications, newspaper articles, particularly from the *Wall Street Journal* and the chemical trade press, and the secondary literature.

I also obtained reports, newsletters, and copies of correspondence from the various environmental, farm, and food policy groups opposed to the drug, including the Canadian Institute for Environmental Law and Policy, the Toronto Food Policy Council, the Ram's Horn, Rural Vermont, and the U.S. National Farmers' Union.

Information regarding the scientific debate was obtained primarily from the FDA's Freedom of Information Summary, and an earlier summary of the human health data and its interpretation, published in *Science* in August 1990. I also read articles from scientific journals including *Science*, *The Lancet*, *Physiological Reviews*, the *Journal of Dairy Science*, the *Journal of the American Veterinary Medical Association*. I also attended

the final meeting of the FDA's Veterinary Medicine Advisory Committee (VMAC) which reviewed the data from the rbGH post-approval monitoring program in November 1996.

My conclusions are based primarily on data from interviews conducted between August 1996 and August 1997. I interviewed 26 individuals, several of whom were interviewed twice. Most of the interviews were conducted face-to-face; some were conducted over the phone due to geographical or time constraints. I interviewed two scientists from the U.S. FDA, both of whom were prominent in the rbGH evaluation, and two other FDA officials. My informant regarding the Canadian regulatory process was the former chief of the division responsible for the animal health review. I spoke with four Monsanto scientists, and the company's Director of Regulatory Affairs, who interacted with the FDA and spoke at Canadian Parliamentary hearings. I also spoke to scientists at universities in Canada and the U.S. who acted as principal investigators for the safety and efficacy trials, one university scientist who had been critical of the process, and members of professional associations (such as the American Medical Association) who authored position statements endorsing the product. In addition, I interviewed biomedical researchers outside the rbGH debate who were investigating growth factor physiology in order to contrast their methodology with that of scientists in the debate.

I located these individuals by contacting the authors of scientific articles and the participants in Congressional and Parliamentary hearings; requesting names from the relevant institutions; and obtaining referrals from other interviewees.

I had no difficulty obtaining interviews with scientists outside the debate. Since the drug is still under review in Canada, and hence the confidentiality of the information submitted in support of the drug application must be maintained, I was unable to obtain interviews with current Health Canada scientists. I was also unable to obtain interviews with some of the drug's critics, and one of the university scientists whose perspective I particularly wanted to obtain. Some of the people I wished to contact could not be reached, and many of the interviews were difficult to obtain. The FDA and Monsanto were initially

reluctant to participate. They received copies of the questions before participating, and the FDA's counsel reviewed the questions beforehand. Interviewees were instructed that they could refuse to answer any question, and they often were unable to provide specific details in response to a particular query, but responded in generalities. Quotes attributed to particular individuals were sent back to them for confirmation and correction; most of the interviewees replied, with minor alterations.

A standard format provided the basis for the interviews. The questions focused on: whether a literature review was conducted and how it was decided what literature was relevant; how the scientists decided what kinds of studies should be conducted; how they proceeded with the analysis of the data; what time period they worked within, and how this affected their analysis; what kinds of evidence would enable them to conclude that a product was "safe" or "unsafe"; what kinds of interaction they had with other organizations or groups; and whether this influenced their decision-making process. This format was heavily influenced by the first interview, with a former FDA official, who raised many of these issues in the course of the discussion.

In addition to these basic questions, I added very specific questions regarding aspects of the research particular to the institution. For example, I asked FDA scientists about the data and conclusions reported in the 1990 *Science* article, and the 1993 Freedom of Information Summary; Monsanto scientists were asked about their published articles, and analysis of the data submitted to the FDA, as were university researchers; biomedical scientists were asked about the content of their own research. I also asked Monsanto scientists and officials about the process of drug development, their reaction to the public controversy, and their interaction with professional associations on this issue.

As well as interviewing scientists and regulators, I spoke to members of Rural Vermont, a farm group opposed to the drug's introduction, and to a member of the Vermont legislature. These interviews were not structured, and related primarily to Rural

Vermont's interactions with the FDA, the reasons for its opposition to the drug, and actions taken since it was introduced.

I took notes during the interviews, and also recorded and transcribed them. I analyzed the transcripts by breaking them down into common themes, and comparing themes across institutional affiliation. I then considered these themes in relation to the literature, particularly work on science and public policy; the history and philosophy of science; and the political economy of agriculture.

4. Chapter Outline

The first three chapters outline the different contexts in which rbGH science took place. Chapter Two locates the development of rbGH within the broader political economy of agricultural biotechnology. It outlines Monsanto's transformation from a chemical producer to a biotechnology or "life sciences" company, and locates this transformation with the broader restructuring of the chemical, oil and pharmaceutical industries, which have invested in biotechnology as a strategy to compensate for declining profits since the oil crisis of the 1970s. It explores the company's rationale for pursuing the development of rbGH, and its relationship with the agricultural colleges and land-grant universities in the U.S., and in Canada. Chapter Three outlines the U.S. regulatory context, including the biotechnology policy framework, the regulatory requirements for the evaluation of animal drugs, the use of legislative and judicial mechanisms by those opposed to the drug, and the history of the controversy. Chapter Four outlines the context of the decision-making process, and the controversy, in Canada; the process itself is explored in Chapter Five. Chapter Five analyses the scientific debate around both the human and animal safety of rbGH, outlining the position taken by each institution - the universities, Monsanto, the U.S. FDA, Health Canada, and the critics - and explaining the reasoning behind each position. Although there was a consensus about the findings from the safety and efficacy trials, the weight given to certain aspects of the findings - and the conclusions about their implications - differed from institution to institution. Chapter Five also examines the public

debate about the product, and its importance to the future commercial success of the product. Although the dissemination of scientific information was perceived as critical to the product's success, the safety debate did not reflect the complexity of the data nor the reasoning linking it to the safety hypothesis. Chapter Six analyzes the findings from the data chapters in relation to the literature outlined above, and concludes that difficulties in the science policy relationship arise at the point where judgements about the data are made. Although there may be widespread agreement about the meaning of the data, its interpretation and social meaning depend on the context from which it is viewed.

Chapter Two

The economic context: The political economy of agricultural biotechnology

1. Introduction

The purposes of this chapter are threefold. First, it sets the economic context, by providing an overview of the development of the biotechnology industry in the US, and its facilitation by government policies. The success of the biotechnology industry was regarded as crucial to the United States' economic future. Although the industry was fostered by government policy, agricultural biotechnology is now dominated by multinational corporations, such as Monsanto, which are exporting their innovations and investing in seed companies and biotechnology firms located around the globe.

Second, it provides a brief outline of the debate about the economic impact of rbGH. The application of technology in dairy farming had led to a steady increase in the milk supply, with the result that huge oversupply problems emerged in the 1980s. Government support for surplus production was declining, however, a process which may be understood in terms of the breakdown of the "surplus regime" outlined in Chapter One. Agricultural economists suggested that the dairy industry would be transformed by the application of biotechnology, and resulting oversupply problems could be eliminated through reliance on market mechanisms rather than government support.

Third, the chapter outlines the relationship between Monsanto, the producer of rbGH, and the universities contracted to undertake animal trials.

The exploration of the economic context provides the background for understanding Monsanto's perspective on the safety debate, and the social and economic issues which fed into the broader policy debate. Since regulators were sensitive to both the need to protect public health, on the one hand, and corporate costs and competitive pressures, on the other,

an overview of the economic context is also necessary to understand what these costs and pressures consisted in.

2. Regulatory Changes and the Commercialization of Genetic Research

The commercial potential of biotechnology was perceived early in its development, and the corporate sector's investment was further encouraged in the early 1980s by a series of regulatory changes instituted by the Reagan Administration. These policies aimed to increase America's capacity for technological innovation by encouraging the commercialization of basic research undertaken at universities and federally-funded institutions. Commercialization was also facilitated through tax incentives, and judicial decisions which granted proprietary rights over previously unpatentable microorganisms, animals, and plants.

The Patent and Trademark Amendment Acts of 1980 (PL 98-260) and 1984 (PL 98-260) aimed to promote efforts to develop a uniform federal patent policy[1] and to commercialize government-funded research by allowing recipients of federal research funds - including universities and small businesses - to patent their innovations (OTA 1990: 55). According to Slaughter and Rhoades, these laws "blurred the boundaries between public and private sectors," and:

> gave new and concrete meaning to the phrase "commodification of knowledge." The act[s] enabled universities to enter the marketplace and to profit directly when universities held equity positions in companies built around the intellectual property of their faculty as well as to profit indirectly when universities licensed intellectual property to private sector firms. (1996: 318)

The National Co-operative Research Act of 1984 (PL 98-462) relaxed anti-trust law to permit research collaboration among previously competitive anti-trust firms; joint research ventures were not regarded as a violation of anti-trust law *per se,* but judged according to "reasonableness" and "relevant factors affecting competition." The Technology Transfer Act of 1986 (PL 99-502) authorized government-operated laboratories to enter into co-operative research arrangements with the private sector. Tax

[1] Prior to 1980, Federal agencies followed 26 different patent policies (OTA 1990: 54).

incentives also encouraged private R & D investment; the Economic Recovery Tax Act (PL 97-34) granted companies a 25% credit for increases in R & D expenditure above base-year expense levels. Relaxation of regulatory guidelines also provided incentives for American companies to manufacture pharmaceuticals and food additives at home rather than overseas; in 1986, the Drug Export Amendments Act permitted drugs which had not been approved for use in the United States to be exported to 21 countries (Slaughter and Rhoades 1996: 320).

As a result of policy decisions, the right to secure proprietary rights over innovations was extended to public institutions; as a result of judicial decisions, the scope of innovations which could be patented was extended to life forms. Prior to 1980, living organisms were not regarded as patentable subject matter under 35 U.S.C. 101 but as products of nature. In 1980, the Supreme Court ruled in *Diamond v. Chakrabarty* that a living, man-made organism was patentable subject matter within the meaning of the Act (OTA 1987: 7). The Court did not address the issue of whether plants were patentable subject matter under the Act. Previously, plant breeders had claimed intellectual property rights under the Plant Patent Act (PPA) of 1930 or the Plant Variety Protection Act (PVPA) of 1970. General patent law, however, offered broader protection than that available under either of the plant patent acts, and in 1985, the Patent and Trademark Office's Board of Appeals and Interferences ruled in *Ex parte Hibberd* that a transgenic corn plant was patentable subject matter. In 1988, the first animal patent was issued to Harvard University for a mouse with a cancer-causing, or "onco" gene, inserted in its DNA.[2] An exclusive license to apply the technology was granted to DuPont, a major sponsor of the Harvard research (OTA 1990: 12).

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[2] In 1987 and 1988, Congressional representatives introduced several bills to prohibit, delay, or abolish federal funding for the patenting of animals. On May 28, 1987 the Senate adopted an amendment to the Supplemental Appropriation Bill to bar the use of appropriated 1987 funds in the patenting of genetically-altered animals. Subsequently, the Senate Committee for the Judiciary held hearings on animal patents and the Constitution (United States House of Representatives 1987: 2). A moratorium on the patenting of animals was also introduced in the House of Representatives in 1987, and a prohibition introduced in 1988. These bills did not gain the support of both Houses, however, and did not become law (O'Connor 1989).

The negotiation of intellectual property agreements as part of the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) and the North American Free Trade Agreement (NAFTA) ensured that intellectual property claims would be respected outside of the United States. Section Five, Article 27 (5) of the international Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) specifies that

> Each Party shall make patents available for any inventions, whether products or processes, in all fields of technology, provided that such inventions are new, result from an inventive step, and are capable of industrial application.

Article 27 (3) allows signatories to exclude the following inventions from patentability:

> (a) diagnostic, therapeutic and surgical methods for the treatment of humans and animals;
> (b) plants and animals other than microrganisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes for such production.

Plant varieties must be covered by an intellectual property system either through patents or a scheme of sui generis protection (i.e. special legislation dealing solely with plant varieties) (McMahon 1995: 24).

Signatories to NAFTA may also exclude plants and animals from patentability. Under Article 1709(2) of NAFTA:

> A party may exclude from patentability inventions if preventing in its country the commercial exploitation of the inventions is necessary to protect ordre public or morality,[3] including to protect human, animal or plant life or health or to avoid serious prejudice to nature or the environment for reasons including the protection of human, animal or plant life, provided that the exclusion is not based solely on the grounds that the Party prohibits commercial exploitation in its territory of the subject matter of the patent.

3. Commercialization and biotechnology

The commercialization of biotechnology has been fostered not only by government policy, but by the belief that the application of biotechnology would have a revolutionary economic impact.[4] Investment in this form of innovation was initiated and sustained by the belief that it represented "the century's third great technological revolution - after atomic fission and computers" (Naj 1989: B1). In 1984, Monsanto's CEO, Richard Mahoney,

[3] To the best of my knowledge, "ordre public and morality" has not been defined.
[4] This belief was also shared by governments which sought to promote biotechnology.

said that "[o]ur initial investigation into genetic engineering made it clear it was going to be at least as important to the [chemical] industry as the petrochemical revolution of the 1930s" (*Business Week* 1984: 64). Biotechnology has also been perceived as another form of information technology rather than as a distinct technological wave.[5] *Barron's* noted that "[b]ecause genes are snippets of information that can be rewritten to produce various outcomes - starchier potatoes, say, or pesticide-resistant soybeans - agricultural biotech is analogous to computer technology" (1995: 10). Similarly, Monsanto's CEO, Robert Shapiro, observed that "[b]iotechnology is, in a sense, a subset of information technology. Just as information technology is the science of encoding data onto silicon wafers, biotechnology is the science of encoding information into living systems" (Shapiro 1996: 8). By 1997, Monsanto announced its discovery of the biological equivalent of Moore's law, which predicted that the information processing capacity of silicon chips would double every 18 to 24 months; the company believed that the speed of knowledge generation in the biosciences was proceeding at the same rate, and would have equally dramatic economic consequences (Monsanto 1997).

In the U.S., the biotechnology industry was created by the interaction of two economic institutions; small startup companies, founded by university scientists and financed by venture capital; and multinational pharmaceutical and chemical companies (Kenney 1986: 132). The establishment of small startup companies devoted to the development of biotechnology was made possible by venture capital investments. Venture capital itself became more formalized in the 1970s; large corporations created divisions which specialized in financing innovative companies with the expectation of realizing a

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[5] Lily Kay has argued that the metaphor of nature as a language pervades the history of the West. Since language is itself historically and culturally specific, the metaphor has taken on new dimensions at different times. With the advent of the computer age, the gene became conceived of as a code, used to transmit information from one generation to the next (Kay, 1995: 5). Following Foucault, Kay believes that communication and control are linked in the current era. Applying the linguistic metaphor to the gene allowed scientists to control the determinants of life:

> Based on this potent linguistic imagery and representation of life as text, the genome could now be read and edited unambiguously by those who know. This writing technology thus laid claim to new levels of control over life. Beyond control of matter there was now control of the word. (Kay, 1995: 3)

500-1000% capital gain when the stock was publicly traded (Kenney 1986: 133, 142). Genentech was one such company. Founded in 1976 by Robert Swanson and former University of California-San Francisco professor, Herbert Boyer, Genentech was the first company completely focused on biotechnology R & D (156). When a stock offering was made in 1980, prices jumped from $35 to $89 within a day, setting a Wall Street record for the fastest per-share price increase (OTA 1991: 4).

By 1983, venture capital sources were no longer as willing to extend further finance; biotechnology startups were relying more on stock offerings as a means of raising capital, and had also developed new mechanisms, such as the R & D limited partnership, to fund production scale-up or clinical trials. Chemical and pharmaceutical multinationals began investing directly in startup companies and forming other strategies for gaining access to their innovations. The chemical industry turned to biotechnology in an attempt to reverse the decline in profits brought about by lack of innovation, increased costs as a result of the 1973 and 1979 oil crises, and the cost of cleaning up environmental damage from earlier product cycles (Kenney 1986: 191-3). By the 1970s, the companies had become commodity producers; to reduce their dependence on low-profit bulk chemicals, they invested in pharmaceuticals and patentable products with a high profit margin.

Kenney has identified four patterns of multinational investment in biotechnology. The multinational may, one, finance biotechnology research at universities. The university secures the patent on the resulting innovation, and the company obtains an exclusive license to market it. Two, the larger corporation may contract with a startup company for the production of patented inventions, which it develops and markets on a commercial scale. Three, it may purchase equity in a startup company, which gives it an inside window into innovations and rival products. Four, it may develop an in-house research capacity, either by establishing its own laboratory or buying a startup (1986: 199).

In the early 1990s, biotech stocks went through another cycle, falling in 1993 and 1994 (Thayer, 1996: 13). In need of further capital, biotech startups entered into alliances

with pharmaceuticals; 66 alliances valued at $3.21 billion were formed in 1994; a further 171 agreements had been reached by the end of 1995 (14). Genentech, which had aimed to be a freestanding corporation (Kenney 1986: 161) sold a 60% stake to Roche for $2.1 billion in 1990, along with the rights to acquire up to 80% of the company by 1999 (Thayer, 1996: 15). A biotech company's value on the stock market was determined by its relationship with a large pharmaceutical firm. The manager of one of the most profitable biotech investment funds limited his investments to those companies which had entered into partnerships with pharmaceuticals:

> The biotech industry is fragmented. Drug development has to be centralized so that resources are properly allocated. For that to work, research should be done by the biotechnology firms, and development should be done by the drug industry. (Brammer, 1995: 30)

According to fund managers, an alliance with a multinational firm indicates the commercial potential of the start-up's technology (see Brammer 1995: Northfield 1996). Getting the maximum benefit from the multinational's vote of confidence can be tricky, however. Stock prices will escalate immediately after a joint agreement has been announced; once finalized, however, the benefits are less lucrative (Northfield 1996: B22).

Conversely, technological innovation by startups is also regarded as crucial for the survival of the multinationals. Dr. Eric Cohen, of the Laboratory of Human Retrovirology at the Université de Montréal, has predicted that "before long, practically every multinational will have allied itself with a genomics company" (Yakaubski and Northfield 1996: B3). Acquisition of startup firms by multinationals has occurred concurrently with global consolidation of the pharmaceutical industry as companies develop a "related-products strategy," focusing on particular segments of the business. In 1996, Ciba-Geigy and Sandoz combined to form the world's largest agribusiness, Novartis, which is comprised of agricultural, pharmaceutical, and nutrition divisions, and has a $2 billion R&D budget. The following year, Novartis acquired Merck's crop-protection business (presumably pesticides) for $910 million (Bagli 1997: C7); Merck, meanwhile, was undergoing its own restructuring, merging its animal health and poultry genetics businesses

with those of Rhone-Poulenc to create Merial Animal Health, now the largest veterinary drug company (Young 1997: 14).

Recent developments suggest that although biotechnology's impact may not be felt in all sectors of the economy, its influence in particular sectors may be profound. The number of acres planted with genetically-modified crops increased six-fold between 1996 and 1997; it is expected to reach 65 million acres by 1998 (Monsanto 1997a: 8). Monsanto reported that its recent research was directed toward the development of specialized crops, that is crops engineered to meet the nutritional or other needs of particular markets; the invention of the "biofactory," or the engineering of crops to produce a non-food product, such as plastic, extended the anticipated trend toward specialization in agriculture (10). *Business Week* reported that the number of applications in agriculture and medicine was growing rapidly, with several types of genetically-engineered cancer therapies currently under development (Carey 1998: 87). In 1997, when the lamb "Dolly" was cloned from adult sheep cells, the rhetoric about biotechnology was reminiscent of the early '80s. *Business Week* hailed the coming of the "Biotech Century", announcing that "biology will define scientific progress in the twenty-first century" (1997: cover). Ernst and Young reported that 79 biotech. drugs - also known as biopharmaceuticals - had been approved by the FDA (*Chemical Week*, 1997: 27).

These developments were predicted ten years ago by the OECD. The OECD argued that biotechnology does not constitute the basis for a new industrial model, because its application is confined to a few sectors of the economy, and it is not expected to generate widespread employment [6] (OECD 1988a: 35-36). The Organization conceded, however, that the application of these techniques "may bring about major qualitative changes in

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[6] The OECD has stated that in order for a technology to have significant economic implications, it must:
a) generate a wide range of new products and/or services;
b) have applications in many sectors of the economy;
c) reduce the costs and improve the performance of existing processes, products and systems;
d) gain widespread social acceptance with minimal opposition, leading to a favourable regulatory framework; and
e) generate strong industrial interest based on perceived profitability and competition advantage. (OECD 1988a: 35)

society" (36). Kenney (1986) stated that biotechnology has the greatest potential to increase productivity and transform production in the pharmaceutical, chemical, agricultural and food processing industries, providing "a common technical base on which [these industries] can be united" (218). This prediction would appear to be fulfilled with the creation of the "life sciences" industry, in which chemical and pharmaceutical companies have applied recombinant technology in the manufacture of both chemicals and drugs, as well as agriculture and food products. The OECD noted the particular relevance of the new biology for the agricultural sector:

> Biotechnology's direct and indirect effects will be felt in an increasing convergence of agriculture and industrial practice, creating a reorientation in relationships between and among agro-suppliers, farmers and the food processing industry, and introducing a new generation of science-based agricultural companies designed to exploit these techniques through products for a variety of agro-related markets. (OECD 1988b: 27)

4. *"A 95-year old startup company":* Monsanto and biotechnology

As the largest investor in biotechnology (Kenney 1986: 212) Monsanto is both an example, and a precursor, of change in the structure of the chemical and pharmaceutical industries. Monsanto's foray into biotechnology in the 1970s was propelled by a belief in the potential of molecular biology to create a new generation of agricultural products when the market for chemicals waned, and a desire to extend the market potential of its existing products.

Ironically, Monsanto's prospects were far brighter in the 1970s than the 60s; two new herbicides, Lasso and Roundup, returned the Agricultural Division's profitability.[7] Earlier losses in 1968, however, provoked the biochemist Ernest Jaworski to think about other means of generating income for the company. "After you've invented all the herbicides you need, all the insecticides you need, all the fungicides, what are you going to do to keep growing? I concluded that a time would come when you couldn't solve all problems with chemicals." (Rogers, 1996: 4-5) Jaworski pushed Monsanto to develop

[7] In 1993, industry analysts estimated that Roundup generated more than $1.4 billion in revenues (Feder, 1993: D1).

molecular biology applications in its agricultural division. He predicted that genetic technology could be applied to create herbicide-resistant plants, which would extend the shelf-life of Monsanto herbicides, as well as create a market for the new technology. In 1982, 80% of Monsanto's profits were in agricultural chemicals (Kenney 1986: 212). The development of Monsanto's biotechnological capacity has been partially financed by sales of a glyphosphate-based herbicide, Roundup, whose market potential has been extended further, as Jaworski envisioned, by the use of biotechnology to develop glyphosphate-resistant crops (Monsanto 1996b: 7).

Monsanto's relationship with universities, startup companies, and the creation of its own "life science" laboratories, parallels the industry's development. Kenney has identified four patterns of multinational investment in biotechnology; Monsanto has engaged in all four patterns of multinational investment identified by Kenney above.

In the early and mid-1970s Monsanto's pharmaceutical development was pursued via its university agreements. In 1974, the company's Vice-President of Technology, Monte Throdahl, finalized an agreement with Harvard Medical School which became a harbinger of future university-corporate research agreements (Rogers 1996; Kenney 1986: 60). Under this arrangement, Monsanto provided two Harvard researchers with $21 million over twelve years. As a result, Harvard changed its policy to permit licensing of patents in exchange for remuneration; previously, patents could only be dedicated to the public. Unlike National Institutes of Health grants, Monsanto funding was not dependent on peer review (Kenney 1986: 59).

Later, Monsanto entered into another agreement, this time with Washington University in St. Louis. The company supported biotechnology research at the Medical School with a $23.5 million grant dispensed over five years. In return, Monsanto received exclusive rights to license any inventions patented by Washington University, and Monsanto scientists and technicians can learn new techniques and collect information from

the university (Kenney 1986: 67). The terms of this agreement were more favourable to Monsanto's interests than the Harvard agreement because:

> The Harvard researchers had been unwilling to share any of the results of their research with Monsanto personnel before it was available through open publication. The informally worded Harvard agreement, intended to provide a window into new technology, turned out to be a closed door to Monsanto. Determined to make alliances that would be more useful to Monsanto, Schneiderman [Senior Vice-President of Research] took care to structure the Washington University relationships so that both parties would profit; it called for Monsanto to invest $23.5 million over five years to establish a program at the Medical School to discover, study, and isolate proteins and peptides regulating cellular functions (Leonard-Barton and Pisano 1990: 5).

Schneiderman's successor, Dr. Philip Needleman, emphasized the role of universities in Monsanto's research strategy:

> The most important external vehicle for Monsanto's discovery base is the university affiliations they have developed. The university professors have no development costs. All their government grants are pure discovery money. So bang for buck, you have access to some of the finest minds. Monsanto's investment in the university research provides a scientific base, a lead for new discoveries far in excess of the cost of investment. There is no small time player if you are going to biotechnology. Either you can clone the genes, have mammalian cell culture, can build vectors, do all the sequencing - or you are a bit player. (Quoted in Leonard-Barton and Pisano, 1990: 12-13)

Later, Monsanto negotiated contracts with startup companies as well as universities, contracting with Genentech to produce rbGH in 1979, and entering into further contracts in the early 1980s. It also pursued equity agreements, purchasing a 12.5% stake in Biogen and a 30% share in Collagen in 1980 (Kenney 1986: 213).

In 1979, the company hired the former Dean of the School of Biological Sciences at the University of California- Irvine, Howard Schneiderman, to direct all corporate research (Rogers, 1996: 7). Schneiderman suggested that Jaworski create a Molecular Biology group within the Corporate Research Division. Monsanto opened its own molecular biology laboratories in 1981. Schneiderman cultivated members of upper management, and gained the support of Richard Mahoney, who became CEO in 1984. The company's in-house capacity was expanded further in 1984 with the opening of a $150 million Life Sciences Centre (Rogers 1997: 16) and with the acquisition of the pharmaceutical company, G.D. Searle, purchased for $2.8 billion in 1985 (Moody's, 1995: 4661). As

CEO, Mahoney continued to foster the company's biotechnology strategy, which was based around three expectations: that Roundup herbicide would remain profitable throughout the 1990s; that agricultural biotechnology would revolutionize agriculture; and that the company's investment in Searle, which exceeded the division's revenues, would eventually be returned as a result of new product development (Shapiro 1996: 3).

By 1995, Monsanto's investment appeared to have paid off.[8] The company reported record net income of $739 million and earnings per share of $6.36, providing shareowners with a 79% return compared to the Standard and Poor's average of 37%. (Monsanto 1995a: inside cover; Shapiro 1995: 1) It had been restructured into 13 business units: five agricultural products units; five chemicals units; the Searle pharmaceuticals unit; and two food additives units, including the Nutrasweet company, producer of the artificial sweetener aspartame (Monsanto 1995: 13).

By 1996, Monsanto had acquired three biotechnology startup companies and another pharmaceutical company; entered into research partnerships with several biotechnology and pharmaceutical companies; and made equity investments in a further three companies, including a 54.6% stake in Calgene, producer of the genetically-modified "Flavr Savr" tomato (Monsanto 1996a: inside cover; Miller and King 1995: B16). In February 1996 it invested $160 million in Dekalb Genetics to collaborate on agricultural biotechnology research, including research into the genetic alteration of corn and soybean seeds. According to William Young of the investment firm Donaldson, Lufkin and Jenrette,

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[8] Monsanto's route to financial success was not as straightforward as it might appear. In 1991, *Business Week* questioned whether the company was "burning money" with its biotech. investments. Monsanto had not yet had a biotech. product approved for commercial release, and its 1990 earnings dropped 20% (Siler and Carey, 1991: 74). One year later, the company eliminated 10% of its workforce - 3,200 people - and wrote down a portion of its rbGH, Nutrasweet, and pharmaceutical inventories (McMurray 1992: A3). These losses took place at a time when the profitability of the entire biotech. revolution was being called into question. At least 24 biotech companies had filed for bankruptcy protection in 1988; the value of biotech stocks was declining before products or processes had been commercialized (Naj, 1989: B1). *The Wall Street Journal* suggested that the failure of biotech. companies was brought about by a different set of conditions than commercial failures in earlier technological revolutions:

> [i]n the waves of technology that spawned the steel, auto and electronics industries, business failures usually had to do with competition for markets. But biotechnology, which promises to use living organisms to deliver new drugs, crops, fertilizers and pesticides, has run afoul of public fears, regulation and patents confusion (Naj 1989: B1).

Monsanto "is almost a cult stock now." George S. Dalman, an analyst at Piper Jaffray, observed that "Monsanto is probably one of the best ways to invest. They understand that technology is a tool that can produce profits by improving existing products, not just creating new ones" (Wyatt 1996: F11).

Monsanto had already begun marketing two products engineered to express genetic characteristics from other organisms. In association with the Asgrow Seed Company, Monsanto had begun marketing herbicide-resistant soybeans. The seeds had been engineered to express resistance to Monsanto's glyphosphate herbicide, Roundup, thereby enabling farmers to use the herbicide directly on the crops without damaging them. The farmer must pay a $5 a bag fee for the soybeans, use Roundup, allow inspection by Monsanto officials, and agree not to supply the seed to other farmers. Genes from the Bacillus thuringiensis, or Bt, bacteria, which code for proteins which can kill insects, had been inserted in Monsanto's NewLeaf potato in order to make the potato resistant to the Colorado beetle. Monsanto had also commenced trials in the Mississippi Delta with cotton seeds inserted with the Bt gene, known as *Bollgard* cotton (Feder 1996: F1).

The company outbid the Swiss multinational Novartis in its acquisition of American seed companies. There are few independent agricultural biotechnology companies left; most have been acquired by a multinational firm, or have been unable to survive without majority equity ownership by a multinational. In 1998, a San Francisco merchant bank created a venture capital fund for agricultural biotechnology startups to counter the field's domination by a small number of firms, particularly Dow Chemical and Monsanto. Bill Freiberg, publisher of the Agbiotech Reporter, said that "[a]ll meaningful biotechnology research is being done by these 8 to 10 giant agricultural chemical companies in conjunction with seed companies...I don't know of any of those early start-up companies that even made one dime of profit on their own." It should be noted that initial injections of capital for the new fund were supplied by European multinationals Bayer and Agrevo; the latter company was created by Hoechst and Schering (Pollack 1998: C12).

As Monsanto redirected its efforts toward biotechnology and pharmaceuticals, it shed its commodity petro chemicals and plastics businesses, and oil and gas operations (Reish, 1995: 13). Restructuring was completed in 1996, when the company announced that it would spin off its chemical businesses and split into two independent, publicly-traded companies. Its herbicide business, the company's most profitable, remained within Monsanto life sciences (Ewing, 1996: A4). A life-sciences company, chaired by Shapiro, would retain the Monsanto name; the chemical business was named "Solutia" (Monsanto 1997b: A14 & A15). According to a Monsanto Vice-President, A. Nicholas Filipello, "[c]hemicals and life sciences are entirely separate businesses, requiring different management and attracting different investors." (Deutsch 1998: C3)[9] Monsanto's Regulatory Affairs Director, Dr. Dave Kowalczyk, explained that a biotechnology-based business requires a different management strategy than a chemical company because:

> The aim with commodity-type chemicals is driving the costs down, efficiencies. You have to be much quicker with biotechnology, any area where you're at the forefront. A year behind and you're out of the competition. You have to try to make it a leaner organization, and more responsive, and it's a different mentality. Old products have been around for 30 years. It's more important for people in that area to spend three months putting together a plan to get a competitive edge. In the area I'm in you need to work quickly to get patents on new products. (Kowalczyk 1997: interview)

The new Monsanto life-sciences business will be organized into "sectors" rather than units; Agricultural, Food and Consumer, Pharmaceutical, Health and Wellness, and Sustainable Development. Its staff will be organized into teams; "Core Capability" teams will be skilled in scientific knowledge, information technology, and management; "Foundation" teams will be skilled in law, regulatory affairs, finance and administration; and a "Global" team will be responsible for identifying business opportunities in developing countries (Monsanto 1997a: 6). As a result of the split, between 1,500 and 2,500 Monsanto employees will lose their jobs (Ewing 1996: A4).

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[9] Not all industry members agree with this position, however. Another major chemical firm, DuPont, has come under pressure to follow Monsanto's strategy and split its chemical from its life-sciences operations, but the company intends to maintain its current structure. DuPont's chief technology officer, Joseph A. Miller Jr., has commented,"Why not use molecular biology and genetics to make plastics and fibers?" (Deutsch, 1998: C3)

"Food. Health. Hope.™" Monsanto's new corporate logo, announced in February 1998, summed up not only Monsanto's metamorphosis from chemical producer to biotechnology investor, but that of a generation of chemical, pharmaceutical, and agricultural companies which have diversified into traditionally demarcated areas. Biotechnology and related technologies - now more frequently known as "life sciences" - have been applied to link the production of food and pharmaceuticals, linking companies which formerly specialized in one of these areas.

Monsanto's position in agricultural biotechnology increased dramatically by mid-1998. In May, the company reached an agreement with Cargill, a U.S. agribusiness firm which currently controls the production and processing of millions of acres of crops. Analysts predicted that this agreement would allow Monsanto to market genetically-engineered seed via Cargill's distribution networks; the final crop could therefore also be processed by Cargill (Kilman and Warren 1998: B8). In June 1998, Monsanto entered a $33.5 billion merger with American Home Products Corporation, a company which the *Wall Street Journal* reported "sells everything from Chap Stick and Dimetapp to Preparation H". The merger would enable Monsanto "to move genetically engineered products...into supermarkets and drugstores." (Kilman 1998: B10) American Home Products had bought into the pesticide business in 1994 with the acquisition of American Cyanamid, and now has a $2 billion market in pesticides. Monsanto's pesticide business had been a major competitor. By the end of the month, Monsanto had acquired Cargill Inc.'s seed businesses in Central and Latin America, Europe, Asia and Africa for $1.4 billion. The deal combined Cargill's distribution network, and its seed resources, with Monsanto's biotechnology capabilities. John McMillan, an analyst for Prudential Securities, observed that "Monsanto has been the Pac-Man of the agricultural industry in the last 18 months...They've bought a number of seed companies, including DeKalb Genetics[Corp], Delta and Pine Land[Co.] and Holden's [Foundation Seeds Inc.]" (Reuters 1998a: B13). Holden's Foundation Seeds, one of the few large independent seed

companies in the U.S., was acquired for $1.02 billion early in 1997, thus gaining access to Holden's store of corn germplasm and networks through which to distribute genetically-modified corn (Rotman 1997: 7). De Kalb Genetics and the Cargill seed companies are two of the top ten largest seed companies in the world; Delta Pine and Land is the largest cotton seed company. Monsanto's purchase of these seed holdings, along with Plant Breeding International, therefore places it as the world's second largest seed company (RAFI 1998a: 2). The Cargill acquisition put Monsanto just ahead of DuPont in the race for dominance of agricultural biotechnology, providing Monsanto with assets, facilities and markets outside, as well as inside, the U.S. DuPont has a joint biotech. venture with America's biggest seed company, Pioneer Hi-Bred International (Kilman 1998: B10). The rapid consolidation of seed companies is part of a broader trend in the industry; between 1972 and 1988, multinational drug companies had acquired shares in 60 seed-producing firms (OECD 1988a: 28). Ten companies now account for 30% of the $23 billion global seed trade (RAFI 1998a: 2). It has been predicted that further acquisitions will take place as other U.S. companies, and European multinationals, respond to this wave of consolidation.

Another trend which appears likely to produce another wave of mergers and acquisitions is the shift to a second generation of biotechnology applications. In the first generation, seeds were engineered to resist, or respond to, particular chemical inputs, whereas new modifications focus on "output" characteristics to meet particular processing specifications. According to the Rural Advancement Fund International (RAFI), a rural advocacy group which has been particularly active on issues affecting developing countries, this will provide the impetus for food and beverage conglomerates to acquire seed interests (RAFI 1998a: 3). Critics have raised concerns about the implications of this trend. The acquisitions have granted several companies control over the seed industry, and, as seeds are the first link in the food chain, unprecedented control over the food supply itself. RAFI has warned that consolidation has "effectively marginalized the role of public sector plant breeding and research," and threatens food security by undermining

biodiversity and eliminating traditional farming practices, such as saving seed from one harvest to the next. (Farmers cannot save patented seed purchased from Monsanto). RAFI has argued that the consolidation in the industry is motivated by desire to extend control over patents, which it regards as particularly pernicious for public research and farmers' rights:

> The rapid formation of a seed oligopoly would be sufficient cause for government concern. But oligopoly hand-in-hand with intellectual property monopoly is a matter of grave concern. Even as the ranks of the seed industry implode, exclusive monopoly over varieties and genetic traits is exploding....In combination with the global trade clout of the WTO, the global seed industry is positioning itself to dictate the future of plant breeding. When governments review the WTO's TRIPS provisions with respect to plants, they will be determining a key element in the fate of world food security. (1998a: 5)

5. Monsanto and rbGH

The gradual redirection of Monsanto's focus toward biotechnology culminated in the restructuring of the company in the mid-1990s. As Monsanto began its trajectory in the late 1970s and early 1980s, rbGH was perceived as a landmark product, the approval of which would simultaneously revolutionize dairy production and advance the U.S. biotechnology industry. This perception was shared by the other three manufacturers of recombinant bGH, Elanco, Upjohn, and American Cyanamid. In 1985, Monsanto predicted that the drug would be commercially available by 1988, and estimated the worldwide market for the product at $1 billion (Siler and Carey 1991: 74).

Industry spokespersons attributed significance to rbGH because of its status as a biotechnology product. At the 1986 House of Representatives hearings into the impact of rbGH, the four manufacturers of the product spoke on each other's behalf about different aspects of its introduction; a spokesperson from Elanco, Edward Roberts, stressed the significance of rbGH for the biotechnology industry. Roberts expressed the view that the regulatory response to rbGH would send an important signal to the industry about the regulation of biotech products in general. The maintenance of the U.S. lead in biotech was perceived as critical to U.S. success in the marketplace and, as the first product of agricultural biotechnology, the approval of rbGH was crucial to investor confidence in the

industry. (Roberts, 1986: 82-84) The *Wall Street Journal* reported that the manufacturers saw themselves:

> ...on the cusp of a genetic revolution. They see $500 million in annual sales if the Food and Drug Administration approves the hormone by the year's end, as expected. They also see it leading the way to a genetic make-over of the food system that will yield everything from leaner pigs to fatter walleyed pike. (Richards 1989: B1)

rbGH enabled Monsanto to launch its biotechnology program; since the company did not yet have an in-house pharmaceutical capability, rbGH was the first molecule available that it could scale-up to industrial production. Monsanto had an historical interest in the creation of an artificial form of growth hormone, having attempted to synthesize a chemical version of growth hormone in the 1960s. After the denouement of this project, Monsanto directed its development efforts toward plant genetics. When Genentech was formed in the 1970s, however, its first applications of recombinant technology were directed toward the development of human pharmaceuticals rather than plant varieties. Genentech adapted the technology used to produce human growth hormones to animal hormones; it was now possible for Monsanto to create the hormone it had attempted to synthesize in the 1960s. Therefore, although Monsanto had an historic interest in the development of growth hormone, Monsanto spokespeople tended to emphasize the role of chance in the development of rbGH. Dr. Bob Collier noted that the choice of rbGH was somewhat arbitrary:

> The science had not been developed to do this in plants, so there wasn't a plant program available...It was a matter of what was available, what wasn't. What had value and what didn't...Monsanto ended up with bST. In retrospect, we may have waited and chosen another molecule...but hindsight's always 20/20. (Collier 1997: interview)

Monsanto's negotiations with Genentech illustrate the conflict between startups and multinationals over technology development. The value of a startup company depends upon the strength of its technical know-how, and it is unwilling to give up the rights to its skills and techniques; the multinational, on the other hand, does not want to fund the

development of a product which may compete with, or reduce demand for, its own product (Kenney 1986). A former Monsanto biochemist noted that:

> Monsanto needed to be able to bring the technology in-house to acquire the necessary skills to scale it up to manufacture on a long-term basis. Although we had opportunities to allow Genentech to do part of that, it was our decision that from a long-term competitive standpoint, we needed to have those skills resident in Monsanto. (Ryan 1997: interview)

The two parties reached an agreement in 1982, and Monsanto licensed the technology to ferment the recombinant organism, and the Genentech patent.

After the rights to the expression system and fermentation techniques had been licensed, Monsanto scientists began producing the material to see if it was effective. They then developed a prolonged-release delivery system for the hormone. Patenting was critical for Monsanto's interest in the technology:

> If you don't have the active patent, or some significant competitive barriers, it [the technology] rapidly becomes a commodity and most pharmaceutical companies have proprietary formulations; if they don't, they operate under an entirely different model, they can't really develop new technologies. The cost of development is too high, it doesn't allow you to develop something you don't have some protection over. (Ryan 1997: interview)

Genentech's development of human growth hormone meant that they had the skills to engineer animal growth hormones. They were only interested in producing human biopharmaceuticals, however, and licensed the rights to the technology to Monsanto (Ryan 1997: interview).

Investment decisions were made on the basis of the company's expectations about market needs and regulatory requirements. The two did not always coincide, however. The marketing department was focused on getting the product to market as quickly as possible in order to acquire the largest portion of market share; the scientists were more focused on obtaining regulatory approval (Collier 1997: interview). Monsanto's initial product was determined by its marketing strategy. The marketing department wanted a "user-friendly" product, that is, one which could be injected as easily and as infrequently as possible. Marketing personnel advised that farmers wanted a formulation which could be injected intramuscularly (I-M), like antibiotics. The FDA rejected the I-M route of administration,

however, because of scarring of the muscle tissue which may have affected meat quality if undetected during inspections (Sechen 1997: interview). Subsequently, the company began trials with a product injected under the skin, or subcutaneously (SC). This lengthened the regulatory process. Bob Collier regarded this as "one of those technical errors - the marketing people said farmers don't want to take time to do subcutaneous injections, they want to give it like antibiotics. It turned out this was a misperception...that drove the whole thing" (Collier 1997: interview).

The company had researched what formulation of the product would be acceptable to farmers, but not whether the product itself was likely to be accepted. The literature demonstrated that milk yield could be increased significantly by injections of pituitary growth hormone, and it was therefore perceived that there would be a large market for the product. Monsanto scientists believed that the introduction of rbGH would have a major impact on the dairy industry and on agriculture generally. At the 1986 Congressional hearings, the manager of the Agricultural Sciences Division, Lee Miller, discussed the huge increase in the productivity of American dairy farms and how rbGH could contribute to continuing productivity gains (Miller, 1987: 107). The company did not foresee the reaction against the product by small farmers, consumers and environmental groups in either the U.S. or in Europe. In fact, the rbGH manufacturing plant was built in Austria because it was expected that Monsanto would obtain approval in Europe prior to the U.S., although authorization in Europe has still not been granted.[10] Company managers and scientists explained the European reaction as related to their concern about agricultural biotechnology in general and desire to maintain trade barriers against hormone-treated beef from the U.S. Once the European Union had succeeded in banning hormone-treated beef, Dr. Collier stated, it was easier to reject other American biotechnology products.

[10] This decision was made prior to the passage of the 1986 Drug Export Amendments Act, which would have allowed the company to export the product to Europe prior to its U.S. authorization if European approval were granted first.

The U.S. was experiencing unprecedented dairy overproduction.[11] The U.S. was already producing more milk than it could consume, and farm income was falling. Since 1965, there had been a relatively constant 1.5 to 2.0% annual increase in milk yield per cow, without a corresponding increase in consumption of milk and milk products (OTA 1991b: 17). By the 1980s, the government was purchasing billions of pounds of surplus dairy produce. In 1981, the formula for the milk price support level changed. Since 1949, it had been based on a percent of parity, a price that would give the farmer the same purchasing power he or she had in a base period. After 1981, the price mechanism was linked instead to the level of government purchases. When purchases exceeded a certain threshold, prices fell; when purchases did not reach the threshold, prices rose (25). In 1985, Congress passed the Food Security Act, a bill which included provisions to reduce the U.S. milk surplus and its consequent drain on government revenues by instituting a whole-herd buyout program, in which thousands of animals were culled, and reducing the support price for milk. In 1990 the government's price support level was reduced to $10.10 per c.w.t., where it was frozen until 1995 (25). These policies affected the traditional dairying regions differently from the west and south. The Pacific coast and Florida have large, industrialized production systems, with average herd sizes from 500 to 1500 animals and the lowest production costs per unit in the country. Farms in the north and north east have herds of 50 to 150 animals and higher production costs; their share of dairy production fell by at least 2% during the 1980s. In 1988 cash income in the Upper Midwest fell below costs (20). Farmers in this region were finding it increasingly difficult to survive; the introduction of another production-enhancing technology would, some organizations believed, increase this pressure further and force small farmers out of business.

[11] The U.S. was not alone in this. In 1987, the European Community spent $3.7 billion to dispose of more than 1.3 million tons of surplus butter, which cost more than $1 billion a year to store. (*The New York Times*, 1987: D2)

At this stage, Professor Bauman, the principal investigator for trials at Cornell, was reporting increases in milk yield of up to 40% from cows in experimental herds injected with rbGH (Bauman et al. 1985). An agricultural economist at Cornell, Professor Robert J. Kalter, used Bauman's data on production increases to make predictions about the effect of rbGH technology adoption across the industry. In this study, Kalter et al. stated that productivity increases could reach as high as 25% in "well managed herds" and predicted that productivity increases of this magnitude would lead to rapid adoption of the technology. The study concluded that as production increased, milk prices would fall; therefore "[t]he number of dairymen and the size of the dairy herd will, by necessity, decline as the market seeks a new equilibrium" (Kalter et al. 1985: 117). At Congressional hearings on the rbGH issue in 1986, Kalter observed that adoption of rbGH technology could cause a reduction in farm numbers, and without price supports there could be a loss of "15,000 farmers in New York State" (Kalter 1986: 151). According to Kalter, the technology may favour larger operators, not because of the nature of the technology itself but because of the cost of additional technologies - such as computer-monitored feeding - which would ensure the success of the product (152). Monsanto did not endorse this position. The manager of the company's Animal Sciences Division, Dr. Lee Miller, argued that the "efficient" dairy farmer would be the primary beneficiary of the technology, and that the efficiency of a farm was not related to its size, but to how well it was managed (Miller 1987: 108). Spokespeople were puzzled by the negative reaction from small farmers, especially in Canada and Europe, because they perceived the technology as "size neutral"; that is, that it did not require a huge capital outlay, unlike earlier dairy innovations such as milking parlours. The company did not forsee that the dairy surpluses of the 1980s would influence the public acceptance of the product, believing that any product that increases efficiency would be well-received by dairy farmers:

> We didn't fully understand the impact. In the late 80s, there was an excess of cheese and butter products, there was storage of huge amounts of cheese, and we're talking about how exciting this production drug is! The first Congressional hearing was in June 1986. At the time of the hearing they had a buyout program;

> Congress spent a huge amount of money to buy 10% of the dairy herd and to keep incentives for farmers not to go back into dairy...then they heard there's a new product to increase milk production by 40%, so that caused some concern. (Kowalczyk 1997: interview)

The company even introduced a 30-day billing method so that farmers would have higher milk receipts from increased production before they had to pay for their rbGH shipment (Collier 1997: interview). Monsanto also offers farmers a discount on the product based on the percentage of the herd being treated, rather than the number of animals (Kowalczyk 1997: interview). Dr. Collier distinguished the "farming family" from the farm itself:

> One of our advisors said, "I'm not interested in saving the family farm, I'm interested in saving the farming family. In other words, the family farm may not be the only unit the farming family wants to work with. They may want to farm but they don't want to farm their own farm, they want to work on someone else's farm. Or they may want a farm unit that's much bigger than what they had, that's 150 acres instead of 100. The farming family is what you want to help. If somebody wants to farm, we should try to help them do that." (Collier 1997: interview)

However, what is suggested by this quote - that the concentration of farm ownership will increase - was a trend which concerned farm groups. Farmers recognized that the application of the technology may - at least initially - provide benefits to individual operators, but argued that the resulting production increases would be damaging in the long run. A representative from the U.S. National Milk Producers' Federation stated that:

> To some degree, therefore, we can continue to look toward a fewer number of dairymen but more efficient dairy farmers who remain, regardless of herd size, if this new technology is adopted. The smaller dairymen, we are told, will be able to retain a comparative advantage with the "larger" dairy for a longer period. In the final analysis, however, even a 15 to 25% overall production increase could have a profound impact upon our industry. More dairy farmers will be forced to adopt the new technology to remain competitive, only to see potential over-production force down farm prices...Gradually, the less efficient will not be able to survive and adjustments will be inevitable. That will hasten the day when technology will force those who remain to either get larger, become more efficient, or both. As you get larger you inevitably must consider new forms of management control and structure such as partnerships and incorporation. Gradually, the smaller, or less efficient dairy farm is forced out. The question we need to ask is, is this progress for America's agricultural system? (Stemler 1987: 185-6)

Some farmers expressed their support for this conception of agriculture at the Congressional hearings; they agreed that in the context of decreasing government support, the technology could help them to remain competitive (see VMAC 1993). However, others

organized to counter this model of competitiveness. Protest against rbGH was expressed most vociferously in two dairy states, Wisconsin and Vermont. The situation for many farmers in these states was desperate; milk prices had not kept pace with rising production costs, driving farmers out of business. The *New York Times* reported that:

> Many dairy farmers see no logic in the drug's development. They say it is simply not needed. This year, 10.5 million cows on 220, 000 farms will produce 147 billion pounds of milk in the United States, a record and 8 billion pounds more than will be consumed. Because of surpluses, farmers are being paid 15% less for their milk than they were in 1981. Since late 1979, the Government has spent nearly $16 billion to buy and store surplus butter, milk and cheese.... Farmers fear that if the Food and Drug Administration approves the hormone, supplies of milk will increase sharply, driving down prices to the extent that only the largest farmers will be able to keep their operations profitable. (Schneider 1988: 45)

In New York State, a farm family estimated that their return for 17-hour days was 35 cents an hour (Halpern 1988: 34).

The concerns of farmers in Wisconsin and Vermont were confirmed with the release of a report from the Office of Technology Assessment (1986) entitled *Technology, Public Policy, and the Changing Structure of American Agriculture*. The report advised that, in order for American agriculture to remain internationally competitive, new technologies should be rapidly adopted; the OTA also acknowledged that adoption would reinforce the trend toward a dual-structure American agricultural system, in which farmers in the South and South-West would be able to produce milk more cheaply and efficiently than those in the North and North-East. According to the report, the different production levels across the country could be attributed to the quality of management, and philosophy and progressiveness of the farmer. Producers in the North-East and Upper Mid-West would need to change their farming practices in order to remain competitive with new production levels in the more "progressive" South and South-West (7). The report stressed the need for careful management in order for rbGH to be effective:

> Poor management results in a near zero response from bST supplement. Facets that contribute to the quality of management (and milk response to bST) include the herd health program, milking practices, nutrition program, and environmental conditions.(4)

It also noted that:

> The ultimate gains to be captured depend not on the technology *per se,* but on the management skills of its adopters.(45)

The report identified bST as one of a series of biotechnologies which would revolutionize the farm industry and render even bST obsolete. Included among these technologies were reproductive techniques which would enable the creation of transgenic cattle, new vaccines and diagnostic kits, and, in food processing, techniques to improve the production of yoghurt and cheese (51).

Farmers in Vermont and Wisconsin, however, wondered whether their past adoption of technology had not, in fact, created the problem they were now confronting, and began to question the viability of increasing productivity. In Vermont, farmer Stanley Christiansen, who in 1969 was known as "one of the most progressive and efficient farmers in Washington County," felt that "he spent a lifetime cutting his own throat." (Hiss 1994: 87) The director of the Dairy Forage Research Center in Madison, Wisconsin, contended that:

> We are in a period of relative luxury...We can afford to take a hard look at our farming systems. We don't need to develop technologies that yield increases at any cost. We do need to introduce tools and policies that mean we'll be able to farm 1,000 or 2,000 years from now. What we're really talking about is a paradigm shift in our thinking about agriculture. (Schneider 1988: 47)

The House of Representatives Committee on Agriculture received a number of enquiries and expressions of concern about rbGH, in response to which a hearing was called in 1986.(U.S. House of Representatives 1986) At the hearings, Robert Kalter and the Deputy Assistant Secretary from the Department of Agriculture, Ewen M. Wilson, acknowledged that the introduction of rbGH could cause a decrease in the number of farmers. They stressed that in spite of this decline, the technology should be introduced in order for the dairy industry to be competitive on the world market, and that a rejection of the technology would put the U.S. at a comparative disadvantage. Ewen M. Wilson stated that:

> The potential risks of bGH, like the technologies that came before, are increased production, lower prices, and fewer farmers. The potential benefits of bGH are greater efficiency, lower costs of production, increased consumption, improved profitability for the remaining dairy farmers, a greater ability to compete in the world dairy market, and also to compete with substitute dairy products...we cannot, nor should we, Mr. Chairman, stop technological developments from taking place. Attempting to halt technology in this country would only place us at a comparative disadvantage relative to other countries which continue to pursue new technology. (Wilson 1987: 7-8)

Farmers' organizations such as Rural Vermont and the Wisconsin Family Farm Defense Fund opposed the drug by forming coalitions with other organizations, lobbying their State and Federal Congressional Representatives, and advocating moratoria and labelling legislation at the State level. In 1986, The Wisconsin Family Farm Defense Fund joined with the Humane Society of the United States and Jeremy Rifkin's Foundation on Economic Trends to co-ordinate action opposing the drug. In 1987, the Foundation on Economic Trends petitioned the FDA to conduct safety and economic consequences of the drug; the petition was rejected because the FDA does not have the mandate to consider the economic impacts of new technology, and because safety data must be submitted by the sponsoring company.

6. University Scientists and rbGH research

In order to meet regulatory requirements for data collection, Monsanto conducted its safety and efficacy trials at six universities in the U.S.: Cornell, Missouri, Arizona, Utah, Florida and Vermont. In Canada, contract research was also contracted at the MacDonald College campus of McGill University, which also was the site of some Elanco trials. The three other manufacturers also conducted their trials at various university campuses in Canada and the U.S. Although data from Canadian sites can be submitted to the FDA, and U.S. data are accepted at Health Canada, Monsanto did not proceed with the formulation tested in Canada, and so information about these trials was not released in the FDA's FOI Summary. Other companies conducted trials at other Canadian campuses; American Cyanamid, for example, contracted its research to the University of Guelph.

The colleges of agriculture at land-grant universities were established in every state and territory in the United States with the passage of the Morill Acts of 1862 and 1890[12]. Their original mission was to provide a practical education for citizens who could not afford higher education. This mission was further defined by subsequent Acts,[13] which prescribed a tripartite role in teaching, research, and extension. In partnership with the states, the United States Department of Agriculture has funded technology transfer and agricultural research and extension at the LGUs. These three functions are intended to be integrated so that technologies appropriate to public needs are developed and transferred to the local population, and skills are taught to local producers and individuals. Cooperative extension is ideally a two-way process, in which the needs of the local population are communicated to the agricultural colleges, and its research and teaching programs are adjusted accordingly. The function of science, as originally envisioned, was intended to serve the public interest through the development and dissemination of new techniques and practices (National Research Council 1996: 87).

The colleges do not exist in isolation, however, but are connected to the agricultural system, as a recent National Research Council (1996) report has recognized. The report noted that farming is now part of a global food and agricultural system, and it is this system to which the colleges must be responsive: "an understanding of the complex needs and evolving characteristics of the food and agricultural system is a necessary condition for the continuing relevance of the land-grant [colleges]." (21) One of the characteristics of this system is that the private sector has a greater role in agricultural research, and information and technology transfer. Under these circumstances, the role of public research and extension may seem to have been marginalized; however, the report also notes that "...extension can help guarantee that information that influences public policy and private

[12] The first Morrill Act of 1862 established land-grant colleges in each U.S. state, territory, and the District of Columbia. The second Morrill Act of 1890 mandated the establishment of colleges for African-Americans located in the Southern states (National Research Council 1996: 1).
[13] The Hatch Act of 1887 mandated the creation of State Agricultural Experiment Stations for the conduct of research in cooperation with the colleges of agriculture; the Smith-Level Act of 1914 was intended to transfer the results of this research to the local population (Hightower 1973: 1n).

decisions regarding the food and agricultural system...is widely accessible, accurate, and science-based" (88). This would seem to suggest that, rather than transferring information and technology based on its own research, at least part of the LGUs mandate is now to disseminate information based on private sector research and development.

As Kenney has pointed out, land grant universities (LGUs) and medical schools have conducted product safety and efficacy trials for as long as these trials have been required (1986: 38). The universities' role in the conduct of rbGH research highlighted the function of the academy in the contemporary agricultural system and led to conflict at the local level. At the 1986 hearings, the Dean of the College of Agricultural Sciences at the University of Madison-Wisconsin expressed some ambivalence about the outcome of the drug's introduction. In Wisconsin, academic scientists recognized that local farmers were confused and angered by the university's decision to proceed with rbGH research in spite of its apparent contradiction with the whole-herd buyout program and the financial pain experienced by farm communities. They decided, however, that although the changes induced by rbGH would disadvantage some farmers and processors, research was necessary in order to forestall further decline in the industry as foreign competitors proceeded with technological applications (Jorgensen 1987: 148-9).

The principal investigators at university sites did not have a personal interest in the objectives of the trial; however, the trial did provide them with an opportunity to conduct their own research. At McGill, provisions for additional funding for research of interest to the principal investigator were built into the contract; this amounted to between $20,000 and $25,000 per contract (Block 1996: interview). At Guelph, funding from American Cyanamid enabled the scientists to obtain matching funds from the provincial government to study animal metabolism. The opportunity to request matching funds was perceived as one way of coping with government cuts to research funding. Through this system, the researchers were able to pursue research which was not necessarily of interest to the

company but which was made possible by funding initially supplied by the company. The trials also enabled them to gain access to sufficient materials (Burton 1997: interview).

Universities also benefitted financially from the company contracts. At McGill, any costs related to the trial, such as labour costs, equipment use, or veterinary bills are charged to the company, with an additional 40% of these costs charged an overhead. McGill charged $450, 000 for the largest rbGH contract (Block 1996: interview).

The companies benefited in several ways from their arrangements with universities. The data collected from a university site was more likely to be accurate. Once a trial had been established at a particular campus it was easier to conduct additional trials there, or for another company to begin trials there; the principal investigator was familiar with the procedure, and technicians had been trained. In some instances, it was possible to conduct a number of different studies at the one site; at Cornell, for example, milk from the animal trials could be used for nutritional composition and human safety studies. Canadian trials also provided companies with data which could potentially be used in their marketing strategy (Block 1996: interview).

University scientists did not regard the publication conditions specified in the contract as restrictive. McGill contracts specify that publication may not be prevented, but may be delayed by 60 to 90 days to permit the company to review the article. According to Elliot Block, this is called an "unrestricted contract, which means it doesn't restrict publication; there's a 60 to 90 day grace period for the company to review the article, and come back with comments. Those comments don't have to be incorporated." One of the McGill contracts (not necessarily with Monsanto) specified that the data could only be published as a co-authored paper with the principal investigators from the other trial sites; other contracts permitted the McGill group to publish its own data separately (1997: interview). Dr. David Barbano at Cornell said he did not recall any language in the contract which delayed publication, and felt that the companies encouraged publication:

> In real life, it usually works in reverse. The companies are so anxious to have you publish the results that the [peer-review] system is too slow. When you submit a

> paper for review in a scientific journal, an eight-month delay is a relatively short delay to get through the review process, and the average would be more like a year and a half and sometimes two and a half years. ...The abstract is a year to three years ahead of the peer-reviewed publication. I've never run into a situation where the company has said you can't present this at a scientific meeting. ...The main thing in the contract is if we were going to present something the company needs to have it in advance, mostly what they want to know is if they're going to read something in the newspaper about it later.

Barbano felt a sense of obligation to inform the company of his public announcements. "Even if it's not spelt out in the contract, as the investigator I always send things ahead of time" (1997: interview).

The principal investigator for American Cyanamid at Guelph also noted that he had published every analysis of the trial data he felt was worthy of publication, and that the company had not opposed any publication, including later publications by a colleague which suggested that the product may negatively affect reproduction in later lactations. During the trial period, however, Burton did feel restricted from discussing the data with scientists at other universities;

> We had discussions with other scientists about the bST response but not about the experiments. In fact, there was some reluctance to talk about this because there were four companies trying to get the products tested and approved so there was a certain amount of competition, and [the companies] didn't want a whole lot of information being spread around about the protocols or the levels of compound being used.

This can be contrasted with the degree of interaction with the company:

> Part of the contract responsibilities was to supply the company with data on a periodic basis and we were in touch with them routinely. The people responsible for monitoring the trials for the company also visited, so there was considerable discussion and the results were made available to them before they were published.

It should also be noted that one of the Canadian researchers pointed out that the number of animal scientists is North America is small, and people within universities, the regulatory agencies, and companies know each other and often trained together. This would suggest that there was perhaps more informal discussion between university scientists than indicated by Burton. However, these comments lend support to Kenney's distinction between the disclosure of results and disclosure of research. Although the companies did not attempt to stop publication, the awareness of the proprietary nature of the research, and

competition between companies, limited discussion of research *procedures* among university scientists.

7. Conclusion

In the 1970s, the petroleum and petrochemical industries faced a crisis in profitability. These industries, which had supplied the agricultural chemicals which contributed to the increased productivity of agriculture, began investing in biotechnology as a means of restoring profitability. They applied biotechnology in the interests not only of developing new products, but of extending the marketability of earlier products (for example, the use of recombinant technology could be applied to engineer herbicide-resistant crops, thus extending the life of the herbicide market). The development of products such as rbGH depended on the perception that biotechnology would form the basis of an alternative growth model, and on state policies which protected intellectual property - both domestically and internationally - and enabled public institutions to claim proprietary rights. In the case of rbGH, development was also dependent on assumptions about farmers' needs and goals. Monsanto scientists and managers saw the impending technological revolution as a means to continue the agricultural trend of the previous thirty years, in which technological applications had been used to increase productive efficiency. The company assumed that this goal was socially acceptable, although the farm crisis of the 1980s had undermined its legitimacy. When resistance to the technology grew, however, the perception of the importance of the biotechnology revolution itself motivated persistence with the product.

Since the drug was approved in the U.S., Monsanto has become the dominant player in agricultural biotechnology. It has restructured to focus on the application of biotechnology in agriculture, pharmaceuticals, and food, and divested itself of its chemical concerns (with the notable exception of agricultural chemicals). The recent acquisition of seed companies has bolstered this strategy. Although Monsanto's actions were motivated by a crisis in the prevailing industrial model, its recent activities will effect the

transformation of that model. As a symbol of that transformation, rbGH inspired reaction against the model, and the potentially negative effects of this particular transformation.

Chapter Three

The U.S. context

1. Introduction

In 1993, the Food and Drug Administration concluded that rbGH was safe for cows, and for the humans who drink their milk. Any indirect risk to human health from animal health problems could be managed within the existing milk monitoring system. The reasoning behind this decision is explored in Chapter Five; the purpose of this chapter is to outline the context in which the FDA conducted its evaluation of rbGH.

During the period of the evaluation, the FDA was subject to two major pressures. Policies aimed to decrease the regulatory burden on industry in general, and the biotechnology industry in particular. As I outlined in Chapter One, the product itself was perceived as a harbinger for the industry, and its regulation accorded disproportionate significance. The symbolic importance of the product meant that advocacy groups, as well as corporations, regarded the signals sent out by the regulatory decision on rbGH as critical for the future development of the industry. Controversy, and subsequently public demands on the FDA's time, grew, with the result that the Agency was in the unusual position of defending the review of a product whose evaluation was not complete.

2. The U.S. experience - overview

The history of bovine growth hormone dates back to 1937, when Soviet scientists discovered that cows produced more milk when injected with pituitary-gland extracts (Asimov and Krouse 1937). The Soviets' results were confirmed by further studies conducted in England in the 1940s (Peel and Bauman 1987: 474).

The first study with rbGH was conducted at Cornell University in 1982, and shortly afterward the four companies took the unusual step of acknowledging that they were developing the hormone (OMB 1994: A1). At this stage, Monsanto was testing a product which was injected into the animal's muscle. This route of administration was later

ruled unacceptable by the FDA because of muscle lesions which might not be detected in meat inspection and could therefore remain in the meat supply. By the late 1980s, Monsanto was injecting the product under the animal's skin; this was finally approved by the FDA. The Agency evaluated the data from both sets of trials in reaching its decision.

In June 1986, the House Committee of Agriculture opened hearings on the drug's potential impact. Representatives from the United States Department of Agriculture, and Food and Drug Administration, and each of the four companies spoke at the hearings, along with academics from land-grant universities, representatives from the Humane Society of the U.S., and anti-biotechnology activist Jeremy Rifkin. At the hearings, Rifkin represented a coalition comprised of the Foundation for Economic Trends, the Humane Society, the Wisconsin Family Farm Defense Fund, and the Wisconsin Secretary of State, Douglas La Follette.

One year later, Rifkin petitioned the FDA to consider the economic consequences of the product's introduction (OMB 1994: A2). This request was denied, as such considerations lay outside the FDA's mandate. The application of economic criteria in the evaluation of biotechnology products had been ruled out with the announcement of the Coordinated Framework in 1986. The Framework, formulated by a committee of senior officials from several departments, specified that biotechnology products and processes would be regulated under existing statutes and by the departments presently charged with administering them. Food and drugs produced using recombinant DNA or other biotechnologies would therefore be regulated by the FDA in accordance with existing law.

The mid-1980s was also a period of controversy about the development of biotechnology in general as well as agricultural biotechnology, and rbGH, in particular. In 1987, the Patent Board of Appeals ruled that a multicellular organism was patentable subject matter; this extended the scope of the Supreme Court's landmark 1980 decision in *Chakrabarty v. Diamond* that a living organism could be patented. In response to the former decision, the Senate Committee of the Judiciary opened hearings into the patenting

of transgenic animals. The ownership of intellectual property in newly-created organisms continued to be recognized by the Patents and Trademarks Office, however. In 1988, the first animal patent was granted to Harvard University for the creation of a transgenic mouse, known as the "onco" mouse because it had been engineered to develop human cancer (OTA 1990).

The rbGH debate intensified in 1989-90. In 1989, a summary of the results from Monsanto's animal toxicity testing was leaked to the most vocal human health critic, Dr. Samuel Epstein of the School of Public Health at the University of Chicago in Illinois. The report indicated a reduction in pregnancy rates and an increase in the use of antibiotics for the treatment of mastitis, a bacterial infection which is commonly treated with antibiotics. Epstein drafted an article which outlined potential public health risks to consumers who drank milk from treated cows. He suggested that the approval of rbGH would lead to the contamination of milk with "toxic and carcinogenic residues" and the risk of spreading antibiotic resistance. Epstein also raised the possibility that elevated milk levels of insulin-like growth factor-I (IGF-I), a growth factor which has an identical sequence in humans and cows, could lead to premature growth in infants and breast cancer in women. In response to this article, Jeremy Rifkin's Foundation on Economic Trends, and a coalition of farm and consumer groups, petitioned the FDA to ban the sale of milk and meat from cows in investigational herds (Epstein 1990). The Agency had permitted the release of milk and meat into the food supply in 1985, after reviewers concluded that food from test animals would not represent a risk to the human population. The Foundation on Economic Trends also wrote to twelve supermarket chains threatening a consumer boycott if they stocked milk from treated animals, and obtained agreement from five of them not to sell such products (OMB 1994: A3).

In an attempt to quell controversy and allay public concerns about the safety of the drug, two senior FDA scientists, Dr. Juskevich from the Division of Toxicology and Dr. Guyer from the Division of Chemistry, wrote a summary of the Agency's human health

evaluation, which was published in the respected journal *Science* in August, 1990. This was the first time the Agency had published data on a product prior to its approval. The article included a brief review of the literature on protein digestion and absorption, and the results of industry studies on the effects of rbGH and insulin-like growth factor on rats. Furthermore, in December, the FDA asked the National Institutes of Health Technology Assessment Conference to review its data on human and animal health. The NIH stated that the milk and meat from treated cows was safe, but made suggestions for further research and acknowledged that not all of the data were available to it.

Two days before the NIH conference, the Consumer Policy Institute of the Consumers' Union released a report stating that the Institute had major concerns which it believed had not been adequately addressed by the FDA. Their primary concern was the consequence of elevated levels of IGF-I and of antibiotic residue in milk (Hansen 1990).

Not only the impact of rbGH, but the Agency's evaluation of it, became contentious in the late 1980s. Epstein's article inspired Congressman John Conyers to request that the Inspector-General for the Department of Health and Human Services conduct an investigation into the FDA's evaluation of the safety data (Epstein 1990b: 580). When the Inspector-General's report was released in 1992, it concluded that there was no evidence that the Agency or the company had manipulated or suppressed animal health data, and that the withholding of such data had been appropriate (OMB 1994: A6). A veterinarian who had worked on the FDA's animal health review of rbGH, Dr. Richard Burroughs, was fired in 1989. He later alleged that his dismissal was due to his expression of concerns about the animal health data, and about the degree of interaction between Agency officials and the drug manufacturers (Burroughs 1994). A researcher at the University of Vermont, Dr. Marla Lyng, had given the farm action group Rural Vermont evidence of deformed calves born to cows on the UVM trials. Rural Vermont began correspondence with the FDA on the issue. A Congressional Representative from Vermont, Bernard Sanders, and several other representatives, asked the General Accounting Office (GAO) to investigate the

FDA's actions regarding the University of Vermont trials, and later claimed that the GAO had abandoned its efforts due to lack of cooperation from Monsanto and the FDA (Christiansen 1995). Sanders and others also requested that the Inspector-General for the Department of Health and Human Services investigate Monsanto's promotion of the drug prior to its approval. The Inspector-General concluded that the company may have violated regulations forbidding pre-approval promotion of the drug, and recommended that the Agency take action against the company to prevent further promotion. After this ban on Monsanto promotional activity, the *Journal of the American Medical Association* and the *Journal of the American Pediatric Association* published articles endorsing the drug's safety in 1991.

At the request of Congressional representatives, the GAO also investigated the Agency's human health evaluation. The GAO (1992c) reported that although it could not find fault with the Agency's review of the data, the scope of the review should be broadened to encompass considerations of an indirect risk to public health arising from a potentially increased incidence of mastitis in cows. Since the disease is commonly treated with antibiotics, an increased incidence of mastitis associated with rbGH use could, therefore, potentially result in a greater likelihood of antibiotic residues entering the milk supply. The GAO's attention to this issue was the result of several years of controversy about the levels of antibiotic residue in the milk supply. In the late 1980s, a test of a small number of milk samples by the FDA revealed levels of drug residues which violated established thresholds; however, the Agency claimed that these residues did not present a risk to human health. Further tests by other organizations also found violative drug residues, but the Agency claimed that these tests had produced false positive results. The Agency later retracted this statement, but still maintained that the results did not warrant public alarm. In response to the controversy, the GAO wrote a report on the monitoring of antibiotics which argued that FDA surveys were not an adequate basis for judgements about the safety of the milk supply.

The FDA called a meeting of its Veterinary Medicine Advisory Committee (VMAC) to examine the GAO's concerns regarding the mastitis issue. At the meeting, the FDA argued that although the data it had reviewed indicated an increased risk of mastitis, it believed that the existing milk monitoring system would enable any additional antibiotic residues to be detected; therefore the risk of such residues contaminating the milk supply was low enough to be considered "manageable." The VMAC concurred with this argument (VMAC 1993).

Also in 1993, the FDA convened a joint meeting of its Veterinary Medicine Advisory Committee, and Food Advisory Committee, to consider whether milk from treated cows should be labelled as such (FDA 1993a). After the meeting, the FDA recognized a consumer interest in labelling by permitting the voluntary labelling of dairy products as "rbGH free," but denied mandatory labelling on the grounds that consumers did not have a material interest in labelling; that is, there were no significant differences between milk from treated and untreated cows which warranted mandatory action. In order to avoid misleading the public, the FDA required that any voluntary label be accompanied by a disclaimer acknowledging that no significant difference had been found between the two kinds of milk (FDA 1994a).

The FDA announced that it had approved the drug for commercial sale on November 5, 1993. This approval was subject to an agreement with Monsanto to monitor the milk from farms using the drug for levels of antibiotic residue, and to proactively seek out reports of animal health problems, for two years following approval. In the Omnibus Budget Reconciliation Act of 1993, Congress enacted a 90-day moratorium which came into effect upon the drug's approval (Schneider 1993: 1). During this period, the Office of Management and Budget completed a study which argued that the drug's introduction would reinforce, but not fundamentally change, productivity increases in the U.S. dairy industry. It predicted that milk prices would fall, resulting in increased price-support costs for the Federal government, but added that this would be partially offset by savings in

government-funded food programs. It also noted that the drug's approval would enhance U.S. leadership in biotechnology (OMB 1994).

Monsanto's rbGH formulation, Posilac, went on sale in the U.S. on February 3, 1994. The product was accompanied by a label which listed over 20 possible side effects for animals, and recommended that farmers should evaluate and/or implement mastitis and reproduction management programs prior to commencing use of the drug (Monsanto 1993). The Monsanto company instituted a marketing program in which farmers could order supplies of Posilac directly from the company, which would be delivered to them within 24 hours. It also provided farmers with a $150.00 voucher to cover the costs of a veterinarian's visit to assess the herd and recommend management techniques before the introduction of Posilac (Monsanto 1994: 1).

One week after approval, the FDA published interim milk labelling guidelines, outlining acceptable wording for product labelling. Although the FDA had not imposed mandatory labelling, the state of Vermont proceeded with mandatory labelling of dairy products from treated cows, a law which was upheld in the Federal court, but later quashed by the Second Circuit Court of Appeals on the grounds that such a law violated a First Amendment right to silence (Chase 1996: 1). Monsanto sued two dairy companies, one in Iowa and one in Texas, for product disparagement after the dairies labelled their milk rbGH-free, (without the FDA recommended disclaimer) but reached an out-of-court settlement with both companies (Gershon 1994: 384).

Consumer groups took the FDA to court, arguing that its authorization of rbGH was "arbitrary and capricious"; however, the court rejected the plaintiffs' arguments.

Controversy about the approval process continued even after the product's release. One month after sales began, the *Los Angeles Times* published an article by Epstein (1994) which claimed that the consumption of milk from treated cows would lead to a higher risk of breast cancer. In April 1994, Representatives Bernard Sanders, George E. Brown, and David R. Obey asked the GAO to examine conflicts of interest between several

FDA employees who had been involved with the rbGH review who had also had previous connections with Monsanto. The GAO found that the employees had no financial conflicts of interest, and had cooperated with FDA guidelines designed to prevent the appearance of such a conflict (GAO 1994).

Monsanto published its own analysis of the data on mastitis in August. The article, co-authored with the principal investigators at university sites in the U.S. and Europe, argued that although an increase in the incidence of mastitis had been shown in herds using the drug, this effect could be accounted for when increased production was taken into account. In fact, when production was factored in, "no effect of rbGH was found" (White et al. 1994: 2250). This article had been eagerly awaited by the drug's critics. Two British researchers, Erik Millstone and Eric Brunner, had asked the company for the raw data from the European trials, and determined that, in their analysis, somatic cell counts (white blood cells associated with mastitis which appear in milk) were higher in milk from treated cows than Monsanto's analysis suggested. The researchers attempted to publish the paper, but Monsanto requested that the British journal *Veterinary Record* not publish it because the authors had not sought permission from the principal investigators at university trials. The company did however note that it would publish an analysis of the pooled data at a later date (Millstone, Brunner and White 1994: 647-8).

Monsanto completed its two-year Post-Approval Monitoring Program in November of 1996. The Program involved a comparative study of milk antibiotic residues before and after approval of the drug, and a 28-herd animal health study. According to the FDA, the study confirmed that the drug label was accurate, and that the pre-approval judgements made by the company and the Agency were borne out by the post-approval data. During the two-year period, farmers in Wisconsin had claimed that Monsanto had not reported the problems they experienced to the FDA, and the Wisconsin Farmers' Union and the National Farmers' Union set up a 1-800 number for farmers to report problems with rbGH. The FDA investigated two claims that Monsanto had not reported adverse drug

experiences promptly, and reported at the final Veterinary Medicine Advisory Committee meeting that problems on these farms could be attributed to management practices rather than to the drug. The Agency had inspected ten of the 28 herds using the drug, and audited data at Monsanto's head office in St. Louis (VMAC 1996).

In 1998, the company reported that "[o]f the nearly 9 million dairy cows in the United States, approximately 30% of the cows are in herds that are supplemented with Posilac." It went on to state that the average farmer supplements at least 50% of his or her herd, which would suggest that at least 15% of the U.S. herd is being treated with Posilac; it is not possible to determine how much higher - or lower - the actual figures may be (Monsanto 1998: 1).

3. The U.S. Regulatory System

The U.S. Food and Drug Administration "regulates 25 cents of every dollar spent by the American consumer, or about $1 trillion worth of goods and services annually...[it] employs over 9000 people and has a budget of $1 billion" (*The Lancet*, 1995: 981). The FDA's actions, therefore, affect not only Americans' health and safety but a significant portion of their economic activity. Throughout its history, the FDA has sought to protect consumers without unduly damaging the interests of the drug, food, and cosmetics manufacturers whose products it regulates. In the 1960s, the thalidomide tragedy in Europe and Canada prompted Congress to institute legislative reform which expanded the powers of the Agency in order "to strengthen the laws designed to keep unfit drugs off the market in the first instance and speed their removal should they reach the market" (United States Senate 1962: 2884). In the 1990s, Republican pressure in Congress has attempted to reverse this direction, and speed drugs *to* the market rather than *from* it (see Goldberg 1996).

4. Biotechnology: The Regulatory Environment in the 1980s

The Reagan Administration decided that, rather than creating a separate body of law to address the development of recombinant technology, biotechnology products should be

regulated under existing law. In 1985 the Office of Science and Technology Policy announced the establishment of the Biotechnology Science Coordinating Council (BSCC), which was comprised of the senior administrators from the FDA, EPA, and NSF.[1] (Kingsbury 1986: 50) Sheila Jasanoff has argued that the BSCC was created by the White House in order

> to seize control of biotechnology policy...ostensibly to provide scientific coordination across the government, but in practice to serve as a possible counterweight to possibly recalcitrant regulatory agencies. The BSCC, in turn, relied on the National Research Council for a still more authoritative exposition of the scientific principles that should govern the regulation of biotechnology. (1995b: 325)

In June 1986, the Office of Science and Technology Policy published its "Coordinated Framework for the Regulation of Biotechnology" in the *Federal Register*. The working group which developed the Framework had concluded that "existing laws as currently implemented would address regulatory needs adequately" (OSTP 1986: 23302). Therefore, "[e]xisting statutes provide a basic network of agency jurisidiction over both research and products." (23303) According to Jasanoff, the Framework documents implied that "biotechnology as a process presented no risks novel enough to require the legislature's attention. Only products needed to be evaluated" (1995b: 157). This meant that foods and drugs produced using recombinant technology would still be regulated by the Food and Drug Administration (FDA) under the Federal Food, Drugs and Cosmetics Act (FFDCA).

On May 29, 1992 the FDA reaffirmed the intentions of the 1986 Coordinated Framework and clarified its interpretation of how the FFDCA should be applied to foods produced using new technologies (primarily biotechnology). The FDA considered "existing statutory authority under Sections 402(a) (1) and 409 fully adequate to ensure safety regardless of process" (FDA 1992: 22989). According to the FDA's interpretation, "the regulatory status of a food, irrespective of the methods by which it is developed, is

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[1] The Council was comprised of: the Commissioner of the FDA; the Director of the NIH; the Assistant Secretary for Agriculture for Marketing and Inspection Services; Assistant Secretary of Agriculture for Science and Education; Assistant Administrator of the EPA for Pesticides and Toxic Substances; Assistant Administrator of the EPA for Research and Development: and the Assistant Director, Biological, Behavioral, and Social Sciences, NSF (Kingsbury, 1986: 50).

dependent upon objective characteristics of the food and the intended use of the food" (22984). A food should not be regulated according to the means or methods by which it is produced, but according to the characteristics of the final product.[2]

In August 1990, President Bush approved the *Principles for the Regulatory Review of Biotechnology*. According to these principles, regulations must:

> -focus on the characteristics and risks of the product, not the process by which it is produced
> -be designed to minimize regulatory burden while assuring the protection of public health and safety
> -accommodate rapid advances in biotechnology - standards should be performance-based, (i.e. set a goal to be met by the technology in any number of ways) rather than design-based (in which the design of the technology is specified by the regulation)
> -performance standards rather than rigid controls should be instituted. (OSTP 1992: 6760)

The President's Council on Competitiveness reiterated the principle that the regulation of biotechnology should be decreased. In its report on National Biotechnology Policy, released in February 1991, the Council stated that "the Administration has sought to eliminate unneeded regulatory burden for all phases of the development of new biotechnology products" (6761). Two months later, the Council issued the *Fact Sheet on Critical Technologies* which argued that regulation should be issued only when the benefit gained from the regulation exceeded the cost of imposing it. Regulations should also be based on "scientific risk assessment"; voluntary private standards and disclosure should be relied on; and licensing should be carried out swiftly, based on criteria clearly defined in advance (6760).

The distinction between biotechnology products and processes was reiterated by FDA scientists, who had been dragged into the rbGH debate. During the period in which the drug was under review, Congress was debating the ethical implications of animal patenting, and the biotechnology issue was once again on the public agenda. In attempting

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[2] These characteristics can be divided into two types. Agronomic characteristics affect plant yield - these include characteristics such as disease, pesticide, or herbicide resistance. Quality characteristics affect the processing, preservation, nutrition, and flavour of the product (FDA 1992: 22985).

to distinguish the rbGH debate from the concurrent biotechnology controversy, FDA reviewers reproduced the distinction at the heart of the Administration's biotechnology policy; rbGH was not an example of biotechnology. Only the process, not the product, was the result of recombinant technique. In their view, a biotechnology product was defined as "transgenic"; that is, an animal or plant which had foreign genetic material incorporated in its DNA. According to this definition, milk or meat from animals treated with rbGH was not a product of biotechnology; "milk and milk coming from treated animals is not really biotech. food or transgenic food - the biotechnology only impacts how the drug is made, it's just a manufacturing process." Since discussions about biotechnology were proceeding during the FDA evaluations, "there was a tendency for people to consider bST in the same light. So the agency and the firm had to do some work to dissuade people from the perception that somehow bST resulted in transgenic food being consumed" (Sechen 1997: interview). Ironically, it would appear that anti-biotechnology activist Jeremy Rifkin would at least partly agree with the distinction between transgenic food and rbGH. At the 1986 hearings, Rifkin stated that the risks posed by rbGH were very different from those posed by the release of genetically-modified organisms (U.S. House of Representatives 1986: 246).

5. Animal Drug Laws and the rbGH review

The FDA is responsible for regulating human and animal drugs as well as food products and cosmetics under the Federal Food, Drug, and Cosmetic Act (FFDCA). Amendments to the Act in 1968 created a separate body of law for the regulation of animal drugs, and led to the establishment of a centre for their evaluation, now known as the Center for Veterinary Medicine. Full authority to determine the human health implications of animal drugs was not granted to the Center until 1983 (Lambert 1997: 277n).

In order to have an animal drug approved for commercial release in the U.S., the drug's manufacturer must lodge an application with the Center for Veterinary Medicine

(CVM).[3] The Office of New Animal Drug Evaluation (NADE) deals with animal drugs prior to approval. The rbGH application was dealt with by the Office's Division of Biometrics and Production Drugs, which evaluates drugs which increase production and production efficiency. At the time of the rbGH review, the primary reviewer,[4] Dr. Suzanne Sechen, assigned portions of the review to the appropriate divisions - food safety to chemistry and toxicology, for example. This function is now carried out by a central document control unit.[5]

The drug sponsor must demonstrate that the product is effective - that is, that the product does what the sponsor claims - and that it is safe. In the case of food-producing animals, the product must be safe for the target animal and for humans who consume milk, meat or other products from it,[6] and the manufacture of the product must not be damaging to the environment (OMB 1994: 9). The environmental safety of the product is considered under the National Environmental Policy Act, the President's Council on Environmental Quality Regulations and the FDA's supplemental regulations. These regulations enable the

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[3] In order to avoid confusion, I will use the term FDA to refer to both the Agency and its Veterinary Medical division, the Center for Veterinary Medicine.

[4] The primary reviewer's role has been described as follows:

> Primary reviewers are animal scientists or veterinarians assigned to a particular drug product under review by the CVM. The primary reviewer has the primary administrative duties associated with the product: making sure that the appropriate people are assigned to review each submission; being the primary contact with the firm; preparing much of the correspondence to the firm; ensuring that the CVM's records regarding the product are accurate; and ensuring that all review requirements are met as the product approaches approval. A primary reviewer also typically has review duties associated with a drug application. In the case of Posilac, Dr. Suzanne Sechen was part of a team of reviewers responsible for evaluating its efficacy and animal safety, along with other CVM animal scientists, veterinarians, and statisticians (Sechen 1998: personal communication).

[5] In 1992, the FDA introduced a computerized system for setting time frames for the evaluation of submissions, according to the amount and complexity of the data submitted, and the purpose of the application. This system is known as the "Submission Tracking and Reporting System" (STARS). (Clinton and Gore, 1996: 5)

[6] In determining whether the drug is safe, the following issues should be considered: the consumption of drug residues or other residues formed as a result of drug use; the cumulative effect of the drug for humans or animals; whether the conditions of use specified on the label are likely to be followed in practice; and "safety factors which in the opinion of experts, qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use of animal experimentation data." (U.S.C. 21§360b(d)(2)) The Animal Drug Amendments incorporated concepts from food additives law, including a clause prohibiting carcinogenic substances in food (known as the Delaney clause.) (Lambert 1997: 278) An animal drug application may be rejected if the drug is found to cause cancer in animals or humans, unless it will not adversely affect the animals for which it is intended, and drug residues will not be found in products intended for human consumption. (360b(d)(1)(H)) The Delaney clause was repealed with the passage of the Food Quality Protection Act on August 3, 1996 (Hanson 1996: 38).

CVM to examine procedures to prevent and control accidental spills of the product or occupational exposure during its manufacture (Young 1987: 62).

To conduct safety and efficacy studies, the manufacturers must establish an Investigational New Animal Drug (INAD) application with the Center for Veterinary Medicine. If the investigational drug is for use in food-producing animals, human food safety data must be submitted to the Agency, which then establishes whether drug residues present any risk to human health. During the investigations, milk or meat from test animals cannot be released into the food supply until after a withdrawal period - that is, a period of time in which that food products are withheld from sale after treatment with the drug - so that no residues are present when the product is consumed. If, however, the food will not contain any drug residues, or if such residues are determined to be harmless, the scientists may decide to allow the consumption of products from animals treated in investigational studies. FDA approval also requires that the manufacturer provide a method for assaying the presence of the drug residues in food products from the animal, as well as the proposed level of residues that are permitted to remain in the food without it being considered adulterated under the FFDCA (Young 1987: 63). The FDA does not, however, require a testing method for any drug which has a zero withdrawal period. Initially, the FDA set a withdrawal period of 5 days for milk and 15 days for meat from cows treated with rbGH; after the FDA had concluded that rbGH posed no health risk to consumers, and that the recombinant product was indistinguishable from pituitary bGH, it ruled that no withdrawal period was necessary (OMB 1994: 11). It ruled that milk and meat from cows treated with rbGH in investigational trials could be sold to the public in 1985 (OMB 1994: A1).

In the late 1980s, the FDA wrote a technical assistance document (TAD) outlining requirements for the collection of efficacy data, and supplemental animal safety information, on investigational trials. The TAD included a section on evaluating mastitis, which later became a significant issue in the safety debate. According to the Regulatory Affairs Director at Monsanto, Dr. Dave Kowalczyk, the four companies were also

represented at the meetings between the FDA and the American Dairy Science Association to create the technical assistance document. The document and its mastitis addendum were available as guidance for the companies. With these documents in mind, the companies could submit a draft protocol to the FDA for comment. Although consultation with the FDA is not a legal requirement, it is in the companies' interest to submit a draft to the Agency, in order to ensure that all the relevant parameters are covered.[7]

Prior to beginning a trial, the manufacturers must submit drug shipment notices indicating the location, expected time-frame, the number and type of animals to be treated, the maximum dose, duration of treatment, and whether the trial is a "pivotal" study. A pivotal study is one used by the Agency to decide the safety and effectiveness of the product. The sponsoring company must identify whether a study is pivotal or non-pivotal when it submits to CVM a notice of drug shipment for each study. The Center is usually involved in developing the design of pivotal studies. Some pivotal studies, such as drug tolerance or toxicology studies, are conducted according to Good Laboratory Practices guidelines. Pivotal studies are often inspected by CVM officials; all data from a pivotal study are to be submitted to the Center as part of a new animal drug application (NADA). A non-pivotal study, on the other hand, is run by the company to look at certain aspects of the drug which may not *directly* concern the CVM The company must submit the results of non-pivotal studies as part of an NADA, but only in the form of a study report; it does not have to submit all the data from non-pivotal studies. This means that field trials are to be conducted in several different geographical locations in the U.S. (OMB 1994: 13). FDA scientists from the Bioresearch Monitoring Program may then inspect the experimental sites

[7] This process has since been formalized with the introduction of the 1996 Animal Drug Availability Act (ADAA), which provides for binding presubmission conferences. A "conference" may encompass more than one meeting between the sponsor and the FDA. (Lambert 1997: 284) Once an agreement establishing an investigational requirement has been reached, it is binding upon both parties. (21 U.S.C.§360b(b)(3)) In response to these amendments, the FDA has implemented regulations to speed up and streamline the animal drug evaluation process. The proposal explained in the National Performance Review suggested that, among other things, the evaluation system be decentralized, so that the sponsor's technical personnel could communicate directly with FDA reviewers; and that the review of one part of the submission would not interfere with another part of the submission. (Clinton and Gore 1996: 4)

to monitor the conduct of the study, adherence to the protocol, and recording of data (OMB 1994: 14). If the results from non-pivotal studies are inconsistent with those from pivotal studies, or suggest adverse effects not demonstrated in the pivotal studies, the FDA may request more data (OMB 1994: 16), and/or the study may be elevated to "pivotal" status (Sechen 1997: interview). This occurred with a non-pivotal study of the Posilac formulation of rbST on injection-site reactions at the University of Vermont, in which a problem appeared which was not anticipated by the FDA and, as a result, the study data were re-classified as pivotal. Only the summarized results from pivotal studies (including the Vermont study demonstrating severe injection site reactions) were released in the Freedom of Information (FOI) summary; results from other, controversial, studies at Vermont were not released because they were not pivotal for the Posilac formulation of rbST. The FDA attempts to inspect the site of every pivotal study; in the rbGH case they "came close" to inspecting every site (Sechen 1997: interview). According to the Dairy Research Director at Monsanto Canada, Dr. Robert J. Collier, the protocols for carrying out the studies were first negotiated in 1983. The trials began in the U.S. in 1985 (Collier 1994: 29).

When the drug manufacturer considers that it has all the data necessary for final approval, it submits a New Animal Drug Application (NADA) which includes the results of the investigational trials, information about the drug's manufacture and stability, a proposed label, and an environmental assessment of the manufacture and use of the product. The CVM reviews the data, asks the sponsor to correct any deficiencies, and approves the drug if the results meet its criteria (Young 1987: 64). Under the Federal Food, Drug and Cosmetics Act, the FDA does not have a mandate to review the social and economic impacts of a drug's introduction (OMB 1994: 10).

Traditionally, the FDA required that companies conduct two key studies to determine the safety of an animal drug; an acute toxicity study, a controlled study in which a small number of animals receives up to 25 times - this was later reduced to 10 times - the

expected dose for up to 14 or 28 days; and a chronic toxicity (also known as 1,3,5X) study in which one, three, and five times the highest expected dose is administered. For Monsanto's product, Posilac, the 1,3,5X study was run for two consecutive lactations (Sechen 1997: interview). Dose titration studies were requested to determine the minimally effective dose - that is, the lowest level at which the drug would have the intended effect, assuming that all doses are safe.[8] For example, in the case of production drugs, a higher dosage could be approved if it induced a greater production response safely (if 750 mg caused higher milk yield), but not if the response was as high at lower levels (if both 750 and 500 mg doses induced the same milk yield, the 500 mg dose would be approved).

For rbGH, the FDA also requested that health data be collected during the efficacy studies: according to Dr. Sechen, the most valuable animal safety data came from the efficacy studies because animals in these studies are managed under conditions more likely to be encountered at commercial dairy farms, and much more animal health data are obtained at doses of the drug likely to be approved because of the larger number of animals. As a consequence, the 1,3,5X study is no longer required for production drugs. The protocols for both the efficacy and animal safety studies specified that each animal should be examined every day and any unusual health observations recorded.

When animal health observations were reported at the trial site, the FDA required that the observer record the date, time, his or her name or initials, the animal ID number, and the nature of the observation. If an abnormality was reported, subsequent treatment was also recorded. This initial documentation is known as "source" or "raw" data, which are transcribed into a data-base at the firm. The company and the principal investigator are expected to maintain this information safely. When auditing the study results, the FDA may request that the sponsor submit a copy of certain portions of the "raw" data, or they may

[8] The 1996 Animal Drug Availability Act (ADAA) amended the optimal dose provision. The new provision required that the dose level must not lead to an amount of drug residue beyond safe tolerance levels; the earlier provisions required that the "optimal" dose should not exceed a level shown to be effective. Thus, a dose higher than the minimally effective level may now be administered provided drug residues resulting from such use do not exceed safe levels. (See Lambert 1997: 21 U.S.C.§360b(d)(1)(F))

examine the originals when doing an inspection at a study site and/or of the firm's data base. The Center for Veterinary Medicine tries to inspect the site of every pivotal study once; twice if the study is run over several lactations.

Under the Act, the Center has 180 days in which to review the application and respond to the sponsor. (§360b(3)(c)) The time limit does not determine the response, however; at the end of this period, the drug may be approved, denied approval, or further information requested (Sechen 1997: interview).

By the late 1980s, the FDA was subject to increasing pressure due to concern from the public and the dairy industry about the safety of the drug. Before 1990, human health concerns were non-specific. Although some reports had mentioned animal health problems (see Schneider 1988), individuals and protest groups raising concerns about the drug did not have access to specific information from the human health trials on which to base their disquiet. Much of the public was not aware that milk or meat from animals used in investigational trials could be authorized by the FDA as safe for consumption before the drug had been approved, provided that sponsors of the investigation drug had provided FDA with adequate information to support the safety of the food[9]; when safety concerns about rbGH were raised, therefore, there was a great deal of alarm about the safety of milk from investigation herds. By 1989, the primary reviewer of the Posilac submission, Dr. Suzanne Sechen, was receiving two or three phone calls a day about rbGH. The FDA was also receiving numerous letters and Congressional requests for information. Time which would normally be spent reviewing the product was taken up with fielding questions. At this stage, the Agency decided to become more "proactive," to discuss the issues publicly rather than responding to individual inquiries, "so that we could get back to work". It is important to recall the statutory requirement to respond to the sponsor no later than 180 days after submission; presumably the reviewers would have had even more difficulty

[9] As noted above, meat and milk will be authorized as safe for consumption provided that sponsors of investigational drug have provided the FDA with adequate information to support the safety of the food.

meeting this if they had chosen to respond to individual inquiries. For the first time, FDA officials began discussing not only the rbGH evaluation process, but the standard animal drug evaluation process, including food safety authorizations. This was an unusual position for FDA evaluators to be in:

> The Agency is not in the business of prospectively defending particular products or classes of products. Under normal circumstances, we can't even acknowledge that such products are under development because that's proprietary information. We would only get into that business if someone brought that to our attention, and said we know you are reviewing this product X and we think it's unsafe, then we're forced, in some cases, to defend ourselves by setting the record straight with the facts of the issue to overcome misunderstandings. (Beaulieu 1997: interview)

The FDA was under increasing pressure to release the corporations' human safety data. Since they are proprietary information, the raw data cannot be released to the public without the companies' permission. Initially, the Agency decided to release an FDA "White Paper," an Agency report released to the public that summarized results of studies evaluating the human safety of rbST, and which described the basis for FDA's decision on human safety of these products. However, the FDA then decided that publishing in a peer-reviewed journal would give the report more credibility. (Sechen and Guidos 1997: interview) The corporations authorized the publication of an article by two FDA scientists, Judith Juskevich from the Division of Toxicology, and Greg Guyer from the Division of Chemistry. Their summary of the FDA's review of the human health data were published in the journal *Science* in August, 1990. Juskevich and Guyer concluded that the use of rbGH in dairy cattle presented no increased health risk to consumers.

In the same week that the *Science* article appeared, William H. Daughaday from Washington University School of Medicine and David M. Barbano from Cornell's Food Science Department published an article in the journal of the American Medical Association. The article stressed that the FDA had decided that milk and meat from rbGH cows was safe for human consumption, and that increases in IGF-I, a growth factor which mediates the action of growth hormone, levels in the cows' milk were modest and less than the natural variation which can occur across a lactation. The article also argued that the technology was

"another milk production management tool" which could also "help dairy farmers meet the growing worldwide demand for food production" (1990: 1004).

Dr. Samuel Epstein, from the School of Public Health at the University of Illinois at Chicago, criticised the FDA's claims in an article published in a non peer-reviewed publication, *International Journal of Health Services* (Gibbons 1990: 852). Epstein's major concerns were the potential effects of IGF-I, and antibiotic resistance and residues. These concerns were shared by the Consumers' Union, which released its analysis in December, two days before the NIH Technology Assessment Conference was convened to address the issue.

The NIH was asked to examine this issue in response to requests for a third-party review from parties associated with the dairy industry and in response to public concern (Sechen 1997: interview). The Technology Assessment Conference on Bovine Somatotropin ran from December 5-7, 1990. The NIH committee concluded that, based on the data it had been presented with, the use of rbGH did not present a public health risk. The committee did suggest, however, that further research should be conducted on the action of insulin-like growth factors, and noted that it did not have sufficient evidence to draw a conclusion about the effect of the drug on the incidence of mastitis, a bacterial infection commonly treated with antibiotics (NIH 1991a).

In the fall of 1990 a researcher with the University of Vermont, Dr. Marla Lyng, provided Rural Vermont with photographs of deformed calves born to cows from the investigational trials. The Chair of the Vermont House and Senate agriculture committees was also presented with the information. Dr. Lyng stated that between August 1989 and August 1990, five severely deformed calves had been born to cows treated with rbGH. She also provided copies of the herd computer health records and a list of cows treated with rbGH, which the Vermont Senate and House committees had analyzed by a consultant-veterinarian (Christiansen 1995: 8). The following year Rural Vermont released a report based on these findings at a joint press conference with the legislature at Vermont State

House on November 18, 1991 (11). In a letter on November 27, Representatives Ted Weiss and Bernard Sanders asked the FDA Commissioner to compare the Rural Vermont data with that provided by Monsanto. According to Vermont state representative, Andrew Christiansen, Commissioner Kessler's reply showed that only one of the UVM trials, the Jersey study, had been reviewed by the FDA; in that study 9 out of 20 treated cows had developed mastitis, compared with 2 out of 20 controls; the calving rate was 100% in control animals, and 85% in treated cows. One of the treated cows aborted (12). The letter noted, however, that the FDA did not accept Monsanto's analysis of this data and that the company would be resubmitting data from at least 11 field trials to conform to FDA protocols. This revelation diminished Rural Vermont's confidence in the earlier public pronouncements made by UVM scientists that rbGH was not causing adverse effects on animal health. According to Christiansen:

> This contradicted years of testimony and public statements by the University of Vermont and Monsanto that there had been no adverse health effects at UVM. In 1989, UVM and Monsanto worked as a team to promote rbGH to farmers. Monsanto hired a UVM extension expert...to run several meetings for farmers...He showed a slide show that was produced by Monsanto. The message was that rbGH would increase feed efficiency and milk yield. It would not change the milk. It would not hurt the cow or affect the calf. It would help the family farm. (12)

In a March 1992 press conference, UVM scientists acknowledged the increased mastitis incidence, and that two cows had severely deformed calves. The scientists also contended that the numbers in the trials were too small to draw any conclusions. Data from the UVM trial were published in the *Journal of Dairy Science* in December 1992, indicating a mastitis incidence and injection-site reactions in the treatment group. The authors also noted, however, that the pre-treatment mastitis incidence was higher in the treatment group, and cautioned against drawing conclusions based on the small sample size (Pell et al. 1992).

The FDA's primary reviewer of Posilac, Dr. Suzanne Sechen, commented that the FDA had compared the Rural Vermont data with that submitted by Monsanto, and found that the Rural Vermont data was inaccurate because some of the animals Rural Vermont had

classified as treated were actually control animals. The reporting of birth defects by Rural Vermont did cause the FDA reviewers to re-examine the Vermont data. By this time, the FDA had received all the Monsanto data submitted in support of the animal drug application for Posilac, and had not encountered other reports of significantly increased birth defects, "so that drew a question in our minds...but we had to delve into it a little more and that required looking into our records for the other bST products [tested in Vermont by Monsanto] and the inspection reports." This revealed that some cows which had calves with birth defects were in fact control animals, and this eliminated an apparent effect due to rbST treatment. Dr. Sechen could not explain the incidence of birth abnormalities reported in the Rural Vermont data:

> I know from growing up on a dairy farm that in a certain year you'd get something you'd never seen before, things pop up which are unusual. Whether there was a specific reason for these things to come up at UVM, we don't know. It wasn't a huge number of animals, but those things are low frequency, so anytime you have them, it's weird - but you do get weird years. (Sechen 1997: interview)

Representative Bernard Sanders requested that the GAO begin an inquiry into the UVM trials, but, according to Andrew Christiansen, the GAO terminated its investigation after eighteen months because it could not obtain data from the UVM or Monsanto.(16) Vermont legislators Senator Howrigan and Representative Starr wrote to the FDA expressing a desire to work with them on the rbGH data. Christiansen says that in his reply, Dr. Guest included the cow identification numbers from the UVM study and alleged that Rural Vermont's analysis was affected by identification errors. Senator Howrigan did not receive this letter; Monsanto representatives did obtain a copy of the letter, however, and distributed it to national news media (13-14). Rural Vermont believed that the confidentiality of its data had been violated by the release, and expressed its disquiet in a series of letters exchanged with the FDA (16).

What was disturbing to the members of the Vermont State Legislature and Rural Vermont was not merely the release of the data, but the apparent contradiction between the data and statements about the drug's safety. The individuals concerned attempted to reach a

resolution of the issue with the FDA, and, likewise, the FDA re-examined the issue and attempted to clarify it. The FDA could not publicly release information about the trials prior to approval, however. The issue was complicated because not all of the Vermont trials tested Posilac, the formulation which was eventually marketed by Monsanto; nor were the Posilac trials pivotal, so the results were not released in the FOI Summary, except for the results from one trial which had been elevated to pivotal status. Pivotal studies had been conducted at Vermont with other Monsanto rbGH formulations.

On November 3 1989 the veterinarian Dr. Richard J. Burroughs, who had been involved with the animal health data review, was fired. He had worked for the agency since 1979 (Burroughs 1994: 6). The FDA alleged that Burroughs was incompetent; Burroughs responded that he had been fired for criticizing the review process. In an interview with *The New York Times*, Burroughs said that he had been fired after a long dispute with his superior over how the corporations' data should be interpreted. Dr. Burroughs added that the Director of the Center for Veterinary Medicine, Dr. Guest, had been meeting too frequently with industry representatives and was criticized last summer by his staff. In response to these claims, the Chair of the House Agriculture Committee, Senator Patrick J. Leahy, announced that the General Accounting Office would investigate Dr. Burroughs' allegations (Schneider 1990: A21).

The GAO investigated the review of rbGH, and concluded that the FDA addressed the critical review guidelines in its studies of the direct effects of the drug on human food safety, animal safety, and drug efficacy. What had not been addressed, however, were the *indirect* effects on human health from animal health problems, primarily mastitis, and the antibiotics used to treat mastitis which could then leave residues in the milk supply. The study recommended that, therefore, the FDA should not approve the commercial release of the hormone until its relationship to mastitis had been adequately assessed (GAO 1992c).

The GAO had not examined whether the level of antibiotic residues in milk and meat would increase as a result of the drug's introduction; but it noted that there was

already concern about the current level of antibiotic residue and the capacity of the milk monitoring system to manage it. The safety of American milk is monitored by the National Conference on Interstate Milk Shipments, a cooperative program established by the FDA, the states, and the industry in accordance with the Milk Ordinance. The FDA is responsible for supervising the states' monitoring activities, introducing new test methods, and recommending additional drugs to be monitored (GAO 1992b). In 1988, the FDA conducted a survey of milk from grocery stores in ten cities, and discovered residues from illegal drugs, including sulfamethazine, an antibiotic which had been found to cause thyroid cancer in mice. However, the Agency claimed that residue concentrations were not high enough to cause human health problems (*New York Times* 1988: A32). The *Wall St Journal* and the Center for Science in the Public Interest followed up these reports in 1989 with further surveys which found evidence of residue contamination. In response, the FDA stated that these tests had produced false positive results because the test methods used were not specific enough; a third, and more reliable, test applied by the Agency in 1990 had not detected any harmful antibiotics in 70 milk samples. Two months later, the Agency contradicted this statement, acknowledging that 58 out of the 70 samples were positive for sulfa drugs, but again noted that these residues were too low to threaten public health (Hilts 1990c: C13). As a result of these conflicting reports, the GAO investigated the FDA's claim that the milk supply was safe. In 1990, it argued that the FDA's claims could not be supported "because limitations in the survey methodologies precluded any overall conclusions" (GAO 1990: 1). The GAO claimed that the surveys were not statistically valid, and that they merely supplied "snapshots in time" of a small number of milk samples; because the surveys showed some evidence of drug residues in milk, they argued that a more thorough examination needed to be conducted in order to determine the extent of contamination. Soon after the report was released, the Agency reviewed the existing program and decided to test a greater number of samples for a greater number of drugs. Each milk tanker was tested for beta-lactam drugs (penicillin, commonly used in mastitis

treatment); the industry was required to notify the state regulatory agency if any milk tanker tested positive for drug residues; and it was also required to institute a random screening program for other drugs at the instruction of the FDA Commissioner (Bishop 1993: 3). However, the GAO's 1992 update of the report concluded that the expanded test program had not been implemented. The states were still testing for only four types of beta-lactam drugs, out of a possible 82 drugs which may leave residues in milk. Sixty-four of the drugs commonly used in the dairy industry may leave residues of concern to human health, and 35 of the 64 are not approved for use on dairy cows. The Agency had begun its own program to test for 12 drugs in milk, but the number of samples taken was small and hence the value of the program limited (GAO 1992b: 2-5). Given these findings, it is not surprising that the GAO argued that the product should not be approved until a consensus had been reached on the mastitis issue.

In response to the GAO report, the Agency held an open public hearing with its Veterinary Medicine Advisory Committee (VMAC). This however was perceived by the reviewers as a means of legitimizing the Agency's actions rather than allowing for public input into the decision-making process: "it was an agency decision to allow public comment as a way of assuring the public" (Sechen 1997: interview). At the meeting, the FDA also stressed improvements to the milk-monitoring system which had been introduced since 1991, and announced that further improvements would be made in the next month (Mitchell 1993). After hearing evidence from FDA scientists, company representatives, academics, and groups opposed to the drug including Rural Vermont, the Humane Society of the United States, and the Center for Science in the Public Interest, the Committee concluded that the use of rbGH presented a manageable risk to public health and that the product was therefore approvable (VMAC 1993: 5).

Anthony Pollina, an aide to Bernard Sanders and former director of Rural Vermont, was disturbed by the FDA's conclusion that the public health risk associated with increased mastitis incidence in treated animals was "manageable." Pollina felt that this categorization

was arbitrary, and requested a meeting with the FDA to have this conclusion explained. A representative from the GAO was present as an observer during the meeting.

> The FDA brought in 19 or 20 people. So, how are you going to win that argument? When we asked them about manageable risk, they had to admit that this was arbitrary. We said, we don't know what manageable risk means. Where did this come from? What do you mean by this? How do you determine what a manageable risk is? They basically admitted that they didn't know....If in this case, this product represents a manageable risk, what does that say about other biotech. products coming down the line? What the law says is that it has to be safe and effective. It doesn't say safe and effective, or a manageable risk. So they were setting, we thought, a very serious precedent by saying this product clearly makes cows sick, we're not sure in the long-term what it does to humans, but we think it's manageable. What they meant was the cows might get sick, but farmers will manage the cows, and that might lead to a greater use of antibiotics, but that's manageable because we check for antibiotics. So they were saying these were risks but these are things we think we can take care of, whoever "we" are. Our question was, if the product is a risk when it's used wisely, what if it's used unwisely? Their response was, well, not every farmer is going to use this, and every farmer that uses it isn't going to use it on all cows, and if you read the label it says you should have a good management program in place. What we wondered was what about farmers who have an old cow and decide to shoot her up with super doses of bGH before she dies? What about farmers who lie about the amount of antibiotics they use? They had no response to that. (Pollina 1997: interview)

Pollina, like scientists and executives at Monsanto, saw rbGH as a precedent-setting case, with regulatory action sending a signal to the biotechnology industry. Just as this perception increased the corporation's desire to see the product approved, Pollina and other activists found it all the more imperative that a thorough review be conducted, and consequently, that human and animal health questions could be answered satisfactorily.

Pollina and Sanders were also concerned that the agency had not taken appropriate action in response to Monsanto's pre-approval promotion of the drug - through the distribution of material, seminars at universities, and market research activities - which violated Federal regulations. 21 C.F.R. 511.1(b)(8)(iv) prohibits a drug manufacturer, or others acting on the manufacturers' behalf, from representing the drug as "safe and effective" until regulatory review is completed and approval authorized (Office of the Inspector General 1994: 1). The Office of the Inspector General believed that violations of this regulation were problematic because "such actions could contribute to the public's misunderstanding about the product, provide the sponsor with an unfair competitive

advantage, and unduly influence the FDA in its role in reviewing a new animal drug" (Office of the Inspector General 1991: 5). Sanders requested an investigation into Monsanto's promotional activity, and the agency's response, in 1991, and again in 1994 after further attempts by Monsanto to distribute information about the drug. Between 1991 and 1993, Monsanto had organized several focus groups and paid farmers $100 to attend; sponsored the production of a video in co-operation with the American Medical Association, one copy of which was released prior to rbGH approval; and made a presentation at Louisiana State University (Office of the Inspector General 1994: 3).

The Inspector General concluded that the Center for Veterinary Medicine had generally responded appropriately to Monsanto's activities. It had sent a warning letter to the company in January 1991 (in anticipation of the forthcoming report), and, although it had not responded to Monsanto's actions since 1991, it did not believe that these actions represented violations of Federal regulations. The Inspector General agreed with this interpretation in two of the activities, but did think that the Louisiana seminar warranted attention. It was also noted that existing regulations did not provide the Center with clear criteria for identifying promotional activities which required regulatory action, and those which did not. Revisions of the regulations were recommended.

From Pollina's perspective, Monsanto's promotional activities, and the agency's failure to respond promptly and forcefully, shed doubt on the autonomy of the FDA evaluation process. He thought that the FDA should have taken much stronger action against the company. Pollina and Sanders discussed the issue with FDA representatives, but were unsatisfied with the outcome:

> You don't know what to do after a while because you feel like the deck is really stacked against you. If you're a member of Congress, you go to the FDA or the Inspector General who investigates the FDA, and if they say this is what's happened, this is the remedy, then where do you go? If the Federal government is so tied to the corporate agenda, where else do you turn? Congress wasn't going to pass a law mandating the labelling of bGH, that was out of the question, we knew...that the industry undertook a strong lobbying effort to cut off any efforts for mandatory labelling. Monsanto started years ahead of time with their propaganda to convince people that the product was good, the product would work, and labelling would be unnecessary. (Pollina 1997: interview)

6. Milk labelling

When the FDA's review of the animal and human health data was complete, it considered the issue of whether milk from rbGH-treated cows should be labelled. Critics who had opposed the drug's introduction advocated product labelling as a means to allow consumers to express their opposition - whatever its basis - by choosing not to purchase milk produced using the drug. However, under existing regulations, milk labelling could be considered false and misleading unless it was based on a material fact, such as a health or safety consideration, or a change in the product's taste, texture, or other characteristics. The safety decision, therefore, also determined the labelling decision; there was little option for consumer choice once the decision that there was little significant difference between milk from treated and untreated cows.

The FDA's statement of May 29, 1992 reaffirming its commitment to the Coordinated Framework for the Regulation of Biotechnology also outlined its interpretation of the regulations regarding food labelling. Section 403 (i) of 21 U.S.C. requires that the producer of a food describe it by its common or usual name. The producer must "reveal all facts that are material in light of representations made or suggested by labeling or with respect to consequences which may result from use" 343(a) 321(n) (FDA 1992: 22991). The FDA concluded that consumers must be informed if a food produced by novel methods is so different from its traditional form that the usual or common name no longer applies to the food; likewise, consumers must be informed if the novel food presents safety or usage problems. The method of manufacture itself is not considered to be material information within the meaning of Section 201(n).

Consumers, however, notified the FDA that they wished to be informed whether a plant or food was developed using genetic engineering. The FDA responded to these concerns in another statement on April 28, 1993. It reiterated its position that, historically, it has limited its interpretation of "materiality" to the attributes of the food itself (FDA

1993c: 25838). Although a number of consumers had pointed out that the FDA had allowed process labelling for irradiated foods, the FDA contended that this was because of the characteristics of irradiated foods, not the irradiation process *per se*. Irradiation could cause changes in the organoleptic properties (taste, smell, texture or colour) of finished foods and that these changes could be significant in light of consumers' perception of the foods as unprocessed (OMB 1994: 17).

On May 6 and 7, the Food Advisory Committee and the Veterinary Medicine Advisory Committee held a joint meeting to discuss the issue. Michael Hansen from the Consumer Policy Institute of the Consumers' Union addressed the meeting. Hansen stated that the Consumers' Union felt that the product should not be approved, but, if approved, milk and other goods from treated cows must be labelled so that consumers could choose whether they wished to purchase milk made using this technology (Hansen 1993a: 1). Hansen submitted that consumers did regard rbGH use as a "material fact" and considered the omission of such information to be misleading. He also posited that the characteristics of the milk do change as a result of rbGH usage; during the early stage of use, rbGH can increase fat content and decrease casein protein. The quality of milk declines when cows are in negative energy balance (that is, expending more energy in milk production than they are consuming); since hormone-treated cows spend a longer period in negative energy balance, thus the milk will be of poorer quality. Consumers could also expect organoleptic changes in the milk related to higher SCC counts which mean that higher amounts of pus and bacteria are present in the milk.(4-10)

The FDA decided that it did not have a legal basis to require labelling of rbGH milk. It believed that there were no significant differences between milk from treated and untreated cows, and that therefore the absence of a label for treated milk could not be regarded as "misleading." The consumers' interest in labelling is not sufficient to influence the FDA's ruling:

> With respect to food labeling, the consumer's right to know has been defined by the Federal Food, Drug and Cosmetic Act. The agency has no basis to impose

> additional requirements once a manufacturer has met the statutory obligation. (OMB 1994: 19)

Milk could be labelled voluntarily by producers not using rbGH on their herds. However, such a label would only be permitted if it were not misleading. Since natural bovine growth hormone is present in milk, the FDA reasoned that a "bST-free" label would not describe the product accurately. Such a label might also imply that the untreated product is safer. Therefore, claims that the milk is from untreated cows would only be permitted if the statement was put "in a proper context"; for example, the information that "no significant difference has been shown between milk derived from rbST-treated and non-rbST treated cows" would put the label in context and prevent it from misleading consumers.

Although the FDA recommended guidelines for voluntary milk labelling, Vermont initially introduced mandatory labelling for milk products produced using bST. After rbGH had been approved by the FDA, Vermont instituted a mandatory labelling law requiring that all meat and milk produced using rbGH must be labelled. If the processor was unsure whether the drug had been used, he or she should err on the side of caution and label the product. Processors were also empowered to ask for an affidavit from farmers up to 90 days before they intended to begin using the drug. Anthony Pollina believed that it was important that those who used the drug should be responsible for notifying consumers of its use. Under voluntary labelling:

> The 92% of farmers who aren't using it have the burden of labelling instead of the 8% who are. The expense of the label, the regulation of the label claim, why should I, as a farmer, who's never used this product, I'm still not using this product, now have to allow myself to be regulated and inspected? There's all these things I have to do simply because I'm doing what I've always done.

Pollina noted that the state government and the Farm Bureau, had argued that "if you labelled your milk bGH-free it implied your milk was better, therefore you could charge a premium for it." Pollina objected to this perspective:

> Our response was you're saying milk without bGH is going to become like a specialty food, and yet it's the same as it was for hundreds of years, and so the consumers with more money would buy the non-bGH milk and everybody else would buy the bGH milk...so essentially bGH-free milk, which is natural milk,

> would become a niche product, which is exactly what's wrong with the way we relate to food in America - something that's real becomes special. (Pollina 1997: interview)

Vermont's mandatory labelling law was challenged by a coalition of food producers[10] *in International Dairy Foods v. Amestoy*. The District court rejected the plaintiffs' case, but the Court of Appeals for the Second Circuit reversed the District court's judgement on the grounds that the First Amendment protects the right to silence as well as the right to speech, and that the violation of this right was not justified by the State's intent to ensure consumers' right to know. In a dissenting opinion, Judge Leval argued that the majority had misinterpreted the State's intent, which was not to fulfill consumer curiosity but to address people's concerns about animal health, biotechnology, and the livelihood of small farmers. On August 30, the Vermont Attorney General agreed to stop enforcing the mandatory law, and decided not to appeal against the Second Circuit's decision, citing prohibitive legal costs. The mandatory law was replaced with legislation for voluntary labelling in April of 1997. Under these provisions, milk producers could declare by affidavit that they had not used rbGH, and the milk handler would in turn produce an affidavit for the Commissioner of Agriculture, Food and Markets, who was authorized to conduct random farm inspection to verify that rbGH was not being used (Centner and Lathrop 1997).

Vermont is not the only state which has passed statutes or administrative guidelines regarding voluntary labelling. Centner and Lathrop comment that "[t]he painstaking efforts taken by legislatures and regulatory officials in many states to regulate products derived from rbST-treated cows show an immense concern over the use of this new drug." (1997: 550) Wisconsin and Minnesota allow milk to be labelled rbGH-free if farmers have produced affidavits to support their claim (544). Michigan, Missouri, North Carolina, Ohio and Utah have made policy guidelines available, based on the FDA's recommendations

[10] The plaintiffs included: the International Dairy Foods Association; Milk Industry Foundation; International Ice Cream Association, National Cheese Institute, Grocery Manufacturers of America Inc. and National Food Processors Association. (Centner and Lathrop 1997: 540n)

(546). Pennsylvania and Maine also permit milk from untreated cows to be identified. On the other hand, several other states - Illinois, Nevada, and Texas - do not permit labelling.

Conflicting labelling laws in different states have created discord. The Vermont ice-cream maker Ben & Jerry's, which owes much of its success to its "all natural" image, sued the State of Illinois and the City of Chicago after regulators threatened to remove ice-cream with the rbGH free label from the supermarket shelves. Ben & Jerry's label also included the FDA disclaimer, but any type of rbGH label was not permitted in this state. The company reached an out-of-court settlement with the State and the City which enabled its products to be sold freely in Illinois (Rural Vermont 1997b), and permitted producers in Illinois to voluntarily label their product. The Illinois battle was important, since Chicago is a regional distribution centre.

7. Approval

On November 5 1993 the FDA approved Monsanto's product, Posilac. The product was to be injected into the cow nine weeks after calving, and once every 14 days until the end of lactation (FDA 1993b: 59946). In the final ruling, it was also announced that approval would not have a significant impact on the human environment, and that an environmental impact statement was not required (59947).

Immediately after approval had been announced, Senator Russell D. Feingold of Wisconsin sponsored a moratorium which delayed the release of the product for 90 days (Schneider 1993: 1). During this period, the Office of Management and Budget produced its assessment of the FDA review and the impact of the product's approval. The OMB report reiterated earlier statements that the product posed no threats to human or animal health, and that it would merely reinforce productivity changes already experienced by the dairy industry. It also added that although lower milk prices were expected to contribute to higher Federal government dairy price-support costs, these would be offset by decreased costs for nutrition programs like Food Stamps and the Special Supplemental Food Program for Women, Infants and Children. Another factor considered significant by the OMB was

the negative impact of a moratorium on the U.S. biotechnology industry; U.S. leadership in the industry, and private investment in research and development, would be enhanced by approval, and hindered by post-approval regulation by the government (1994: iii-iv). The moratorium was lifted on February 5 1994.

As a condition of the drug's approval, the FDA had stipulated that Monsanto establish a post-approval monitoring program (which became known as PAMP). This involved tracking the milk production and drug residues from treated herds in 21 dairy states for two years. After 12 months, the amount of milk discarded (because of drug residues) in the post-approval period would be compared with the pre-approval period. Twenty-four commercial dairy herds would be monitored for mastitis, animal drug use and resulting milk loss. Monsanto was also ordered to report all animal health complaints to the FDA every 90 days as part of a pro-active system in which the company sought out adverse experience reports (Department of Health and Human Services 1993).

By October, the company estimated that 7% of dairy farms, or 10,000 farmers, had adopted the drug. Milk production was 3% higher than in September of the previous year, which the Department of Agriculture attributed to the drug's introduction. Prices had dropped by ten cents, to $12.70 per hundred pounds of milk. *The New York Times* reported that some dairy farmers were experiencing animal health problems after administering the drug on their farm; a dairy producer from New York had stopped using the drug, and sold 34 of his 200 cows after they developed mastitis; another farmer in New York reported similar problems (Schneider 1994a: 11). In late summer 1994, the Wisconsin Farmers' Union and the National Farmers' Union based in Denver Colarado set up a toll-free hotline to record information from farmers who had experienced problems with rbGH. A number of farmers reported problems which had led them to cull cows treated with the drug. The Farmers' Union investigated whether Monsanto had reported similar problems to the FDA. It obtained access to Monsanto's report by filing a Freedom of Information Act (FOIA) request and found that it also included incidents of death,

outbreaks of mastitis, spontaneous abortions and other health problems. The Farmers' Union observed that 68 of the 96 reports had been forwarded to the FDA on September 1; however, the FDA had told the Farmers' Union that any serious problem, or any adverse reaction not listed on the label, should be reported to the agency no less than 15 days after the manufacturer becomes aware of the problem. In October, the agency reported that Monsanto was conveying adverse reaction reports immediately (Kastel 1995: 3-9).

Monsanto, meanwhile, had been proclaiming the success of its product and referred to its marketing program as "unparalleled in the agricultural industry." The company was selling Posilac directly to farmers. Federal Express delivered the product to the farmers' door within 48 hours of ordering. Monsanto also provided a disposal system for syringes. Along with the first order of the drug, farmers receive a $150 voucher to pay for a veterinarian's assessment of their herd (Monsanto 1994a: 1). In a supplement to its Quarterly Report, Monsanto cited USDA estimates that the product would be adopted by farmers for use in 10 to 15 per cent of the U.S. dairy herd within a year of commercial release. With this adoption rate, Monsanto expected its Animal Science division would break even in 1994 and become an income contributor in 1995 (Monsanto 1994a: 1). In its 1995 annual report, Monsanto announced that Posilac "has already become the world's best-selling veterinary product to dairy producers." In spite of this:

> It isn't yet profitable because of unsatisfactory manufacturing costs worsened by currency translation (it's made in Austria). We expect Posilac to become profitable this year as sales growth and improved manufacturing bring unit costs down. (Monsanto 1995a: 3)

By January 31, 1995 Monsanto had sold 14.5 million doses of Posilac to 13,000 dairy farmers. 2.7 million cows had been injected with the drug. Monsanto stopped releasing Posilac sales figures in February; spokespeople for the company claimed that there was still "steady growth" in the level of Posilac usage. A survey of farmers undertaken by Rockwood Research during the summer of 1995 found that 20% of farmers had tried the product; 87% of the farmers who had not tried Posilac said they would not use it in the

future. In October, Monsanto introduced a 10% discount plan for farmers who purchased a six-month supply of the drug (Stayer 1995: 1 & 8).

In February, Monsanto sued the Pure Milk Company of Waco, Texas, for labelling its milk from untreated cows. The company took the case to court in June, 1995. Monsanto alleged that, under product disparagement theory, the labelling implied that there was something wrong with the milk from treated cows (Consumers' Union 1995: 1). Pure Milk had used a "no" symbol - a red circle with a line crossed through it - around its "no bST treated cows" caption. The two parties reached an agreement in private on Thursday, June 15. Details of the arrangement were not disclosed; but Pure Milk announced it would continue to label its products as untreated (Kilpatrick 1995). Monsanto had brought a similar suit against the Swiss Valley Farms Company of Davenport, Iowa (Gershon 1994: 384).

The integrity of FDA officials was questioned in April, 1994. In a letter to the GAO, Representatives George E. Brown Jr., David R. Obey, and Bernard Sanders asked the office to investigate the role of three officials in the approval process. The representatives argued that these officials had ties with Monsanto which conflicted with their role as evaluators of Monsanto's application for drug approval. The officials were: Michael R. Taylor, deputy commissioner for policy, who joined the agency in 1991 after working for the law firm King and Spalding, which represents Monsanto; Margaret A. Miller, deputy director of the agency's office of new animal drugs, who was a former Monsanto employee; and Suzanne Sechen, a data reviewer, who had worked as a graduate student for Professor Dale Bauman, who had conducted the Cornell trials on rbGH for Monsanto. A spokesman for the FDA, Jim O' Hara, responded that Dr. Miller was not involved in the decision to authorize bST use, and that the Agency's ethics and program integrity division had determined that Susan Sechen's involvement did not pose any conflict of interest prior to her joining the bST review. The FDA Commissioner, David Kessler, had defended Michael Taylor against conflict-of-interest charges from FET

President Jeremy Rifkin in March. Kessler pointed out that Taylor had refrained from any involvement with Monsanto or other King and Spalding clients for a year after he joined the agency in 1991 (Schwartz 1994: A3).

The GAO concluded that none of the three officials had conflicting financial interests, nor did their role at the FDA transgress Office of Government Ethics standards regarding the appearance of loss of impartiality. The GAO did, however, identify several articles authored, or co-authored, by Drs. Sechen and Miller, some of which were written with the FDA listed as their address, "whose publication may have been contrary to FDA's requirements for prior approval of outside activities." (GAO 1994: 1) The ethics standards which applied to these officials had changed in 1993. Prior to 1993, FDA employees who had worked for a company were required to refrain from regulatory work involving that company for one year after commencing employment with the Agency, and prohibited for life from working on any issue or product they had had direct involvement with at that company. In 1993, the lifetime prohibition was lifted, and employees in a "covered relationship" (i.e. prior employment) were to refrain from regulatory actions involving their previous employer for one year.

According to these standards, Dr. Miller was not to be involved with regulatory action related to Monsanto for one year after her employment, and, prior to 1993, was prohibited from ever taking regulatory action on issues related to her work at the company. She did, however, help draft the FDA's answer to a Foundation on Economic Trends petition seeking to ban the sale of milk and meat from cows treated in investigational trials. As Director of the Division of Toxicology and Environmental Sciences, she took steps to avoid reviewing material from the rbGH application, when she later became Branch Chief for Hormones and Pharmaceutical Agents in this Division. However, she signed the Freedom of Information document on human health safety. The GAO did not regard either of these actions as problematic, because they did not bear on the health and safety review itself, although the Office did note that Miller's signature constituted a "technical violation."

In 1993, Dr. Miller was asked by senior FDA officials to brief the Commissioner, Dr. David Kessler, on issues relating to the drug. It was reported that:

> At a meeting that probably took place in mid-to-late August 1993, the Commissioner asked the Acting Center Director whom he would choose to take to a Congressional hearing to represent FDA's position, if the agency approved sometribove. The Acting Center Director named Margaret Miller, at which point someone said that Dr. Miller had worked for Monsanto. This was the first time that the Commissioner had heard of her prior Monsanto affiliation and he was reported to have been visibly surprised. He ordered an investigation into whether Dr. Miller had engaged in conduct creating a conflict of interest. On November 4, 1993 the FDA reported on its investigation. The agency concluded that although "Dr. Miller's participation in general bST matters does raise questions...she has not violated FDA's Standards of Conduct or the Office of Government Ethics Standards of Conduct." (GAO 1994: 15)

Michael Taylor, like Dr. Miller, was required to avoid Monsanto-related regulatory action for one year. He also advised Dr. Kessler that he would not be involved with policy decisions relating to the Posilac application. However, in 1993 Taylor signed the guidance on the voluntary labeling of milk and milk products from treated cows. (20) He also took part in discussions during the drafting process, but according to other FDA employees he did not seek to influence the content of the guidance. Since by the time these guidelines were drafted he had been with the agency for over a year, no regulations were violated. With regard to Dr. Sechen, the GAO concluded that she could not have a conflict of interest because she had never been a Monsanto employee.

Pollina was unhappy with the GAO's conclusions; he believed the officials investigated "clearly" had a conflict of interest either because of their employment history, or because they had conducted research on Monsanto's product. He was particularly disturbed by the implication that "the FDA didn't know when their employees were doing official duties and when they were doing outside activities, which doesn't give you a lot of confidence..." He regarded Dr. Miller's discussions with Commissioner Kessler as problematic because the issues on which her opinion was sought - such as the biological significance of the increases in mastitis and the likelihood of milk antibiotic contamination - were central to the approval of the product. (Pollina 1997: interview)

Consumers also used the judicial system to challenge the FDA's approval of rbGH and its failure to impose a mandatory labelling requirement on milk and other dairy produce made from the milk of treated cows. In *Stauber v. Shalala* plaintiffs argued that: the FDA's approval was arbitrary and capricious[11] because it had not fully considered the implications of either increased mastitis incidence or higher milk IGF-I concentrations; it had not requested an environmental impact statement; and it had failed to require mandatory labelling of products derived from treated animals. The Court dismissed these arguments on the grounds that the FDA's decision regarding these matters was not arbitrary and capricious. With regard to the failure to request an environmental impact statement, the Court noted that the FDA had decided that such a statement was not necessary after it had reviewed an environmental assessment from Monsanto which concluded that Posilac would not have a significant impact on the environment within the meaning of the National Environmental Policy Act (NEPA). An environmental impact statement is not required if the environmental assessment determines that no impact will occur. The socio-economic impact of the drug's introduction can only be required if an environmental impact statement is also necessary, i.e. if there is evidence of potential environmental harm. Therefore, the Court denied all of the plaintiffs' arguments on the labelling issue, responding that labelling can only be required if there is a material difference - i.e. a difference in the taste, smell or shelf-life of the product; consumer interest is relevant only if a material difference can be detected.

Centner and Lathrop have argued that this interpretation misconstrues the FDA's guidelines, which did allow for consumer interest to be expressed via voluntary labelling:

> The *Stauber* court does not seem to have fully analyzed the FDA's Interim Guidance and misbranding laws as they may apply to production and processing methods. Part of the reasoning for the Interim Guidance was that consumer groups

[11] In *Stauber v. Shalala* (895 F. Supp. 1178 W.D. Wis. 1995), the Court held that the FDA's decision to approve a drug "may be set aside upon judicial review only if agency's determination is arbitrary and capricious, abuse of discretion or other wise not in accordance with law." The Court also noted that "[t]he arbitrary and capricious standard is highly deferential; even if a reviewing court disagrees with an agency's action, the court must uphold the action if the agency considered all relevant factors and the court can discern a rational basis for the agency's choice."

> were interested in production techniques, even if there was not a perceptible difference between rbST- and non-rbST-derived milk. After acknowledging no significant physical differences in the milk, the FDA recognized consumer interest by allowing voluntary labeling. (1997: 531)

At the end of November, 1996 the Veterinary Medicine Advisory Committee heard the final report on the findings from the Post-Approval Monitoring Program (PAMP). FDA officials stated that there was no increase in the amount of milk discarded due to antibiotic residues since the start of rbGH sales. The evaluation of 28 commercial herds concluded that the experience with the drug reflected most of the predictions on the label: mastitis was increased; feet and leg injuries were higher, and the use of medications increased. Some of the reproductive problems in the pre-treatment studies were not found in the commercial herds, and the incidence of mastitis was lower than originally determined; however, the regime for assessing mastitis incidence was less rigorous than in the university studies (VMAC 1996). The FDA said that it had inspected farms in New York and Florida - presumably those that had been reported in the media as having significant animal health problems as a result of the drug - and discovered that the problems "related more to farm management practices than to the use of Posilac." (VMAC 1996: 29) Kronfeld argued that these kind of judgements actually inhibited the reporting of adverse drug experiences:

> This has worked a bit against reporting because when a farmer reports that he's got a mastitis problem, Monsanto approaches him. They have an animal scientist and veterinarian and tell him to look at the label, the FDA agrees with us, it's management which is responsible for the mastitis, it's not the drug itself. This must be very discouraging for the farmer, and, in fact, I've had a number of farmers call me and I've talked with other people who have said that farmers are being discouraged from reporting adverse effects by this vigorous, enthusiastic, proactive program which will try to pin the disease on the farmer's management rather than on the drug. (VMAC 1996: 112).

8. Conclusion

The U.S. regulatory process was intensely controversial and took place in the context of a number of different pressures. American regulators were subject to Congressional scrutiny as the degree of controversy increased the frequency of public inquiries. The structure of the political system enabled opponents of the drug to have the regulatory process investigated by the Inspector-General of the Department of Health and

Human Services, and conflict-of-interest allegations investigated by the GAO. It also ensured that the FDA's decision with regard to the human health decision was debated publicly, and that assumptions on which the decisions about antibiotics were based were investigated further in post-approval studies.

The Agency's actions were also under scrutiny by the industry. The Reagan and Bush Administrations had encouraged biotechnology through a series of legislative changes designed to encourage private R&D, and had emphasized the importance of decreasing the regulatory burden on the industry. Its products were not regulated by a separate statute, but under existing law. Throughout the 1980s, policies continued the de-regulatory trend.

Since the product has been approved, regulatory reform has also been applied to animal drug law, in order to simplify, and speed up, the review process. The use of animal drugs at the veterinarian's discretion, rather than in accordance with the drug label, has also been codified.

On the rbGH issue, the FDA was caught between de-regulatory impulses on the one hand, and public alarm on the other. This caused the Agency to defend the legitimacy of its processes, and to release a summary of some of the data used in the evaluation. This was neither scientifically nor politically satisfactory, however, and the issue persisted beyond the approval of the product.

Chapter Four

The Canadian context

1. Introduction

The purpose of this chapter is to describe the context within which Canadian regulatory decision-making occurred. Canadian regulators found that the drug did not represent a threat to human safety. Nevertheless, they have had reservations about the animal health data, which resulted in a decision not to approve the drug. Scientists within the Bureau of Veterinary drugs have questioned the human health decision on the grounds that animal health problems may also pose a threat to human health, and that the human safety data were not sufficient evidence on which to base a decision. The reasoning behind these questions will be discussed in Chapter Five.

It is impossible to identify any one factor which may explain the difference in the Canadian and American interpretation of the data. However, there are several factors which differentiate the Canadian and the U.S. political and economic context. Although the Canadian government has stated its support for biotechnology, and certain policies have been changed to fulfill this goal, many others have not. Canadian patent law, for example, differs from that of its major trading partners. The Canadian dairy system, unlike the U.S., is based on a supply management system. The Bureau of Veterinary Drugs' regulatory process has, until very recently, been subject to less scrutiny by the legislature than the U.S. FDA, and has communicated far less frequently with the public. The science and public policy literature would suggest that this should simplify and streamline the Canadian process. However, the reverse has been the case. The nature of the system may have served to decrease pressure on scientists to defend the decision.

2. Overview of rbGH in Canada

Controversy about the drug intensified in Canada in 1994, after it had been approved in the U.S.. Initially, two companies, Monsanto, and the Provel division of Eli

Lilly Inc., applied for regulatory approval, or a Notice of Compliance (NOC) in Canada. Monsanto submitted an application for a product under the trade name Nutrilac in 1990. Provel asked for its submission to be placed on hold in May, 1996, pending the outcome of Monsanto's submission. The evaluation of Monsanto's product is being undertaken by the Bureau of Veterinary Drugs within Health Canada, which approved the sale of milk and meat from test trials in 1988 (Senate of Canada 1998). The review is still continuing.

The application for rbGH was submitted before any decision had been made regarding regulatory policy for biotechnology products. In 1993, the Canadian government announced its guidelines for biotechnology regulation. The principles by which the Canadian government decided to regulate biotechnology products were very similar to those articulated in the U.S. Coordinated Framework. As in the Framework, Canadian government departments agreed that biotechnology products should be regulated under existing law, by the relevant government departments. This decision was challenged by the Canadian Institute for Environmental Law and Policy, which advocated the regulation of biotechnology products under a separate section of the Canadian Environmental Protection Act. Currently, biotechnology products may be regulated under the Canadian Environmental Protection Act if they are not already covered by Federal statutes, and restrictions may be imposed on their manufacture or application in Canada if they are determined to be "toxic." The Institute argued that other statutes should only prevail if they were at least equivalent to minimum assessment standards set by CEPA. The government rejected this recommendation, and proposed that CEPA products which could be regulated under other acts should be exempted from CEPA requirements. However, Health Canada is undertaking an environmental and health assessment of rbGH under a memo of understanding with Environment Canada (Senate of Canada 1998).

In June 1994, the House of Commons Standing Committee on Agriculture opened hearings on the potential effects of the drug's introduction in Canada. After the hearings, the Committee on Agriculture recommended that the government legislate a twelve-month

moratorium on the drug's introduction to allow for investigations of the product's probable impact in Canada. One of the committee's major concerns was the impact that increased productivity resulting from the drug's introduction would have on Canada's dairy supply management system.

The government rejected the Committee's request for a legislated moratorium but reached a voluntary agreement with the companies to withhold the drug from sale for another twelve months (Government of Canada 1994). The companies, however, were aware that the moratorium would make little difference to their plans to market the drug because Health Canada was unlikely to approve it in the interim period. The government also appointed a Task Force to investigate the concerns raised by the Committee: the costs and benefits to the Canadian dairy industry; animal health; animal genetics; and consumer reaction. The Task Force reported to the Minister of Agriculture and Agri-Food in May 1995, but made no recommendations.

The Toronto Food Policy Council, a division of the City of Toronto's Board of Health, was concerned about the government's reaction to rbGH and critical of its response to the Committee's recommendations. The Council held a public forum on the issue, and produced a report which recommended that rbGH not be licensed in Canada until further questions about the drug and the evaluation process had been examined. The Council expressed concerns about IGF-I; the animal health impact; consumer acceptance, and its resulting impact on human health; the economic viability of the dairy sector (City of Toronto Board of Health 1994a: 3). The Toronto Board of Health wrote to the Minister of Health informing her of the Council's recommendations and the Board's support for this position (Caplan 1994).

The voluntary moratorium ended in June, 1995. It was expected that Health Canada would announce the drug's approval shortly after the moratorium ended. The National Dairy Council of Canada, which represents milk processing companies, sought another moratorium on the drug, as did the National Farmers' Union, and the Council of Canadians

(McLaughlin 1995). The Council of Canadians placed full-page newspaper advertisements against rbGH and organized letter-writing campaigns (Saunders 1995b: A10). Opposition from the Dairy Farmers of Canada was more muted. The DFC supported the extension of a moratorium, but not beyond the period necessary for Health Canada to complete its review of the product; beyond that, the organization believed that farmers should be able to make a choice whether or not to use the product. The House of Commons Standing Committee on Health recommended a two-year extension of the moratorium, and the Committee on Agriculture suggested an indefinite moratorium would be appropriate (McLaughlin 1995).

The government did not extend the moratorium. Health Canada, however, requested further data on animal health. Monsanto Canada suggested that the product would be approved for Canadian release by the end of 1996 (Stoneman 1995: A1). In early 1997, however, the product had still not been approved; there was some suggestion that approval may take place by the summer.

As in the U.S., the Canadian drug review process was dogged by claims of corporate influence. At the end of November 1994, the CBC's current affairs program Fifth Estate broadcast a report which alleged that Monsanto officials had offered Health Canada officials one to two million dollars if the product were approved without the submission of further studies. Monsanto demanded a retraction from the program, stating that the allegation of bribery was a misrepresentation of its position; what it had proposed was to increase its research spending in Canada, depending on Canadian sales of the product, once it was approved (Bueckert 1994).

Further allegations of industry influence were raised in 1997, when the *Globe and Mail* reported that reviewers at Health Canada had complained that their concerns about the potential public health risks of human and animal drugs were being ignored by senior managers (Eggertson 1997). In order to examine internal concerns about the review of rbGH, the Bureau of Veterinary Drugs created an internal investigative team, comprised of two reviewers from the Bureau, one from the Bureau of Chemical Safety in the Foods

Directorate, and one from the Therapeutic Products Directorate (human drugs). This team submitted a report to another internal group, the rbST Advisory Committee, which made further recommendations and comments to the investigators (Senate of Canada 1998).

The Bureau has also requested the establishment of two expert panels to examine human and animal safety issues. Human safety will be evaluated by a panel convened by the Royal College of Physicians and Surgeons; animal safety will be considered by a panel from the Canadian Veterinary Medical Association. The panels will also review the report made by the internal investigative teams and will make recommendations which Health Canada will consider. It was expected that the panels will report in September 1998; at the time of writing, however, a report had not yet been released (Senate of Canada 1998).

Health Canada has also considered the results from the U.S. post-approval studies, and a second human health evaluation conducted by the WHO/FAO Joint Expert Committee on Food Additives released in February 1998 (Senate of Canada 1998).

3. Background: Biotechnology in Canada

The Canadian government has introduced a number of measures to encourage the development of the biotechnology industry. However, a number of Canada's patent laws are different from those of its trading partners, particularly the U.S., and funding for basic scientific research is much lower than in the U.S..

3.1. Canadian Patent Law

The Canadian intellectual property rights regime has been challenged by the introduction of the North American Free Trade Agreement (NAFTA) which came into effect on January 1, 1994 and the Uruguay Round of the General Agreement on Tariff and Trade negotiations (GATT). The Agreement to create the World Trade Organization (WTO) entered into force on January 1, 1995 (NAFTA Secretariat 1996: 10).

As a result of the GATT and NAFTA negotiations, Canada's intellectual property regime - which differentiated between drugs produced in Canada and those produced elsewhere - was altered to provide increased protection for brand-name pharmaceutical

companies. However, several elements of patent law have remained unchanged under NAFTA and GATT provisions. One, although microorganisms must be patentable, signatories are not required to provide patent protection for higher life forms (animals and plants). Two, Canada does not offer patent term restoration, in which some of the patent time lost in the clinical trial and regulatory review period is restored to the patent owner. Three, Canada has no procedure for opposing patents once they have been issued (NBAC 1998: 51).

In order to be considered patentable under the Canadian *Patent Act*, an invention must be "new" and "inventive" (McMahon, 1995: 24). Unicellular living organisms have been patentable since the 1982 Patent Appeal Board ruling in the Abitibi case (which pre-dated NAFTA and the GATT). The Patent Appeal Board found that since the organism had been created by an inventive step, was useful, and had not existed previously in nature, it constituted patentable subject matter (14). Higher life-forms, including plants and animals, are not patentable in Canada. An application to patent the "Harvard," or "onco" mouse was filed with the Canadian Patent Office in August 1995, and rejected.[1] The application had been accepted in the U.S. in 1988 and in Europe in 1992 (19).

Neither GATT nor NAFTA require that plants and animals must be patentable, and certain provisions enable parties to the agreement to reject patent applications if a proprietary claim threatens human, animal or plant life, or "*ordre public* or morality" (See NAFTA Article 1702(9)).

However, other aspects of Canada's patent law have been changed in response to the Agreements. In 1993, in order to meet Canada's obligations under the agreements which were then being negotiated, Bill C-91 was introduced. The new bill was intended to promote the development of the drug industry in Canada, while still ensuring that drugs were available at "non-excessive" prices (Manley 1997). Bill C-91 eliminated compulsory

[1] In May 1998 the Federal Court of Canada rejected Harvard University's appeal against the patenting decision, ruling that "a complex life form does not fit within the current parameters of the Patent Act." (*Maclean's Magazine*, 1998a: 42)

licensing, whereby patented drugs could be produced in Canada seven years after the brand-name manufacturer had been approved by Health Canada, and could be imported ten years after approval. Compulsory licenses were not granted for drugs which had been developed in Canada (Food and Drug Law Group, 1994: 325). The compulsory licensing provisions had helped contain drug prices and fostered the development of the Canadian generic drug industry.

Article 1703 of NAFTA enforces the principle of non-discrimination and national treatment in the protection and enforcement of intellectual property rights; the protection provided to domestic claimants must also be extended to other signatories (333). Compulsory licenses may be granted, but only under certain restrictions.[2] Under both the WTO Agreement and NAFTA, the same level of intellectual property protection is to be provided across sectors; Canada's differential protection for the drug industry contravened this obligation.

In addition to eliminating compulsory licensing, Bill C-91 introduced regulations which linked the issuance of a Notice of Compliance (regulatory approval) with the drug's patent status. For example, if a brand-name manufacturer contested the validity of a generic competitor's patent claim, Health Canada would not issue a Notice of Compliance to the generic manufacturer until the patent issues had been resolved, or a certain time period had elapsed.[3] The confidentiality of data submitted by drug manufacturers was also protected by Bill C-91. Paragraph Five of Article 1711 of NAFTA requires that data submitted to a regulatory agency to determine the safety and effectiveness of a product must not be disclosed by the agency, unless the disclosure is necessary to protect the public or the data is protected from unfair commercial use (Food and Drug Law Group 1994: 337).

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[2] Article 1709, Paragraph 10 outlines the conditions under which a compulsory license may be granted. First, a license must have been sought from the patent holder on reasonable commercial terms. Second, the license must be granted predominantly to supply the domestic market. Third, if the circumstances which meant that licensing was required change, the license is to be terminated. The patent holder must be paid adequate remuneration. Fourth, a license should not be granted to permit the exploitation of another patent (Food and Drugs Law Group, 1994: 335).

[3] Under Bill C-91, this period was 30 months. Recent changes to the regulations have reduced this to 24 months (Manley 1998).

In order to limit price increases due to extended patent protection for brand-name drug manufacturers, the legislation strengthened the powers of the Patented Medicine Prices Review Board (PMPRB) and allowed exceptions to patent infringement for regulatory approval and stockpiling (Manley 1997).

Since 1993, the Canadian biotechnology industry has expanded dramatically, a development which the industry attributes to Bill C-91. The number of Canadian biotechnology companies has doubled, and the industry employs 8,000 people, 3,000 more than the generic companies (McKenna 1997: B4).

3.2 Biotechnology Policy in Canada

The development of a Canadian biotechnology industry has also been encouraged by a system of government grants which "incubated biotechnology companies in their infancy." (Scoffield 1998: B6) In 1983, the government created a National Biotechnology Strategy which was designed, among other things, to attract investment to Canada and focus biotechnology R&D in areas of "strategic importance" (Envision Research, 1997: 11).

This strategy was pursued into the 1990s. Biotechnology had been one of the six sectors slated for regulatory improvement in the government's report, *Building a More Innovative Economy*. The government defined biotechnology as an "enabling technology" which could transform the basis on which industries can compete (Industry Canada 1994: 63). According to the report, the biotechnology industry had specified regulatory uncertainty as the main obstacle to the industry's development in Canada, therefore action was required to ensure continued investment in this country (30). A number of regulations, including those pursuant to the Fertilizers Act, Seeds Act, and Food and Drugs Act, were revised by the end of 1996.

In the 1995 Budget, the government set out a strategy that future science and technology research "would be concentrated more strategically on activities that foster innovation, rapid commercialization, and value-added production" (Minister of Finance

1996: 74). To achieve this goal, the government announced in 1996 that it was reallocating $270 million to technology development programs over the next three years. One such program, Technology Partnerships Canada, was to operate on the basis of risk-sharing with the private sector. Areas funded by the program included biotechnology and other "enabling" technologies such as advanced manufacturing and materials technologies, aerospace, and defense conversion. With existing resources from Industry Canada, the Technology Partnerships program was expected to have funding of $250 million by 1998-99. A Technology Network to promote technology diffusion was to be launched, and the current system of tax incentives for scientific research and experimental development evaluated (75-6).

The Canadian government has also supported the biotechnology industry through its funding of basic research by organizations such as the Medical Research Council (MRC). According to the President of the MRC, two-thirds of Canadian biotechnology companies started after receiving seed money from the organization, including BioChem Pharma, the manufacturer of the world's best-selling AIDS drug. The money available through this source is diminishing, however; MRC funding dropped to 1992 levels in 1997-98 (Scoffield 1998: B1). The National Biotechnology Advisory Committee (NBAC 1998) noted that "Canada's once world-class biotechnology science base is eroding under cuts in public funding" (32). In the United States, the NIH budget was $10.7 billion in 1997, having risen 16.3 per cent in the previous three years. In the same period, the MRC budget declined by 10.7% to $238 million, representing 1/45 of the NIH budget (35). Since 1994, venture capital funding has increased; however, investment has gone toward development rather than basic research (Scoffield 1998: B6).

3.3. Biotechnology Regulation in Canada

Biotechnology is defined in the Canadian Environmental Protection Act (CEPA) as "the application of science and engineering in the direct and indirect use of living organisms

or parts or products of living organisms in their natural or modified forms" (CEPA S.2 (3)(1)).

In 1992, Cabinet agreed to adopt common principles for the regulation of biotechnology products, which had been formulated by nine federal departments, including Health Canada and Environment Canada, and led by the Minister of Agriculture and AgriFood. The three main principles were:

> -the recognition of the primacy of health and safety standards
> -the use of existing legislation and existing institutions to administer them
> -pre-release assessment of the risks involved in releasing organisms into the environment. (Morrissey 1995: 80)

On January 11, 1993 the Federal government announced that these principles would form a regulatory framework for biotechnology. As in the U.S. Coordinated Framework, biotechnology products would be regulated by government departments under existing legislation. The goal of the framework was to achieve a "balance" between the benefits of the technology and the need to protect the environment, human health, and safety; the government wished to foster a favourable climate for investment, development, and innovation, while at the same time minimizing environmental risks (Envision Research 1997: 38).

Under this proposal, the introduction of biotechnology products would be administered by different departments; biological pesticides, for example, would be regulated under the Pest Control Products Act, transgenic seeds under the Seeds Act, and pharmaceutical drugs - including rbGH - under the Food and Drugs Act, the responsibility of Health Canada. Any products not covered by existing statutes would be regulated under the Part II of CEPA, "Toxic Substances."

CEPA was passed on June 30, 1988. It had replaced or subsumed a number of earlier Acts to protect the environment (House of Commons Standing Committee on Environment and Sustainable Development 1995: 23). Section 139 of the Act stipulated that a Parliamentary committee would review its provisions within five years (ix). This task was undertaken by the Standing Committee on the Environment and Sustainable

Development. The committee endorsed a proposal developed by the Canadian Institute for Environmental Law and Policy (CIELAP) for the regulation of biotechnology. It stated that

> The committee recommends that CEPA be amended to include a new part to deal specifically with the products of biotechnology. This new part will include minimum notification and assessment standards for all products of biotechnology released into the environment, including those regulated under other federal Acts. Other federal statutes shall prevail over CEPA in regard to the environmental impact assessment of products of biotechnology only if their notification, assessment and regulatory standards are at least equivalent to those prescribed under CEPA.(124)

The government did not accept the committee's recommendations, and maintained CEPA as a safety net for biotechnology products which were not adequately covered by regulations administered in other departments. A spokeperson from CIELAP criticized the proposed changes to CEPA as weakening existing law relating to biotechnology (Matas 1995: A1 and A2).

In 1997, Industry Canada was charged with the task of revitalizing the National Biotechnology Strategy. The creation of a publicly-acceptable ethical framework to guide regulatory policy was regarded as important for the successful renewal of the Strategy. With this end in mind, Industry Canada made $200,000 available for research into the regulation of biotechnology in other jurisdictions; Health Canada has established a series of Round Table discussions across the country to obtain public input on regulatory policy. Although the Round Table discussions were purportedly intended to obtain public input on biotechnology policy, the subsequent reports noted that lack of advance notice meant that many interested parties were unable to attend (Government of Canada 1998b: 3).

4. Dairy Farming in Canada

Jurisdiction over Canadian agriculture is divided between the federal and provincial governments. The responsibility for administering dairy price supports was taken over by the Canadian Dairy Commission (CDC) in 1966 (Skogstad 1987: 47). In 1969, the Dairy Farmers of Canada (DFC) instituted a plan which placed quotas on industrial milk and cream (used for the production of foods such as cheese or yoghurt, rather than for direct consumption). Farmers were eligible for a federal government subsidy only on goods

produced within the quota allocated by the provincial milk board. Since 1975, the CDC has administered the quota system in conjunction with the Canadian Milk Supply Management Committee (CMSMC) which represents each provincial marketing board (103-4).

Import restrictions were a crucial part of maintaining the system, and Canada had imposed quotas on the import of dairy goods. Under the Uruguay Round GATT provisions, quotas were no longer permitted as a form of import restriction, and were replaced by tariffs of up to 351%. The U.S. government protested that tariffs on poultry and dairy goods conflicted with Canada's obligation under NAFTA to eliminate tariffs by June 1, 1998. A five-member trade panel ruled in Canada's favour on July 15, 1996, thus allowing Canada to maintain its high border tariffs indefinitely (Fagan 1996: A8).

Although protected from international competition, Canadian dairies have undergone significant structural adjustment due to technological change. Technological adoption has resulted in a near-doubling of milk yield per cow, and led to fewer and larger dairy farms. In 1965, the average herd size was 14 cows; in 1985, it was 53 (Stonehouse 1987: 5), rising to 56 in 1996 (Canadian Dairy Network: personal correspondence). A 1990 analysis suggested that this tendency would be reinforced with rbGH adoption:

> The high degree of managerial skill required to profitably utilize BST, combined with early adoption of this technology by certain producers, would encourage high-cost producers to leave the dairy industry. Early adopters of BST, facing decreases in cow numbers...could be expected to purchase more quota to ensure full utilization of fixed resources. This is likely to accelerate the ongoing rationalization process of fewer but larger dairy farms with higher yields per cow. (Stennes et al. 1990: 78)

In recent years, the Canadian government has introduced changes to agricultural policy. In 1991, the Agricultural Stabilization Act was repealed, and replaced with the Farm Income Protection Act (FIPA). In the 1992 Budget, the government announced a 10% decrease in the dairy subsidy effective from 1993. A 15% decrease was announced in the 1995 Budget (*Canada Gazette* 1995), followed by a further 15% decrease in 1996. In the 1996 Budget, the government announced that from August 1997, the subsidy would be

phased out entirely over five years (Department of Finance 1996: 41). This was later changed to delay the phase-out for six months (CDC 1997).

5. rbGH in Canada

rbGH is regulated under the *Food and Drugs Act* administered by Health Canada. According to Ray Mowling of Monsanto Canada, Monsanto prepared its application for licensing between 1987 and 1990, and submitted the application in 1990 (Senate of Canada 1998). Since rbGH is regarded as a veterinary drug, the product evaluation is being carried out by the Bureau of Veterinary Drugs (BVD) within the Department's Health Protection Branch. In order to be considered for review, the drug's manufacturer must submit information including: a description of the drug; its brand name; a list of ingredients; a description of the plant and equipment to be used in manufacturing; the method of manufacture; details of tests to determine its potency, purity, stablity and safety; reports on its safety under conditions of use; substantial evidence of its clinical effectiveness for the purpose indicated; names and qualifications of the invetigators to whom the drug has been sold; and a draft of the label to be used (Health Canada 1995a: 3). The studies to determine safety and efficacy include toxicity studies, pharmacology and residues studies, and animal safety studies (Foster 1994: 47). If the Bureau is not satisfied that the information provided is sufficient, it can request additional data from the manufacturer. Once the review has been completed and the drug has met the requirements under Section C.08.002 of the Food and Drug Regulations, the regulations stipulate that the Minister of Health shall issue a Notice of Compliance (NOC) (Health Canada 1995: 3).

On March 7, 1994 the Standing Committee on Agriculture and AgriFood commenced hearings on the impact of the drug's introduction in Canada. A number of departments and organisations were represented at the hearings, including Agriculture and AgriFood, Health Canada, Monsanto and Eli Lilly, the Animal Health Institute, the Dairy Farmers of Canada, the National Dairy Council, the Consumers' Association of Canada and the Canadian Consumers' Association. A representative from the U.S. Consumer

Policy Institute, Dr Michael Hansen, and the veterinarian Dr Richard Burroughs, who claimed that he had been fired from the FDA for criticizing the review process, also spoke at the hearings. The committee also received briefs from over 60 organisations and individuals.

Spokespeople from the Dairy Farmers of Canada and the National Dairy Council expressed concern about consumer reaction to milk from rbGH cows. The President of the Dairy Farmers of Canada, Peter Oosterhoff, requested a 180-day moratorium if an NOC was issued so that consumers could be educated about the safety of the drug and there would not be an adverse consumer reaction (Oosterhoff 1994: 22).The National Dairy Council President, Kempton Matte, requested a two-year delay in approval and/or use of the drug in Canada (Matte 1994: 4). The President of the Fédération Nationale des Associations des Consommateurs du Québec (FNACQ), Lise Pilon, said her organization had adopted a position of extreme caution on biotechnology (Pilon 1994: 24).

Members from the Canadian Animal Health Institute (CAHI) also spoke at the hearings. Based in Guelph, Ontario, the Institute is registered as a trade organization and is funded by more than 30 chemical, pharmaceutical and biotechnology companies, including Monsanto and Eli Lilly. It produces and distributes scientific literature on products manufactured by these companies. According to its Executive Director, Jean Szkotnicki, promoting rbGH had been the Institute's biggest program in recent years (Saunders 1995b: A13).

At the hearings, scientists from CAHI and Monsanto emphasized the legitimacy of the scientific evidence which verified the drug's safety. Szkotnicki asserted that the manufacturers of rbGH had released their world-wide body of human safety data for publication in the *Science* article; its conclusions had been verified by a number of respected organizations which had found that the consumption of products containing rbGH was safe for humans. She also noted that a scientific panel of the Canadian Medical Association, the Canadian Pediatric Society, the Canadian Veterinary Medical Association,

and the University of Toronto Faculty of Medicine had found the drug to be safe, as had the FAO/WHO Joint Expert Committee on Food Additives (Szkotnicki 1994: 24).

After the hearings, the Standing Committee produced a report which was released in April. The report argued that there were a number of outstanding issues which needed to be investigated further. One was that the Canadian dairy supply management system was currently subject to change since one of the pillars of the system, import quotas, had been removed with the implementation of the GATT. The introduction of rbST, the committee argued, would put additional stress on the system. It also pointed out that because the Canadian dairy system is different from that of the United States, American economic impact studies could not accurately predict the effects in Canada, nor could studies which ignored changes affecting the supply management system. (A study by Deloitte and Touche for the Canadian Animal Health Institute was cited as an example of this.) The risk of anitbiotic residues in milk, of great concern in the U.S., was not regarded as a problem in Canada because of stringent antibiotic testing. However, animal health concerns, particularly mastitis, were still an issue. An adverse consumer reaction was regarded as critical to the Canadian industry. Again, the committee believed that tracking the U.S. consumer reaction would not necessarily prefigure the Canadian response. Nor had the impact on Canada's export of breeding animals, semen and embryos - valued at $100 million - been determined. Therefore, the committee recommended, first, that the government legislate a one-year moratorium on the use of rbGH in Canada. Second, that this period should be used to review the impact of its introduction, including the issues described above. Third, that a government-industry task force be struck to undertake this task. Fourth, that imported dairy products be labelled to demonstrate their conformity with the Canadian moratorium. Fifth, that mechanisms should be implemented to ensure greater transparency in the regulatory system. Sixth, that Health Canada and Agriculture and Agri-Food Canada should establish consistent procedures for handling biotechnology products;

and seventh, that the government make provisions for assessing the likely socio-economic and environmental effects of these products.

The government responded to the recommendations in August. Rather than a legislated moratorium, the government had obtained a voluntary delay from the manufacturers until July 1, 1995. It endorsed the committee's second and third recommendations for an impact study, and established a task force to carry out the review. The government also said that it endorsed recommendation four; however, in its interpretation, such labelling was implied by existing requirements that imported dairy products must show their country of origin. Countries which had licensed rbST were listed in an appendix to the report. It also noted that all milk contains trace amounts of natural bST, which is indistinguishable from the synthetically produced version; that no country had required mandatory milk labelling; and that the FDA guidelines did not permit labels to state that milk is bST-free or that it is safer than milk from untreated cows.

The government endorsed the recommendation for greater transparency in the decision-making process; however, its response was to maintain the existing process. It said that it would continue to provide information, while respecting the limitations on disclosure imposed by the confidentiality provisions of the Canadian Access to Information Act and Article 1711(5) of the North American Free Trade Agreement (NAFTA) and Article 39(3) of the GATT. Recommendation 6 was also endorsed; however, this endorsement did not signify any change in the government's approach to biotechnology. It noted that regulations and guidelines for agricultural products were discussed at a multi-stakeholder forum held in November, 1993. Development of the regulatory process was continuing; Agriculture and Agri-Food Canada, and Health and Industry Canada, would develop consistent procedures for handling biotechnology products. Recommendation 7 was partly endorsed. It was pointed out that risk-based environmental safety assessment was already an accepted component of the regulatory review process. Furthermore:

> Assessment of the possible socio-economic effects of biotechnology products is not supported as a regulatory criterion because these factors could pre-empt decisions

> based on safety, and effectiveness. The standard procedure in Canada and other industrialized countries is to regulate products based on scientific principles. Products are assessed for safety and effectiveness. Once safety and effectiveness have been reviewed, it is the marketplace in Canada which then decides on the market acceptance of the product, based on benefits such as price and individual values and preferences. (Government of Canada 1994: 8)

While Parliamentary committees and government task forces had been investigating the issue, farm, environmental, and food policy groups had not been silent. These groups had chosen a number of methods for voicing their opposition to the introduction of rbGH.

The Toronto Food Policy Council (TFPC) was among these groups. It was established in December 1990 by Toronto City Council, following a recommendation of the *Healthy Toronto 2000 report.* It operates as a subcommittee of the City's Board of Health, and its members include City Councillors, and volunteers from business, farm, consumer, labour, multicultural, anti-hunger advocacy, faith and community development groups. In its examination of rbGH, the Council concluded:

> That the approval of rBGH would represent a very significant failure in the Canadian food and agriculture policy making system. This failure stems primarily from a drug review process that does not require consideration of issues such as long-term public health implications (in this case, consumer acceptance of dairy products), and the impacts on the structure of the dairy industry and dairy farmers. Nor does the review process begin with the most basic questions: what problem is rBGH designed to solve? Is there a problem with the quality of the Canadian milk supply? Do we have a milk shortage in this country? Is milk production inefficient? (Toronto Food Policy Council 1995: 11)

The TFPC wrote a letter to the Minister of Agriculture and Agri-Food, Ralph Goodale, critiquing the government's response. It applauded the government's implementation of a voluntary moratorium and its support for a system of biotechnology review, but it did not believe that the government's response to recommendations 4, 5 and 7 constituted an endorsement of them, nor that the Task Force appointed to examine the issue could "do anything but support the government's desire to approve the product." (Toronto Food Policy Council 1994b) With regard to recommendation 4, the Council argued that the Agriculture Committee had called for changes in the labelling system so consumers and regulators could determine whether imported products contained milk from treated cows, whereas the government's response indicated that the status quo was fine,

and ignored the fact that mandatory labelling legislation had been passed by some U.S. states. On recommendation 5, the TFPC pointed out that there was no evidence that the government intended to make any changes to the review process. It argued that recommendation 7 had not even been "partly" endorsed. An environmental assessment should be carried out for rbGH because "[a]ny sound environmental assessment is rooted in a belief that actions have a whole series of interconnected reactions, and that only a comprehensive determination of these relationships can lead to an understanding of the implications." The interactions in the rbGH case would include manure and manure management, feed demands, pesticide and fertilizer use, regional concentrations of dairy production and land use patterns. It pointed out that socio-economic criteria had been used by the European Community to reject rbGH. Finally, the TFPC recommended that the composition of the Task Force must be changed so that at least half its members had concerns about rbGH licensing; that its mandate should not be restricted to a review of existing documents, but should allow organizations to submit briefs and appear before it; the government should take action to ensure that the moratorium is respected by importers; and no NOC should be issued before the Task Force reports.

The TFPC produced a document on *The Current Status of the Licensing of Recombinant Bovine Growth Hormone (rBGH).* Clause 5 of the report, which recommended action to be taken by the Board of Health, was presented to City Council at its meeting on March 28 and 29, and was referred back to the Board of Health for further consideration and the hearing of deputations (City of Toronto Board of Health 1994a). On April 28, 1994 the Board of Health held a meeting to consider the recommendations of the TFPC and hear from other interested parties. Twenty-six people attended the meeting, including farmers, members of the public, representatives from farm groups and J.D. Nattress from Monsanto,Terry Clark from Eli Lilly, and Jean Szkotnicki from the Canadian Animal Health Institute (City of Toronto Board of Health 1994b).

The Board of Health resubmitted Clause 2 from *The Current Status of the Licensing of Recombinant Bovine Growth Hormone* to the City Council on May 30 and 31. At this meeting, the Board of Health adopted the Council's recommendations. These were that the Board of Health should inform the Federal and Provincial governments that the Board does not believe the licensing of rbGH should be approved at this time; that it request Health Canada and Agriculture Canada to require labelling of all foods produced by genetic engineering; that it request licensing bodies to provide an analysis of the socio-economic impact of these technologies on the communities affected; that it continue to express its concerns about the impact of genetic engineering on the environment and biodiversity; and that it forward a copy of the report from the TFPC to all school boards in Ontario requesting that, in the event of licensing of rBGH, they consider passing a resolution requesting that milk should be labelled; that dairy suppliers indicate whether rBGH- produced milk is being sold to the schools; and that parents be so advised by the school boards (City of Toronto Board of Health 1994a: 3). A letter was sent to the federal and provincial health and agriculture Ministers, and to the Chairman of the Standing Committee on Agriculture, informing them of the Council's action.

Meanwhile, the government put together a task force to examine the issues suggested by the committee. The Task Force was comprised of Ray Mowling from Monsanto and Terry Clark from Eli Lilly; Brian Morrissey from Agriculture and Agri-Food; David Head from Industry Canada; Dairy Farmers of Canada President Peter Oosterhoff; Dale Tulloch from the National Dairy Council of Canada; and Ruth Jackson, from the Consumers' Association of Canada.

The Task Force met monthly from October 3, 1994 until the release of its report in March 1995. It presented a progress report to the Standing Committee on December 14, 1994 and went on a trip to New York State in March 1995. The Task Force was a fact-finding body; therefore it made no recommendations to the government.

An examination of the economic impact of rbST adoption was undertaken by the Policy Branch of Agriculture and Agri-Food Canada. It findings were dependent on the proportion of farmers adopting the drug, cows treated, length of treatment, yield increase per cow, impact on costs of production and consumer reaction. While noting that adoption of the drug should not increase over-quota production levels in Canada, since it could be used as a management tool to improve the efficiency of production at existing levels rather than increasing production, it also pointed out possible adverse effects if the public reduced its consumption of milk because of concerns about the drug. A 3 per cent decline in fluid milk consumption could reduce farm profitability by approximately 2.4% (Agriculture and AgriFood Canada 1995: i-v).

Four scientists reviewed the impact of rbST adoption on genetic evaluation and improvement programs in Canada (Dekkers et al. 1995: i-ii). Genetic improvement programs rely on the integrity of evaluation programs which record the animal's milk production levels and her genealogy. These programs have been in place in Canada since 1881: 65% of Canadian farmers participate in genetic evaluation programs, and 75% make use of the records produced by them (Daniel 1996: 1). Dekkers et al. stated that the introduction of rbST would reduce the accuracy of genetic evaluations because once injected with bST, the cow's production level may no longer be indicative of her genetic capacity. They predicted that this could reduce rates of genetic improvement by 3 to 7%, and recommended that the use of rbST in Canada be recorded in order to minimize the impact on genetic evaluation. They also stated, however, that the approval of the product should not be contingent on its potential impact on improvement and evaluation programs[4] (Dekkers et al. 1995: i-ii).

[4] A member of the Toronto Food Policy Council and proprietor of a multi-breed dairy company, Mr. Vic Daniel, has argued that the erosion of the genetic evaluation and improvement programs presents a threat to Canada's food security. Since the Animal Pedigree Act, which establishes the legal basis for the incorporation of breed associations, is recognized under NAFTA, the hormone could be rejected in compliance with Article 712 of the Sanitary and Phytosanitary Measures Agreement permiting each party to introduce measures necessary for the protection of human life or health (Daniel 1996).

The report on U.S. consumer reactions noted that there had been little change in consumption in the U.S., but that this had been achieved by not differentiating between treated and untreated milk. In states where consumers had reacted to the drug, sales of rbST free milk were marketed due to consumer demand, but that demand now seemed to be declining. The exceptions to this were Wisconsin and Vermont, in which a dual marketing system had been important in maintaining consumption levels. This seemed to have "started as much from farm and rural living concerns as from consumers" (Brinkman 1995: i-ii).

Health Canada's contribution to the Task Force report outlined the procedure for obtaining a NOC. In an Appendix, Health Canada also listed the human and animal safety issues identified by people who wrote to the Task Force, and said that these would be included in its evaluations. These included, among others, cancer, allergies, IGF-I, antibiotic resistance, general health concerns, labelling, and a monitoring system for the drug (Health Canada 1995a: Appendix).

The Council of Canadians, an Ottawa-based public interest organization which had campaigned against Canada' s participation in the FTA and NAFTA and for the preservation of Canada's social programs, critiqued the Task Force report and the government's conduct of the rbGH review. It questioned the Task Force trip to New York State in which the scientist and the veterinarian interviewed by the group, Dr. Dale Bauman and Dr. Les de Groff, had both worked closely with Monsanto. It also referred to recent scientific evidence on both animal and human health problems, including recent evidence on the bioactivity of IGF-I (Council of Canadians 1995a: 2).

On June 9, the Council wrote to the Chair of the Standing Committee on Agriculture, Bob Speller, appealing to his committee and the Standing Committee on Health to put rbGH on their agenda and highlighting the need to establish a process to examine questions not asked by the Task Force and regulatory systems (Council of Canadians 1995b).

On June 18, the House of Commons Committee on Health called for a two-year moratorium if rbGH was approved (McLaughlin 1995). In response to this, Health Canada re-stated its criteria for licensing animal drugs and reiterated its examination of health and labelling issues raised by the Task Force report. Health Canada also released its summary of the Human Safety Evaluation of rbST, a review of the scientific literature on rbGH and IGF-I.

The manufacturers were alarmed by these developments. In a letter to MPs dated June 16, (marked "confidential") Monsanto Canada's Vice-President of Legal and Public Affairs, Ray Mowling, wrote that "I believe this issue is being used by the Council of Canadians and other special interest groups to dismantle the regulatory system" (Mowling 1995). Anticipating that a legislated moratorium would be imposed when the voluntary delay expired on July 1, Monsanto and Eli Lilly threatened to withdraw research investments from Canada if such a ban were implemented. Spokesmen for the companies said that Monsanto would consider reducing its expenditure of $6.5 million in Canada if a two-year moratorium were enforced, and Eli Lilly might shift funding from its Canadian subsidiary (Saunders 1995b: B7). The companies later denied having made such statements. The companies did argue that the introduction of rbGH would be essential if Canadian dairies were to compete with increased imports from the US as the provisions of the GATT and NAFTA gradually led to the erosion of Canadian import protection. A representative from Eli Lilly claimed that an inefficient regulatory system, open to pressure from external interests, created a less hospitable environment for investment in Canada (McLaughlin 1995).

Allegations had previously been made that Monsanto had offered a bribe to Health Canada to fast-track approval of rbGH. The CBC broadcast "Big Milk, Big Money, Big Muscle" on Fifth Estate on November 29, 1994 alleged that four or five years earlier, Monsanto had offered money to the department for "animal-related biotechnology research in Canada". A memo written by Dr. M.S. Haydon, an official with the BVD, said that

money was offered on condition "that the company receive approval to market their drug in Canada without being required to submit data from any further studies or trials." In December, Monsanto said that it had "proposed a commitment to future research based on potential sales of bovine somatotropin following its approval for use in Canada," but denied that it had offered a bribe to the department and demanded a retraction from Fifth Estate (Bueckert 1994).

Soon after allegations of the bribe were broadcast, the Health Minister, Diane Marleau, faced conflict-of-interest questions about the Director of the BVD, Dr. Leonard Ritter. Dr. Ritter had been on unpaid leave from the Bureau since June 1993. As a witness at the Standing Committee hearings in March, he had said that he was a former public servant. On December 7, the Minister said that she had asked the Deputy Minister to determine whether Dr. Ritter had contravened conflict-of-interest guidelines (Ha 1994: A5). The Canadian Animal Health Institute later complained to the Ontario Press Council that a *Globe and Mail* article in which Dr. Ritter's testimony had been discussed misrepresented the Institute, but this claim was dismissed by the Council (*The Globe and Mail* 1996: A11).

On August 3, the co-ordinator of the Toronto Food Policy Council, Rod McCrae, commented to the Board of Health on the Health Canada's summary of the human safety data. As a result of his comments, the Board of Health Chair, Peter Tabuns, sent a letter to Bob Speller regarding the Health Canada evaluation. The major concern expressed was that it had ignored recent evidence disputing accepted knowledge, since most of the literature cited had been published before 1991, and therefore more recent work on the effects of the hormone had not been taken into account. The letter also stated that rbGH adoption could prove hazardous to health if people reduced their milk consumption in order to avoid problems associated with it; Health Canada had not considered this possibility in its review (Tabuns 1995).

In August, over 50 public interest groups composed a joint letter urging the Prime Minister to legislate a one-year moratorium in the event that Health Canada issued a NOC for Posilac (CIELAP 1994). The National Farmers' Union had also sent a letter to the Prime Minister in June, expressing concern and trepidation over letters from Monsanto and Provel which "would seem to suggest alternatives for the circumvention of the Standing Committee on Agriculture." (Macklin 1994) As a part of its "Safe Milk Campaign" the Council of Canadians had encouraged members of the public to write to their Member of Parliament, the Minister of Health, and the Executive Director of the Dairy Farmers of Canada, expressing their opposition to the drug and suggesting that the federal government follow Europe's example and ban it until at least the year 2000.

In September, Health Canada asked Monsanto for more data on animal health safety. Ray Mowling said that compiling the data would delay approval until at least the end of 1996. According to Mowling, the request was put during a series of meetings with Health Canada officials and no written notice was given (Stoneman 1995).

In 1997, scientists within the Bureau of Veterinary Drugs went to the media with allegations that they had been pressured by senior managers to approve drugs of questionable safety. Bureau scientists were unhappy with the conduct of the rbGH evaluation, particularly the human safety review. They stated that although they still had questions about the drug's safety, the safety of milk from treated cows had been affirmed by the Chief of the Bureau's Human Safety Division; this issue went before mediation (Eggertson 1997b). In 1998, the scientists, claiming that their concerns had not been addressed within the Bureau, took their case to the Public Service Review Board. Their grievance was that they had been pressured by their superiors to approve drugs, including rbST, when they felt that further testing was warranted. Failure to comply with their managers' demands had resulted in their removal from the evaluation.

While the grievance proceedings were taking place, the Director-General of the Health Protection Branch, Dr. George Patterson, asked one of the concerned scientists, Dr.

Shiv Chopra, to report on deficiencies or "gaps" in the existing rbST evaluation. Dr. Chopra asked for the involvement of other scientists, and a team of four reviewers, two of whom were from divisions outside the Bureau, reviewed the process so far. Their intention was not to come to a conclusion regarding the drug's safety, but to review the existing process and to highlight any issues that the Bureau had failed to address. This committee's report was referred to an rbST advisory committee within the Bureau. In the meantime, the Senate Committee on Agriculture and Forestry convened hearings into the Health Canada review. These hearings were primarily the result of action by Senator Whelan, a former Minister of Agriculture. At the first session, which took place in June, the committee heard from the Director-General, the Assistant Deputy Minister, and representatives from Monsanto.

Dr. George Patterson referred to the internal committee review as an "internal gap analysis" and noted that the review committee had submitted its report, which was reviewed by an rbST Advisory Team, whose comments would be incorporated into the original report (Senate of Canada 1998). The *Toronto Star* reported that "[s]enior Health Canada officials have directed the report's authors to kill sections that name names and accuse the original drug reviewers of not being as thorough as the Food and Drugs Act requires." (Eggertson 1998a: A6) This allegation was denied by a spokesperson for the Minster of Health, Allan Rock, who said that the report was in its draft stages and was still to be completed (Eggertson 1998b: A16).

Health Canada has also requested that the Canadian Veterinary Medical Association,[5] and the Royal College of Physicians and Surgeons, each establish a panel to review the animal and human health data respectively. Dr. Patterson reported that these panels were expected to make their recommendations in the fall (Senate of Canada 1998).

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[5] At the House of Commons Agriculture Committee hearings, a representative from the Canadian Animal Health Institute, Dr. Jean Szkotnicki, stated that the Canadian Veterinary Medical Association, among other organizations, had come to the conclusion that the milk from cows treated with rbST is safe (Szkotnicki 1994).

After these reports were presented, Health Canada announced that it would not approve bovine growth hormone (Health Canada 1999).

6. Conclusion

Both the Canadian and the U.S. regulatory systems exist in the context of the broader political economy. In the U.S., changes in the political economy - particularly industrial restructuring around technological innovation - were facilitated by government policy, and judicial decisions.

In Canada, the state has also accepted that technological innovation is best facilitated in collaboration with the private sector, and has developed strategies to foster the biotechnology industry, including the provision of financial support. It has also followed the U.S. example in regulating the products of biotechnology through existing statutes rather than a separate statute, although products not covered by existing Acts will be covered under CEPA.

With respect to the Canadian dairy system, GATT and NAFTA have not yet had a direct impact, since quota restrictions have been replaced by tariffication. However, some of the concern about rbGH in Canada has been regarding the extent to which the drug would effect structural adjustment which will take place as subsidies are phased out.

Other aspects of the Canadian system are also distinctive. Canadian courts have refused to recognize the patentability of higher life forms, and other aspects of patent law are not in conformity with Canada's trading partners. Although CEPA was not amended in accordance with critics' recommendations, the process of reviewing the Act generated debate about the future of biotechnology regulation. Although action has so far been inadequate, government advisory committees have recognized the importance of public input on the future direction of biotechnology policy.

There have been fewer mechanisms available via which these kind of concerns could be introduced to the regulatory process than in the United States. In Canada, however, the requests for investigation have come from within the Bureau, rather than

outside it. In the U.S., in contrast, both managers and reviewers responded to external queries, but did so by defending the validity of their interpretation. Canadian reviewers, on the other hand, have not accepted that the data from the animal health studies support a conclusion of "safety," and some scientists have questioned the Bureau's own conclusions on human health. In the next chapter, I explore the consequences of the Canadian structure for the interpretation of the data.

Chapter Five
The scientific debate

1. Introduction

This chapter outlines the scientific debate, and analyzes the various actors' contribution to it. The chapter argues that there was a high degree of consensus about the data from safety and efficacy studies. There was agreement that the data showed little evidence of human health problems; however, there was debate about whether counterinstances in the data warranted further investigation, or whether the existing evidence was a sufficient basis for judgement. There was also agreement that there was a statistically-significant increase in animal health disorders; in this case, there was a debate about the extent of the problem, and whether it could be managed by farmers. In order to make judgements on these issues, regulators made assumptions based on their knowledge of scientific literature, and of existing dairy practices. These assumptions varied according to context.

The chapter is divided into three sections. The first section analyzes the human health debate. It is divided into sub-sections, each of which examine the position of various actors in the debate, and which also examines the methodology and interpretation of researchers *outside* the debate, in cancer and basic research. The second section analyzes the animal health debate, and shows how assumptions about manageability were important to the policy debate. The third section analyzes the importance of the debate itself, and the pressures that involvement in it imposed on scientists.

2. The human health debate

The human health debate focused on two issues: whether recombinant bGH in milk was more likely than natural bGH to induce adverse reactions; and whether insulin-like growth factor-I (IGF-I), a hormone-like substance which mediates the action of growth hormone, would present a health risk if concentrations were elevated in the milk from treated cows. Research conducted during the period of the rbGH debate - although quite

separately from it - provided evidence that insulin-like growth factors played a role in the development of some malignant tumours, including breast cancer. Epstein (1990a and b: 1996) raised the alarming possibility that the widespread consumption of milk from treated cows was a potential cancer risk. Another important issue was whether the widespread use of the drug would result in higher antibiotic usage, and hence greater risk of consumption of antibiotic residues in milk, and resistance in the general population. Since this question is connected to animal health concerns, it will be discussed in the animal health section.

2.1. The FDA's interpretation: natural and recombinant bovine growth hormone

Bovine growth hormone is composed of a sequence of 191 amino acids. The recombinant hormone developed by the companies had a slightly different amino acid sequence from the natural molecule.[1] Monsanto's Posilac substituted the amino acid methionine for alanine at the NH2-terminus end of the protein (the end of the amino acid chain).

rbGH was the first protein hormone for use in food animals. FDA scientists expected that it was extremely unlikely that recombinant bGH would produce any effects in humans, because the natural bovine hormone had been ineffective in the treatment of human growth hormone deficiencies. Like other protein hormones, growth hormone induces changes in human cells by binding to receptors on the cell surface. Bovine growth hormone is sufficiently different from human growth hormone that it will not bind to human receptors. Its activity is species-specific or species-limited[2]; rats, for example, can respond to growth hormone from a number of species, but humans can only respond to that from other primates.

In order to determine whether rbGH residues presented a risk to human health, FDA scientists reviewed the reports from the 1950s on attempts to develop a biologically

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[1] The Upjohn company's product was the exception to this; it produced a recombinant hormone with the same amino acid sequence.

[2] This term is used by Bauman (1992: 3434) and Hammond et al. (1990). Juskevich and Guyer (1990) used the term "species-specific." (877)

active form of bGH for human use. They also reviewed the literature on protein digestion and absorption in adults and newborns which indicated that, in adults, most proteins are broken into smaller peptides or amino acids and do not survive digestion intact[3]. The results for newborn infants were conflicting; however, where evidence of protein absorption existed, the amount absorbed was insignificant (Juskevich and Guyer 1990: 876). Both the kind of studies which should be requested, and the interpretation of those studies, were influenced by the reviewers' understanding of the existing literature (877). In the Toxicology division, therefore:

> The general feeling was there were no safety issues with bGH itself. A lot was known about it. It had been studied extensively for years because they had attempted to make bGH active in humans when they were looking for another source for growth hormone deficiencies. So I don't think there was any doubt in anyone's mind that bGH was never going to be active, so it was never going to be any kind of safety issue. (Juskevich 1996: interview)

Although Agency scientists believed that rbGH would not be biologically active in humans, they requested several oral toxicity studies in order to determine whether the product was orally active (that is, whether it could survive digestion and be absorbed into the bloodstream intact). The longest of these studies was a 90-day oral toxicity study by Monsanto. In this study, rats were treated with up to 50 milligrams of rbGH per kilogram of body weight per day; as a positive control, another group of rats were administered subcutaneous (under the skin) injections of rbGH. Rats receiving injections of rbGH showed an increase in body weight gain and feed consumption, and the weight of their organs (for example heart, liver, kidney, and spleen) increased. Ratios of organ weight to body weight were also increased for certain organs. In contrast, no significant changes were observed in the rats treated orally. At the low dose of rbGH given orally, absolute spleen weight increased, but the FDA reviewers decided that this finding was incidental because it was not dose-dependent. Increases in ratios of organ weight to body weight

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[3] Proteins which have low molecular weights or high specific activities, or both, display some oral activity. Synthetic thyrotropin-releasing factor (TRF) which has a molecular weight of 330 daltons, and synthetic gonadotropin-releasing hormone (GnRH) which has a molecular weight of 1,100 daltons, are orally active. bGH and IGF-I have molecular weights of 22,000 and 7,800 respectively (Juskevich and Guyer, 1990: 876).

were sporadic and also interpreted as incidental. It was therefore concluded that rbGH was not orally active (Juskevich and Guyer 1990: 878).

In order to determine whether the body responded differently to the recombinant form of the hormone than the natural variant, the Agency reviewed a study in Holsteins which demonstrated that the drug was cleared from the body in the same way as the natural-sequence hormone. This study confirmed a report indicating that monkeys responded similarly to recombinant and natural variants of growth hormone (878).

Since rbGH was not orally active, and did not have a potential for biological activity in humans, studies to determine the residue levels of rbGH in milk were not required. The companies, however, developed radioimmunoassay procedures to try to determine rbGH levels, but the procedures were unable to distinguish between the natural and recombinant variants. Measurements of total bGH levels were not statistically different in milk from treated cows. Pasteurization also renders up to 90% of bGH ineffective (Juskevich and Guyer 1990: 878). On the basis of these findings, the Agency authorized the release of milk from treated herds into the milk supply in 1985. If a drug is deemed to have a potential effect on human safety, a withdrawal period is set during which meat or milk must be withheld from sale; initially milk was withheld for four days following treatment (876) but once it was concluded that rbGH would not have any adverse effects on human health, no withdrawal period was established.

Critics, however, argued that rbGH may have allergic and immunogenic (inducing an immune response) effects when consumed in milk (Epstein 1990a and b: 81; Kronfeld 1991: 256). In response, Juskevich and Guyer (1991) stated that they had considered the potential allergenicity and immunogenicity of rbGH, and decided that the likelihood of these problems was insignificant.[4]

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[4] Their conclusion was based on several considerations: the consumer is exposed to a wide number of foreign proteins every time he or she eats a protein product; there is no reason to suspect that bGH is any more likely to cause adverse effects than any of these other proteins; bGH is a much smaller component of milk than other proteins; rbGH is not significantly different from the natural molecule; and rbGH will be broken down during digestion.

2.2. Insulin-like growth factors: a potential cancer risk?

Insulin-like growth factors affect growth, development, and metabolism (Stewart and Rotwein 1996). They exert their effects by binding to receptors at the surface of the cell, thereby setting off a chain of reactions inside it. There are two forms of this growth factor. Insulin-like growth factor I (IGF-I) consists of 70 amino acids. IGF-I is produced by the liver in response to growth hormone stimulation. Like hormones, it circulates in the blood to effect changes in cells distant from the liver.[5] However, unlike hormones, IGF-I may also be produced by the cells on which it acts, or on cells proximate to the site of action. Insulin-like growth factor II (IGF-II), on the other hand, is not regulated by growth hormone. It consists of 67 amino acids, and plays an important role in foetal growth (Pollak et al. 1987: 223).

The effect of IGF-I has been of concern because, unlike growth hormone, bovine and human IGF-I are structurally identical (Sara and Hall 1990). Early reports suggested that IGF-I concentrations were higher in milk from treated cows. The FDA summary published in *Science* stated that the milk from treated cows had up to 25% more IGF-I. The consequences of potentially elevated milk IGF-I levels has been an explosive public health issue because of Epstein's suggestion that this could lead to an increased risk of breast cancer. In the late 1980s, medical researchers had begun to investigate the possibility that the insulin-like growth factors may play a role in the development of certain kinds of tumours; some research suggested that higher levels of IGF-I in circulation were associated with a higher incidence of particular types of cancer. This research has continued into the 1990s; however, there are many questions which have yet to be resolved about the relationship between growth factors and cancer. (See section below.)

The FDA rejected this assertion, stating that "the suggestion that IGF-I in milk can induce or promote breast cancer in humans is scientifically unfounded and misguided." (FDA 1994b: 2) It was opposed on the grounds that IGF-I in milk would not be absorbed

[5] When circulating in the blood, IGF-I is bound to carrier proteins.

into the bloodstream intact. In the unlikely event that any molecules of the growth factor did survive digestion, insignificant amounts would be absorbed. The consumption of dietary IGF-I does not affect the development of human disease.

The Agency's statements on the likelihood of absorption were based on its evaluation of IGF-I oral toxicity studies. The FDA had not examined the IGF-I question prior to authorizing a zero withdrawal period for milk and meat from treated cows. However, when the safety of ingested IGF-I became an issue, the Toxicology Branch Chief undertook an extensive literature search on all growth factors that could possibly be affected by growth hormone and decided that "the only one that was of any concern was IGF-I." Basic research indicated that it was difficult to obtain an effect by injecting the growth factor because binding proteins "mopped up" circulating IGF-I, rendering it inactive. She also searched the literature on protein absorption in adults, new borns, and children, as well as on the oral activity of insulin, which has a similar protein structure to IGF-I:

> The picture that came from the whole thing from my point of view was the likelihood that you were going to see any significant safety problems from IGF-I was non-existent. It was a protein; there was no indication that it would be absorbed, or that it would not be broken down after you take it orally; and even if some minor amount got absorbed, it wasn't enough to produce an effect. Plus there are already levels of growth factor in milk, and that any increase would probably be negligible in terms of the residues. (Juskevich 1996: interview)

The paradigm about the biological activity of bGH was extended to IGF-I, about which much less was known. As Dr. Juskevich put it, "there weren't 30 years of studies about IGF-I"; however, since it was a protein, data about IGF-I could be assimilated into the paradigm about protein absorption and the studies were therefore the same length as the rbGH studies. She was so convinced about the unlikelihood of health problems from ingested IGF-I that she felt oral activity studies were unnecessary. However, the Director of the FDA's Center for Veterinary Medicine advocated laboratory tests for IGF-I

(Juskevich 1996: interview).[6] In retrospect, Dr. Juskevich felt that this decision was correct, not for scientific but for political reasons:

> It was apparent that the scientific reasoning behind what we did really didn't matter to people. No one seemed to be listening much to the science to start with, so I think it was a very wise decision that those studies were done. They showed us exactly what we expected; it wasn't orally active, well we didn't expect it to be orally active - and at what levels.

At the request of the FDA, Elanco and Monsanto[7] conducted two-week oral toxicity studies. When proteins are given therapeutically, the effects are visible within a few days; so fourteen days was regarded as a sufficient amount of time to establish the oral activity of IGF-I. At the end of the treatment period, body and organ weights, and bone dimensions, were measured. Monsanto's study was conducted with normal rats; Elanco's, with hypophysectomized rats (rats which had had their pituitary glands removed, thereby making them more sensitive to growth factor). The Elanco study was composed of a negative control group, a group orally treated with recombinant IGF-I at 0.01, 0.1, or 1.0 milligrams per kilogram per day, and a positive control group, which were continuously. administered IGF-I subcutaneously. The rats treated subcutaneously showed increased body weight and increased relative kidney and spleen weights[8]; these changes were not apparent in the rats treated orally. The Monsanto study was conducted by Hazelton Laboratories in Washington, DC. Since a large number of rats was treated in the study, some of which were implanted with minipumps, treatment was initiated over two days. Rats were orally treated with rIGF at 0.02, 0.2, or 2.0 milligrams per kilogram per day, or by subcutaneous infusion. The subcutaneous and orally-treated groups each had a negative control group, and a positive control group was treated with porcine growth hormone

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[6] In the *Science* report, Juskevich and Guyer (1990) note that "because of the general lack of information in the scientific literature regarding the oral activity of IGF-I, the CVM decided to obtain more information." (879)

[7] Oral toxicity studies were requested from all companies that were pursuing approval at the time. Whether the companies conducted the studies depended on whether they planned to develop their formulation for regulatory approval (Juskevich 1998: personal correspondence).

[8] The rats in the group treated by subcutaneous infusion also showed an increased neutrophil count; decreased blood urea nitrogen (BUN), creatinine, and albumin (Juskevich and Guyer 1990: 880).

(Juskevich and Guyer 1990: 880). On the basis of this study, it was determined that rIGF-I is not orally active at doses of up to 2 mg/kg per day (881).

Some clinical signs were seen in orally treated rats, but these were not interpreted as treatment-related. One block of male rats treated at the highest dosage showed a slight but significant increase in body weight in the latter half of the study, with a significant daily weight gain (880). However, this sign only occurred in the high-dose group which started treatment on day two; the high-dose group initiated on the first day did not have a significant weight increase. (Ryan 1997: interview) Male rats in the other dosage blocks did not show weight increases, nor did any of the females; nor were serum levels of IGF-I increased in the high-dose group. It was therefore concluded that this sign was probably not treatment-related.[9] Liver weights for the high dose males were increased, as were heart weights for the low-dose group. Female rats in the medium-dose oral group showed a slight decrease in haemoglobin; this effect was not attributed to treatment since it was not accompanied by changes in other clinical parameters.[10] The width of the epiphysis (end of a long bone) was decreased in both male and female rats; the length of the tibia (shin bone) was increased in the low and high-dose males, but these signs were not consistent with the effects normally induced by IGF-I (Juskevich and Guyer 1990: 880-881).

These statistically-significant counterinstances were not surprising. According to the former Branch Chief of Toxicology, "if you do enough measurements, in any toxicology study that you look at, something pops up as statistically significant." What the reviewer[11] had to decide upon was whether a statistically significant result was also biologically significant; that is, whether it could be attributed to the drug. In order to be

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[9] Other clinical signs also remained unchanged in the high-dose group: "serum levels of IGF-I were not increased in the HD [high-dose] animals as they were in the positive control groups, and there were no changes in hematology, clinical chemistry and urinalysis parameters, or organ weights that were consistent with the effects of GH or IGF-I as observed in the positive control groups." (Juskevich and Guyer 1990: 881)

[10] There were no "concomitant changes in erythrocyte count or hematocrit." (Juskevich and Guyer 1990: 881)

[11] Dr. Juskevich did not review the studies, nor did she make the initial decision on the significance of the findings. She did, however, discuss the decision with the reviewer, and agreed with them (Juskevich 1998: personal correspondence).

regarded as biologically significant, the effect needed to fit several expectations. One, if an effect was apparent at a lower dose, it would also be expected at a higher dose; indications observed only at a lower dose level were therefore regarded as insignificant. Second, if the effect occurred in only one group of animals and not another, the effect was more likely to be assigned as a random effect. Third, since the drug has a variety of related effects, if a change is exhibited in only one parameter without the other concomitant changes in other parameters, it was not attributed to the drug. The reviewer's reading of these studies enabled her to differentiate between facts which were biologically significant and those which were insignificant; from within the paradigm, anomalies could remain anomalous, and further explanation was not necessary. Dr. Juskevich was aware that this method was problematic for the critics and the public; "because it's one of those things that almost seems like scientific magic, where you make things go away that you don't want to see, but it isn't, it's a time-worn method of going through these studies and determining what's statistics and what's real."

From her perspective, then, the critics' argument that increased IGF-I levels in the milk of rbGH-treated cows could present a human health risk was nonsensical; "there are postulations that make absolutely no sense based on what's known in particular areas of science. I thought the arguments they were raising were just out there somewhere." According to Dr. Juskevich, rbGH became a safety issue, rather than an economic issue, when Jeremy Rifkin became involved in the debate; it was then picked up by the media as a health issue. (At the 1986 hearings, Rifkin argued that the economic consequences of the drug's introduction were dire. He also expressed concern about adverse animal health effects. In 1989, he became more vocal on the human health issue; on the basis of health claims raised by Epstein, he and a coalition of farm, consumer and animal rights groups petitioned the FDA to ban the sale of milk from experimental herds. The petition was not successful).

From Dr. Juskevich's perspective, however, there are always more questions which could be researched; the regulatory scientist's job is to make a decision from the information she has available:

> I'm not saying that regulatory work isn't good science, but it's not the same mindset when you have to make a decision about something because otherwise you always end up with one more unanswered question and nothing would get approved, because you would always have one more unanswered question. I could say, for example, this drug causes liver damage, I'd really like to know what the mechanism of that is, but that's irrelevant for whether the drug gets approved or not.

(Dr. Juskevich wished to emphasize that this does not mean that reviewers act only on the available information if that information does not properly address safety concerns, but that irrelevant information would not be requested, e.g. if a drug caused liver damage, a decision could be made without understanding the relationship between the drug and the effect on the liver).

The scope of the studies, and the context in which they are interpreted, is therefore determined by existing knowledge:

> You can only design studies that you think are the most relevant to determining whether you're going to have any problems with something, and take the available information from the literature to get a picture of things. For instance, there's a lot of free IGF in saliva, so, if you believe that IGF is absorbed every time you swallow you increase your plasma levels of IGF. So, obviously then, it's not a problem, because if it were, you'd have all kinds of growth effects from doing that. This is not proof; but this is an indication that it's not a big deal. So when you look at quantities in saliva compared to milk, it's probably not going to be important. And there will always be people who will say it's that one extra molecule that's going to put you over the edge, and you can always make that argument, and I can never say well you're wrong, but based on logic it doesn't really make any sense.

Dr. Juskevich was aware of the effect of FDA decisions on the drug manufacturers. It was necessary to develop new guidelines for trials with protein hormones, not only to improve the accuracy of the scientific information, but to avoid requesting more studies from the companies when initial studies proved irrelevant to the reviewers' concerns.[12] "When we did go back to the companies and tell them we had to do another study they were not very happy. In fact I thought they were going to slit my throat." Dr. Juskevich

[12] The provisions of the 1996 Animal Drug Availability Act (ADAA) were intended to prevent this outcome by making an agreement reached at the presubmission conference binding.

distinguished between "reasonable" and "unreasonable" requests for further studies. Although she believed that scientists had to be assured about the validity of their decision, she also understood companies' frustration with the decision-making process and believed that requests must be kept within reasonable limits:

> I think it's unreasonable for the companies to say you can't keep coming back and asking us for information. But I understand their point of view because in some cases I think they feel it's hopeless; they're always going to be asked for more and more. I'd say if a scientist is being reasonable they are justified in requesting any additional studies. If, on the other hand, they're just off on their own thing, it's up to the supervisors to deal with that situation.

She also perceived that the IGF study would not be a useful one for the companies to carry out, because at the time IGF was not readily available, and so the companies were going to have to produce it themselves for use in the clinical trials. Since there were four companies vying to get to the marketplace first, producing the IGF and conducting the clinical trials was perceived as an additional competitive pressure. Monsanto, however, was prepared to meet the regulatory guidelines. Monsanto's toxicologist during the regulatory review period said that based on the company's review of the literature, he had anticipated the need for IGF-I studies prior to the FDA's request. According to the Monsanto's Regulatory Affairs Director, the company was able to direct its resources to meeting regulatory requirements because its personnel were not diverted by other biotechnology products (Kowalczyk 1997: interview).

Dr. Juskevich stressed that when the data is submitted, there is no company input into the decision-making process: "they may come and bring you additional information, but they are never involved in any decision about the adequacy of the study, or the interpretation of the study."

In order to draw a conclusion about human safety, Dr. Juskevich also considered information about the existing levels of IGF-I in milk, the effect of pasteurization and processing for infant formula, and levels in breast milk. It was found that IGF-I, unlike rbGH, is not destroyed by pasteurization. In order to determine whether increased milk concentrations would effect newborns fed infant formula, they examined the heat-treatment

process, and found that the growth factor was denatured, and hence unlikely to result in increased infant exposure (882).

Their summary of the FDA's review of the human health data was published in the journal *Science* in August, 1990. Juskevich and Guyer concluded that the use of rbGH in dairy cattle presented no increased health risk to consumers because rbGH was neither orally nor biologically active, and, although the concentration of IGF-I increased, human health would not be adversely affected because it was not orally active.

2.3. The critics' interpretation

The critics had raised concerns about IGF-I prior to the publication of the *Science* article. They also cited the counter-instances in Juskevich and Guyer's report as evidence that, contrary to the authors' conclusions, IGF-I was orally active. The British critic T.B. Mepham questioned their dismissal of these results, arguing that the counterinstances should be taken at face value, or the experiments should be repeated. Mepham calculated that if a 10 kilogram infant consuming one litre of milk per day were exposed to the highest concentration of milk IGF-I reported - 25 μg/litre - this would represent one-eighth of the dose shown to effect changes in clinical parameters in rats. However, since a safety margin of 100 times the dose effective in animals should be applied to human subjects, Mepham argued that infants would be exposed to 12.5 times the recommended minimum (Mepham 1992: 737).

Epstein repeated these claims in support of his argument that infants would be exposed to increased health risks. He posited that the introduction of rbGH would potentially lead to "premature growth stimulation in infants, gynecomastia in young children, and breast cancer in women" (1990: 80). He drew on the work of cancer scientists examining the role of IGF-I in the development of various kinds of cancer, including breast cancer, and advanced this position on the grounds that "[t]here is unequivocal evidence that a wide range of intact proteins are absorbed across the gut wall in a wide range of species including humans" (1996: 175). Epstein cited Juskevich and

Guyer's article, and another article on protein absorption. Juskevich and Guyer had acknowledged the evidence that proteins may be absorbed; antibodies to food proteins have been identified. However, they qualified this evidence by also noting that oral activity will only be displayed in proteins with low molecular weights or high specific activities, or both. Since both rbGH and IGF-I were significantly larger molecules than those proteins which are known to be absorbed, Juskevich and Guyer (1990: 876) believed it was unlikely that they could be absorbed intact. Epstein cited data from the Monsanto and Elanco Lilly studies presented by the FDA scientists as evidence which contradicted this conclusion, although Juskevich and Guyer had regarded these results as sporadic and not treatment-related. In contrast, Epstein claimed that the fact that a body weight increase in the rats occurred in only one group raised "questions about the validity of the experimental design"; and criticized the FDA for not providing data to support the conclusion that there were no increases in serum IGF-I of test rats (1996: 177). He also claimed that the presentation of the data were misleading, since the dosages of treated rats were administered in mg/kg, whereas the positive controls were infused with doses of mg/rat.

The Consumers' Union was also concerned about the IGF-I issue, and released its analysis in December, two days before the NIH Technology Assessment Conference was convened to address the issue. The author of the review, Dr. Michael Hansen, stated that:

> We believe that the FDA has not adequately addressed several major human health questions regarding bGH/bST use. The most critical of these relate to possible elevated levels of the chemical intermediary IGF-I and of antibiotics in the milk and meat of treated cows. (1990: 22)

The NIH was asked to convene a Technology Assessment Conference to address human health concerns associated with rbST in response to requests for a third-party review from parties associated with the diary industry and in response to public concern.[13] The Technology Assessment Conference on Bovine Somatotropin ran from December 5-7, 1990. The NIH, the National Institute of Child Health and Human Development, and the

[13] *Animal Pharm* reported that the review was requested by Senate Agriculture Committee chairman Patrick Leahy (1990: 12).

National Institute of Diabetes and Digestive and Kidney Diseases convened the conference. A panel reviewed the literature, assessed presentations from scientists, and heard comments from the audience. Not all of the animal health data were available, since the FDA's review was not yet complete. In examining the IGF-I issue, the NIH noted that:

> Milk from rBST-treated cows contains higher concentrations of IGF-I. The importance of the increased amounts of IGF-I in milk from rBST-treated cows is uncertain....Whether the small additional amount of IGF-I in milk from rBST-treated cows has a local effect on the esophagus, stomach, or intestine is unknown. (NIH 1991b: 1425)

It was suggested that further research should be conducted to "determine the acute and chronic local actions, if any, in the upper gastrointestinal tract." However, in a version of the report published in *Nutrition Reviews*, the panel also stated that "it did not consider that decisions on the commercial use of rBST should be delayed until these studies are completed" (NIH 1991a: 231). This would seem to imply that the NIH recognized the limitations of the FDA's mandate, and a distinction between "regulatory" and research science. The NIH concluded that "as currently used in the United States, meat and milk from rBST-treated cows are as safe as that from untreated cows" (NIH 1991b: 1425). In the draft of the report, the NIH had added that the FDA had a large body of data which was not available to the committee; it presumed that "an evaluation and analysis of this data will be forthcoming" (NIH 1991c: 11).

In the early 1990s, some studies (e.g. Olanrewaju et al. 1992) were published which provided evidence that IGF-I did not break down in the gut, and effected growth of cells in the gut tissue. A study by Olanrewaju et al. (1992) established evidence that the cells lining the gastrointestinal tract grew when exposed to IGF-I at levels equivalent to those in bovine milk (Epstein 1996: 180). One study also provided evidence that casein - a protein found in milk - protected another growth factor, epidermal growth factor, from digestion; this led to the inference that IGF-I in milk would be more likely to survive digestion than the growth factor alone. On the basis of this evidence, Epstein suggested that

rbGH- milk consumption could affect the risk of gastrointestinal cancer. He also cited the NIH report which advocated further research.

By 1994, most critics were no longer concerned that IGF-I might represent a breast cancer risk. However, they still had questions about the effect of elevated levels of milk IGF-I on the gut. The Consumers' Union research associate, Dr. Michael Hansen, stated that some of the questions about IGF-I had been answered during the NIH panel review, and, in a letter to *The Lancet*, Mepham and others stated that "IGF-I is unlikely to have systemic effects" (1994: 1446). However, the authors were concerned that milk from treated cows may have an adverse effect on the gastrointestinal tract, citing the Olanrewaju et al. study.

In 1995, a study by Xian et al. posited that casein may protect IGF-I from degrading during digestion. Critics had drawn on similar studies of epidermal growth factor to argue that IGF-I in milk may also be protected; this study provided evidence that this was the case. The Toronto Food Policy Council drew on this finding in its campaign against rbGH-introduction (Tabuns 1995: 1). In an interview, however, Xian has stressed the difficulty of drawing conclusions for human health on the basis of his studies (Xian 1997).

Mepham had also questioned whether the IGF-I in milk from treated cows may be more potent than that in the milk of untreated animals, citing Francis et. al. who had reported that bovine colostrum contains a truncated form of IGF-I (-3N:IGF-I) which, in animal experiments, was shown to be more potent than growth factor with a normal amino-acid sequence. This form of the peptide, however, is underestimated by standard assay techniques. Since, Mepham argued, the changes induced by bST may mimic those of early lactation, the more potent form of IGF-I may also appear in the milk of treated cows. Mepham's speculations about the potential changes in the structure of the peptide in the milk of treated cows were quoted by Epstein in the United States. Epstein, however, extrapolates from Mepham's work to suggest that current assay techniques result in a

"potential 40-fold underestimate" of IGF-I, considering that -3N:IGF-I is "10 times more potent" (1996: 175). Taking the highest level of milk IGF-I reported by Monsanto, 25 µg/litre, Epstein suggested that the consumption of milk from treated cows could result in a daily intake of "1000µg blood equivalents" since IGF-I in rbGH milk may be up to 40 times more potent than blood IGF-I (176). Epstein therefore criticized the FDA for administering recombinant IGF-I in the oral toxicity studies, rather than IGF-I from the milk of treated cows, which may be more bioactive.

2.4. Monsanto's interpretation

Monsanto's decision to proceed with the development of rbGH was also dependent on an initial assessment of the product's safety, which it based on conventional scientific knowledge and results from the short-term trials. The company had expected that because the product was a natural compound, there would be no human food safety issues, and the regulatory process would move more quickly (Kowalczyk 1997: interview).

When analyzing the two-week rat studies from Hazleton Laboratories, Monsanto scientists concluded that neither rbGH, nor IGF-I, was orally active. Monsanto scientists had examined the effects of IGF-I in what they believed was the worst-case scenario; when IGF-I was introduced as a bolus, directly into the animal's stomach, rather than periodically with food. One group of rats did show a statistically significant increase in organ weight; however, since this increase did not occur in the other block, company scientists concluded that the effect was not drug-related. The FDA concurred with this analysis. A toxicologist for Monsanto, Dr. Bruce Hammond, stated that the doses in the feeding studies were thousands of times higher than humans would be exposed to from drinking milk. He also added that:

> The levels of IGF-I in cows' milk are similar to the levels in human saliva and much less than the amounts in human blood (200ng/ml). Thus given the normal levels of IGF-I in human fluids that bathe human tissues, the contribution of IGF-I from consumption of milk if it could all be absorbed (which is highly unlikely since it is digested in the gut) is miniscule compared to the levels of IGF-I that naturally circulate in body fluids. (Hammond 1997: interview)

The *Science* article stated that IGF-I levels in milk from treated animals were up to 25% higher than milk from untreated cows. Monsanto, one the other hand, argued that more recent studies had shown that there is no significant difference in IGF-I concentrations. In support of this claim, Monsanto has cited a study by the Joint World Health Organization/Food and Agriculture Organization Expert Committee on Food Additives (JECFA) which stated that "the most definitive and comprehensive studies show that IGF-I concentrations are not altered after rbST treatment." (1993: 41, quoted in Collier et al. 1994). It has been noted that scientists at JECFA concluded that the weight of evidence indicated bST treatment did not increase IGF-I levels in milk.

2.5. The university scientists' interpretation

University scientists did not produce the human safety data on the oral activity of rbGH or IGF-I for Monsanto's FDA submission. However, Canadian university scientists at Guelph conducted studies for Cyanamid, and conducted their own studies on the bioactivity of milk from treated cows. (See Groenewegen et al. 1990) At McGill, scientists evaluated the IGF-I literature in their review of the drug's safety (see Burton et al. 1994). University scientists' expectations were informed by knowledge of the literature. At Guelph, Burton was not concerned about the safety of the product because there was no evidence in the literature that the hormone caused human health problems; for example the 1950s studies on bGH as a treatment for human dwarfism had not reported abnormalities. He also felt that "bGH/bST and the growth factors have been there as long as we've been drinking milk and haven't caused any identifiable problems."

University scientists also considered the effect of the drug's use on the nutritional value of the milk. In this area, there was agreement that the data showed a difference in nutritional composition between milk from treated and untreated cows; in order to assess the meaning of that difference, however, the experimental results were compared with milk from the existing supply. A food scientist at Cornell University, Dr. David Barbano, examined treated milk's nutritional composition as well as its processing characteristics.

When assessing the composition of milk from treated cows, Barbano began from the assumption that milk composition changes over the course of lactation, and compared differences in milk from treated cows to the fluctuation in milk from the population of untreated animals:

> The question was, given all that variation, when you use bST, are you going to be able to see some clear difference in that milk from what the normal variation is in the milk supply. That was the context in which we were looking at things and I think the important thing is if you make the assumption that all milk is the same all the time that is, from my point of view, the wrong starting point. Anything you look at with sensitive analytical measures you can probably come up with something that's a difference from a statistical point of view. But the question is does it make any difference to the consumer from a practical point of view? We didn't feel that any variation that you could detect in a controlled study would be of practical importance from the standpoint of well, should I stop drinking this milk because it contains so much less calcium? The answer is no, it doesn't change within a normal variation. (Barbano 1997: interview)

In the interview, Barbano applied this reasoning to IGF-I levels; an article he co-authored with a respected IGF-I scientist, Dr. William Daughaday, presented this viewpoint.

> IGF-I varies tremendously according to the stage of lactation. In early lactation, most individual cows have IGF-I levels in their milk that are 10 to 15 times the average level...The view at that time was that even though we could measure a difference, for the average consumer picking up a quart of milk it would be hard to measure any difference in the milk supply.

Like the Monsanto scientists, Barbano noted that more recent studies disputed the IGF-I increase; "I think since then there have been more reports that it's questionable whether there is an increase in IGF-I."

Critics, however, have rejected this comparison. T. B. Mepham disputed the position that IGF-I increases fall within a range of normal variation, noting that widespread adoption of the drug would lead to a mean increase in growth factor concentration. In support of his position, Mepham quoted the suggestions by the NIH and the American Medical Association's Council on Scientific Affairs that the effects of IGF-I should be investigated further. A review article by several Canadian animal scientists has also claimed that "the majority of studies to date...indicate that milk IGF-I concentration varies from 1 to 9 mL-l [litre] for untreated cows and is 25-70% greater for rbGH-treated cows" (Burton et al. 1994: 189).

2.6. Health Canada's interpretation

Health Canada's human health evaluation reached the same conclusion as the FDA. According to former Branch Chief Dr. William Drennan, when evaluating an animal drug, the primary concern is human safety; "if for any reason the Human Safety Division said no, this is a potential danger to humans, especially to children, it's not going to be marketed, that's it."

As in the U.S., it would appear that normal scientific understandings about proteins influenced the human health decision, which was made by the Chief of the Human Safety Division, Dr. Man-Sen Yong, who determined in 1990 that the use of the drug did not represent a risk to human health. Dr. Drennan accepted Dr. Yong's reasoning, and agreed that because the product was a protein hormone, "it had no potential for causing human health problems." He was aware that concerns had been raised about a human health risk from increased levels of IGF-I, but believed that there was no scientific justification for those concerns. Dr. Drennan claimed that Dr. Yong had resisted external pressure to change his decision, and admired him for his fortitude, because he believed that the human health decision *was* scientifically justified.

The *Globe and Mail* has reported that Dr. Yong's decision caused dissent within the Bureau, however. A scientist, who spoke anonymously, claimed that Dr. Yong did not show other human-safety reviewers the information on which he based his decision: "[t]he issue of IGF[insulin-like growth factors] has not been discussed. It's never been discussed [by human safety reviewers] never evaluated by anyone else" (Eggertson 1997: A10). The *Globe* reported that this case was undergoing mediation. It does not seem unusual, however, for a safety decision to be made by one individual; at the FDA, the decision was made by one reviewer, whose conclusions were supported by the Chief of the branch. At Health Canada, with fewer reviewers and resources than the FDA, the decision-making process does not seem unjustified; it does seem, however, that dissent has not been

adequately addressed. An internal review[14] of the safety decision stated that the oral absorption of IGF-I and rbST was not adequately addressed:

> Records indicate that the manufacturer of this product did not subject it to any of the normally required long-term toxicology experimentation and tests for human safety, nor at any time did the chief of human safety division, Dr. M.S. Yong, appear to have asked for these tests from this or any other manufacturer of rbST submissions.

In response, Dr. Yong wrote:

> There is no reason for more exhaustive and longer toxicological studies in laboratory animals just because rbST is a hormone. This statement reflects the team's prejudice against hormones in general and rbST in particular. (Eggertson 1998a: A6)

2.7. Cancer and IGF-I Research

Epstein made the association with breast cancer on the basis of studies which reported that elevated levels of IGF-I receptors were present in malignant breast tissue, and a study by Pollak et al. which reported that tamoxifen, a drug widely used in the treatment of breast cancer, reduces IGF-I levels in circulation (1996: 181). Since the 1980s cancer researchers have examined the relationship between IGF-I and II and certain types of tumours. In normal cells, growth factors play a role in stimulating cellular division (mitogenesis) via a "signalling pathway"; that is, they are involved in effecting a series of reactions within the cell which culminate in cell division. Growth factors also have mitogenic effects in malignant cells, in which the signalling pathway has been subverted in such a way that growth is no longer regulated as it is in normal cells (Aaronson 1991). It is known that some types of tumour are associated with high levels of IGF-I in circulation. What is controversial is whether growth factors *effect* malignant transformation and, if so, how. It is possible, for example, that these increased levels of IGF-I are an effect, rather than a cause, of tumour growth.

Pollak et al. have found evidence that some types of tumours require IGF-I in order for malignant cells to proliferate (1990), and believe this evidence is supported by further

[14] The internal review committee was comprised of two reviewers from the Bureau of Veterinary Drugs, one from the Bureau of Chemical Safety in the foods directorate, and one from the Therapeutics Products Directorate (human drugs) (Senate Committee on Agriculture and Forestry 1998).

studies which have identified IGF receptors in tumour specimens (1987). If this hypothesis is correct, Pollak believes therapies could be developed which may reduce the proliferation of IGF-I dependent tumours by reducing growth factor serum levels (Pollak 1996: interview). He has found that tamoxifen[15], a drug used in the treatment of certain types of breast cancer, reduces IGF-I serum levels by approximately 25% and has speculated that its therapeutic effectiveness may be partially attributed to this reduction. In laboratory studies, treatment with a somatostatin analogue (a drug which inhibits growth hormone secretion) in combination with tamoxifen resulted in further suppression of serum levels (Hung and Pollak, 1993: 121).

In experimental cancers, according to Stewart and Rotwein, there is "impressive evidence supporting a role for the IGF-IR [receptor]" including evidence that the receptor may stimulate cell division, prevent programmed cell death, and interact with oncogenes and other growth-factor signalling pathways. However:

> There are only correlative data demonstrating the importance of the receptor in human cancers....no studies have been performed yet that directly implicate the IGF-IR in the initiation or propagation of human cancers, nor have any therapies been initiated to test the hypothesis that IGF-IR function is critical for tumorigenesis in humans. (1996: 1018)

Several hypotheses have been advanced to account for the correlation between an overexpression of IGF-I receptors and the proliferation of malignant cells. One hypothesis suggests that tumours which exhibit the IGF-I receptor may depend on IGF-I in circulation to proliferate. Second, it is possible that malignant cells produce their own IGF-I (auctocrine secretion). There is some evidence that tumours produce both their own IGF-I and the corollary receptors, known as the "autocrine loop." Third, cancers which have an over-expression of IGF-I receptors may be hypersensitive to IGF-I in circulation (Pollak et al. 1987: 228).

Pollak's hypothesis is limited to tumours which respond to IGF-I in circulation (Pollak et al. 1989). It is not known what proportion of cancers are dependent on IGF-I.

[15] Tamoxifen is an anti-estrogen which binds to estrogen receptors in tissue and thus prevents estrogen binding (AHFS Drug Directory 1997: 862).

Lowering of growth factor levels cannot be expected to slow the proliferation of malignant cells which produce their own IGF-I. Pollak has limited his hypothesis, and qualified his statements about the role of IGF-I in cancer:

> Even if the hypothesis is true, it would represent an incremental step forward, it would not represent a cure for cancer. It would be another treatment that would be clinically useful. There are no scientific grounds for saying that if this is true, breast cancer will be a thing of the past. If it's true, we'll be able to help some of the women some of the time in non-trivial ways. It would not be like penicillin for breast cancer. (Pollak 1996: interview)

Pollak will investigate this hypothesis further over a three-year period in which he will test the effectiveness of the tamoxifen/somatostatin analogue combination - drugs which reduce levels of both growth hormone and IGF-I in circulation - in reducing the proliferation of breast tumours. Recently, Pollak has published evidence that men with high IGF-I levels have a greater risk of prostate cancer (*Maclean's Magazine*, 1998a: 58; Chan et al. 1998).

Research into the relationship between IGF-I and cancer would not be possible without thirty years of basic research which enabled the growth factor to be identified and its physiological function to be explored.

The hypothesis that growth hormone was mediated by another substance was first posited in the 1950s. Three separate lines of investigation developed to try to identify this substance and its mechanism of action. One group wished to explain an earlier observation which indicated that a substance other than growth hormone was necessary to effect certain types of reactions. In attempting to develop a bioassay to measure growth hormone excess or deficiency, a researcher had observed that cartilage uptake of sulfate was not stimulated by serum from growth-hormone deficient rats, nor by growth hormone itself; after the rats were injected with growth hormone, however, their serum *was* effective. This suggested that a factor which was dependent on, and distinguishable from, growth hormone could induce certain types of activity; it was termed "sulfation factor activity" (SFA). Another group discovered that bioassays for insulin measured far more insulin-like activity than could be explained by levels of insulin measured by radioimmunoassay; this activity could not be suppressed with antibodies, so the group defined it as "non-suppressible insulin-like

activity" (NSILA). A third group identified a substance which promoted the growth of cells in culture as multiplication-stimulating activity (MSA). The term somatomedin, which implied GH regulation, was agreed upon in 1972 to refer to the substance which had displayed this range of activities (Sara and Hall, 1990: 591; Van Wyk 1997: interview). The peptides have been referred to as IGFs since 1987 as a result of the discovery that IGF-II was not directly regulated by growth hormone (Sara and Hall 1990: 592).

The scientists I spoke to who were involved in basic or medical research had not been aware of the controversy surrounding rbGH while they were conducting their own investigations. They had not considered questions about the safety of rbGH because their own work was not motivated by the controversy. In conversation, none of the scientists thought it likely that rbGH posed a human safety risk, either because they assumed it would be broken down during digestion or because even at elevated levels, the amounts of IGF-I in milk would be too small to cause systemic effects.

In fact, Dr. Harvey Guyda, a paediatric endocrinologist at McGill University, has objected to Epstein's statements because he believes that the concentration of IGF-I in milk from rbGH-treated cows is too low to be biologically active in humans and is indistinguishable from untreated cows, and because the level of IGF-I in circulation implies very little about the growth factor's local activity; "to talk about the concentration of IGF in blood or milk is really silly because it has little relevance at the tissue site of action." (1996: interview) In Guyda's view, the complexity of the system, and the amounts of IGF involved, make it extremely unlikely that IGF-I concentrations in milk would have any adverse effects on human health.

> IGF is digested in milk and is therefore subject to proteolytic degradation. There's very little evidence that very much IGF survives although some data suggest that there may be some there, but we're talking about concentrations that are not very biologically active, usually less than 10 micrograms per litre; occasionally a very sensitive system will respond to less than 10, but very few. So you're talking about something that even if it weren't digested, what would be left would be of such low concentration that it's unlikely to have a significant impact. That's the main argument from the scientific point of view about the whole IGF furor, and people like Rifkin et al. are just blowing it up without any scientific background. It's fear-mongering. My works linking IGF to breast cancer then get transposed to bST

> hysteria and nobody's stopped to think what are we talking about here? We're talking about small amounts of a very potent peptide, certainly, but the concentrations are so small, and not any different in the treated or untreated state, that it wouldn't have any major impact in my opinion. (1996: interview)

At the request of the Canadian Animal Health Institute (CAHI), Guyda agreed to be on a "speakers' list" of experts who could be contacted for comment by the media or other organizations, and spoke at the Canadian House of Commons committee hearings into the drug's impact in 1994.

Dr. Judson Van Wyk, who had identified IGF-I as a growth hormone mediator, did not expect that the use of growth hormone would lead to adverse human health effects. However, he added that:

> There should be some concern about indirect effects produced by substances stimulated by rbGH in cattle and secreted into their milk. Mediators, such as IGF-I, are active in humans, and, because of their smaller molecular weight, could get across the gut and cause biological effects in humans. If there is a problem, this can best be determined by long term studies of animals reared on milk from cows treated with rbGH. Such animals should be studied to see whether they have abnormal growth or a higher incidence of teratological effects [birth defects] or cancer. I don't expect to see any adverse effect or any other detectable difference from control animals; however, that's the only kind of study that would address such concerns, since it would gloss over mechanisms and tell us what is the net effect. (Van Wyk 1997: interview)

Dr. Edward Seidel, one of the authors of the Olanrewaju et al. report, was concerned that conventional assumptions about protein digestion and absorption may not be correct, and that further experimental work needed to be done in order to demonstrate the validity of these assumptions. Seidel's work focuses on the growth and proliferation of gastrointestinal mucosa. He has posited that the FDA's measurement of gross organ weights were not sensitive enough to measure a growth response in the lining of the gastrointestinal tract; gross organ indices only detect massive changes.

> Measuring organ weight is not a sensitive enough method to look for a trophic [growth] effect. You've got to take the tissue apart and examine it. They would never have found the answer they were looking for by weighing gastrointestinal tissue; they'd have to get a massive response. (1997: interview)

In the Freedom of Information Summary, the FDA stated that on microscopic examination, the gastrointestinal tract of orally-treated rats was not different from that of normal rats

(FDA 1993d: Section 7c). To accept this conclusion, which differs from that of his own studies, Seidel wanted to see more information about how the experiment was conducted and what methods of measurement were used (Seidel 1997: interview).

Scientists engaged in basic and applied medical research proceeded differently than regulatory scientists. Clinical scientists' work was usually based on clinical findings, and it aimed to explore unresolved questions which had been overlooked in mainstream science. Alternately, it brought separate bodies of theory together which had not previously been linked. Scientists engaged in basic research emphasized the importance of collaboration for the progression of their work. Those working on the development of cancer therapies also stressed the importance of collaboration. However, collaboration with the private sector seemed to be more significant than in the past, because the drugs being administered were supplied by the pharmaceutical industry; whereas government funding had previously subsidized the development of hormones used in research.

Basic research into the mechanism of IGF action was inspired by puzzles which remained from earlier findings. The sulfation factor assay, which had provided evidence that growth hormone was mediated by another factor, was replaced by a radioimmunoassay for GH in the early 1960s; however, scientists at the University of North Carolina at Chapel Hill, one of the centres of IGF investigation, felt that the phenomena identified by the earlier assay had not been adequately explained (Van Wyk 1997: interview). Scientists at McGill University wanted to explore IGF-II physiology because they felt this area was still open for investigation; other centres had already focused on IGF-I (Guyda 1996: interview). At East Carolina University's School of Medicine, the examination of the effects of IGFs on gastrointestinal mucosa was partially inspired by questioning of accepted scientific wisdom about protein digestion, which argues that large proteins are broken down in the digestive system and cannot therefore be absorbed directly into the blood stream:

> For years it was thought that large proteins were degraded in the lumen of the stomach which has an acid pH and would be precipitated out of solution and their

> structure destroyed by the acidic environment. That turns out not to be the case; all these peptides are extracted in acid, they're very acid-safe. So they're not destroyed in the lumen of the stomach under acid conditions there. They reach the small intestine and they may well be digested there by pancreatic digestive enzymes secreted in the lumen of the gut. ...I would predict that they would be degraded in the small intestine, but I'm not sure anyone has looked at it carefully and *shown* that they're degraded in the lumen of the small intestine. (Seidel 1997: interview)

Usually, the medical researchers' hypotheses were initially based on clinical observations. Guyda's work at McGill started from this basis; Seidel's research began in response to observations by the surgical group, which suggested that something which came out of the pancreas along with bile from the liver had a growth-inducing effect on the cells of the small intestine. His research group had been working with IGF-I as a growth factor to stimulate the cell line they were examining, and decided to determine whether IGF-I was present in these pancreatic secretions. In Dr. Pollak's case, epidemiological evidence spurred his own experiments; he was trying to link existing, but currently separate, bodies of epidemiological and experimental knowledge. Epidemiological evidence suggested that, for example, the peak incidence of osteogenic sarcoma (bone cancer) is during the teen years; Dr. Pollak linked this to the pubertal rise in IGF-I, and this clinical clue suggested the possibility that IGF-I was related to cancer. Experiments with transgenic mice provided further evidence in support of the hypothesis that cancers need IGFs for their well-being. Human cancers grown in IGF-I deficient mice demonstrated that some cancers cannot proliferate as easily in this environment. To investigate his hypothesis further, Dr. Pollak performed tissue culture experiments, growing tumour cells with or without IGF-I, and then began treating animals with drugs which lowered IGF-I serum levels. The animals had been genetically altered to express human tumours.

Clinical scientists also mentioned the role of chance in determining the outcome of their research. The McGill group's work examining the effect of tamoxifen on IGF-I levels came about through "happenstance" - a chance observation that patients taking tamoxifen had lower IGF-I levels than those in the control group:

> So, there's no plan. Dr. Pollak had this question and we had this technology and we put it together. That's how a lot of research takes place; a fortunate association of technology and ideas. (Guyda 1996: interview)

Technological availability was extremely important. Guyda and others explored the above observation further in a series of *in vitro* experiments to examine the effects of tamoxifen on GH and IGFs. This line of investigation could only be pursued because microbiological tools were available (Guyda 1996: interview).

Collaboration, and learning from the work of other researchers, was also important in developing scientists' understanding of the structure and function of IGF-I. Breakthroughs in the Chapel Hill group's work came as a result of collaboration with others, or through reasoning by analogy from other groups' discoveries. Judson Van Wyk took an initial hypothesis that the substance was bound to something in the same way that haem is bound to globin, and spent a year's sabbatical at the Karolinska Institute in Sweden, trying to purify the substance by separating ligands (growth factors) from carrier proteins. The method used to isolate insulin, an acid-ethanol extraction technique, was successful in purifying the substance. It was his associate who discovered that the substance they had been purifying also showed insulin-like properties; this discovery linked their work to that of the Swiss group who were investigating insulin-like activity. The Chapel Hill group's work accelerated further after publication of an article on the structure of nerve growth factor (Bradshaw et al. 1974), demonstrating that this factor had an homology with insulin. This led members of the group to ask whether the factor they had identified as "somatomedin" also had an homology with insulin; the easiest way to do this was to determine if somatomedin interacted with the insulin receptor. They were able to demonstrate that it cross-reacted with the receptor, and that there was no insulin in the material (Van Wyk 1997: interview).

Van Wyk regarded the involvement of others, particularly the physician and Ph.D. investigators in his training program, as essential to the development of his work, because the research direction was guided by their questions and concerns. Since 1962, the training

program has been supported by an NIH training grant shared with the Department of Medicine. Funding for the training program had a catalytic effect on research at Chapel Hill. According to Van Wyk, the involvement of clinician investigators is critical to the development of research because medical training is shallow, but broad; Ph.D. research, on the other hand, is more deeply but more narrowly focused. The combination of both forms of training was, in his view, ideal for medical research. He was concerned that changes in health care funding would adversely affect basic research:

> It's hard to get U.S. residents to be interested in basic science. It's not just here; it's everywhere. I think it's going to be a tragedy if we continue the flight of physician investigators into HMOs and practice plans - they discourage this kind of research - and specialty training. (Van Wyk 1997: interview)

Security of tenure and funding was also important for research progression. A lifetime research professorship enabled Van Wyk to continue working on the IGF project even in periods when research was not yielding any apparent results. An NIH research grant funded research into the effect of hormones on children's growth; the training grant supported the work of physician and Ph.D. investigators in the program (Van Wyk 1997: interview). Similarly, in Canada, National Research Council funding supported IGF-II research at McGill University, and subsidized the production of the peptide, which the McGill group supplied themselves in order to carry out research (Guyda 1996: interview). The East Carolina scientists' work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the NIH, and the North Carolina Institute of Nutrition. Scientists at the Cooperative Research Centre for Tissue Growth and Repair, Adelaide, Australia also supply the growth factor for their own research; their funding is provided by the Australian government (Xian et al. 1995: Xian 1997: interview).

Collaboration for cancer researchers in the 1980s involves relationships with the private sector and is partly the outcome of reduced government funding. Harvey Guyda stated that it enabled the researchers to gain access to the technological expertise necessary, for example, to culture cells *in vitro*, to isolate the peptides or to look at the receptor levels in the sample (Guyda 1996: interview). Pollak collaborated with scientists at Jackson

Laboratory in the U.S. in order to be able to use mice from the facility, and with other clinicians in order to carry out the clinical trial. In order to test a drug's therapeutic potential, he needed to collaborate with pharmaceutical companies. Basic researchers, who had manufactured their own supply of research material, did not appear to rely on pharmaceutical industry support to the same extent.

Collaboration was not instantaneous, but required active lobbying. Pollak had to convince clinicians that the hypothesis was clinically relevant; and the pharmaceutical industry that their product was potentially effective in order to have a supply of drugs for testing. He saw his action as lobbying "not to convince them that this was the answer, but just that it was a worthwhile question." On why the pharmaceutical industry was important, Pollak commented that:

> You can't run a clinical trial without a drug. No-one else but the pharmaceutical industry can manufacture the drugs, so you have to work with a drug company if you want to work with drugs. As it turned out, the drug we wanted to work with already exists, so my job convincing them to get involved and finance it was not as difficult as if they had to invent a new compound, there was already one we know reduces IGF-I levels in breast cancer. It was invented by basic scientists, but the first clinical application was in acromegaly...When it was invented the last thing they were thinking of was breast cancer. It does not represent the optimum way of lowering IGF-I bioactivity; but it represents an immediately available, practical and safe way to do so. (1996: Interview)

All the scientists acknowledged the difficulties of extrapolating from their experimental work with cell lines or animals to the human population. In Pollak's view, the clinical relevance of the hypothesis cannot be definitively determined until a long-term human trial has been conducted. This trial is currently in progress; in 1996, Pollak obtained $3 million from the National Cancer Institute of Canada for a cross-Canada trial with 800 women over nine years to test the efficacy of breast-cancer drugs which reduce serum IGF-I concentrations (1996: Interview). Xian found that casein had a protective effect on IGF-I *in vitro*, but could not predict whether drinking milk would protect it from digestion (1997: interview). Guyda stressed that his publications qualify the implications of his research because:

> What you measure in the circulation may not reflect at all what's going on at the cell surface. The action is much more localized within the tissue itself, than what's in the plasma - which is the only thing you're able to measure - is just serving as a reservoir delivering peptides to the sites, but whether they act may depend on the particular concentration on an active receptor. (1996: Interview)

As noted above, in Guyda's view the complexity of the system means that adverse effects are unlikely to result from the consumption of milk after rbGH treatment.

2.8. Other human health concerns

IGF-I has been the major human health concern. However, the nutritional composition of milk, and other consequences of the drug's introduction not examined by regulatory bodies have also been discussed. Juskevich and Guyer (1990) concluded that rbGH treatment did not have a significant impact on the nutritional quality of milk. Kronfeld (1989: 288) and Mepham (1992) have questioned the conclusion that milk from treated cows has the same nutritional value as that from milk in its current form. Mepham (1992) and the Toronto Food Policy Council (City of Toronto Board of Health 1991: 4) have also argued that rbGH could have negative consequences for public health if the public reduced its dairy consumption in order to avoid products from treated animals. Mepham's concerns about dairy consumption were based on European Community surveys of consumers' attitude toward biotechnology, in which respondents reported that they believed genetic engineering may involve risks to health and the environment, and that they did not trust information about biotechnology which came from industry. Since most of the information about rbGH came from industry or industry-sponsored sources, Mepham expected a consumer backlash against milk if the product were licensed. The rejection of milk would lead to reduced calcium and nutrient intake - possibly effecting an increase in osteoporosis - and substitution with less nutritious beverages, containing more sugar (1992: 738).

Dr. Michael Hansen from the Policy Institute of the Consumers' Union has also raised the possibility that the drug's approval could hasten the spread of bovine spongiform encepalopathy (BSE), also known as "mad cow" disease. Hansen claimed that treated

animals require more energy-dense food than those not treated, and that rendered cattle were used to supplement the energy- and protein-density of feed. Hansen acknowledged that there were no reported cases of BSE in the United States, but argued that the existing BSE surveillance plan may not be identifying the population most at risk.[16] In the U.S. 100, 000 cows simply keel over and die for no apparent reason ("downer cow" disease); Hansen pointed to a study from which it could be inferred that this disease may be a variant of BSE.

2.9. Summary

The consensus on human health was that although rbGH treatment led to higher milk IGF-I concentrations, it was unlikely to have any adverse effect on human health, because neither the growth hormone, nor the growth factor, were likely to enter the body in sufficient quantities to exert any effect on human tissues. Although there was little disagreement across institutions about the likelihood of human health problems arising, there were differences between them regarding the premises on which this conclusion was based. Different institutions came to different conclusions regarding whether or not milk IGF-I concentrations increased; whether the growth factor was orally active, how much more research should be conducted to determine this, and whether existing regulatory practices were sufficient to establish the interpretations reached.

In addition to the rbGH debate, the debate about the role of IGF-I in the development of human cancer was also complex. Each site of investigation contended with scientific complexity and uncertainty. Cancer scientists have determined that some tumours are dependent on IGF-I; however, it is not known how many more may be influenced by growth factor levels, nor what the relationship is. Basic scientists have understood much regarding the role of IGF-I, but its relationship to other growth factors and hormones is still being explored. The idea that large proteins are broken down during digestion is

[16] According to Hansen, "the only two risk categories of cows sampled are rabies-suspect cattle that are rabies negative, and cattle over two years of age that have been given protein supplements for a good part of their diet and have developed signs of neurological disease." (1993: 9)

accepted, but some research has indicated that other proteins may affect this process, and led to the suggestion that this assumption should be questioned further.

In a public controversy, however, ambiguities and social and experimental constraints are less likely to be acknowledged. This is partly a function of regulatory requirements, which prescribe that products must be determined to be "safe" or "unsafe". It is also a function of the commercial ownership of scientific data. In order to release scientific data, the regulators must obtain the consent of its proprietors, the manufacturers and university scientists. Under these circumstances, not all the data will be released, calling into question the validity of the statements based upon it.

3. Animal health

The major animal health issues were mastitis, a bacterial infection which causes inflammation of the cow's udder, reproductive problems, and lameness. By the time the drug was approved in the U.S., it was almost universally agreed that rbGH treatment correlated with an increase in the incidence of these diseases. What was controversial was the extent of the increase, whether it could be directly attributed to the drug, and whether farmers could manage it. Critics argued that the increase was an animal welfare, and hence an ethical, issue, and that the management debate did not adequately address welfare concerns. As noted above, animal health also has a human health dimension. Although this was publicly examined in the U.S., the scope of the question was limited to antibiotic residues in milk. In Canada, however, dissenting scientists have been more concerned about increased antibiotic resistance.

3.1. The FDA's interpretation

In order to avoid releasing proprietary information, the primary reviewer of Posilac, Dr. Suzanne Sechen,[17] described the general process used by the Center for Veterinary Medicine scientists to advise drug sponsors on appropriate designs of studies to evaluate

[17] Dr. Sechen became the primary reviewer for rbGH in 1988, after competing a Ph.D. in animal science at Cornell. She was also an intern at the FDA in 1986.

the efficacy and animal safety of investigational drugs.[18] Like the reviewers of the human health data, reviewers of efficacy and animal health data relied on their training and scientific knowledge when deciding what kinds of studies should be undertaken. This knowledge included an understanding of "dairy management, the physiology of milk production, and what kind of changes might occur as a result of a production drug." They also relied on their knowledge of dairy farming to form judgements about "what farmers would need to know about the effect of such a product on their animals." Reviewers typically have Ph.D.'s in animal science and/or statistics, or they have Doctorates in Veterinary Medicine. Graduate school training includes research in their particular areas of expertise, such as animal nutrition, reproduction, physiology, or genetics. Veterinarians at CVM gain clinical experience during their training. Some reviewers also have gained scientific/veterinary knowledge through employment prior to joining CVM. Some reviewers have additional farming knowledge from their own experience of growing up on a farm, and from their experience with investigational herds during their animal science training or prior employment. Center scientists and veterinarians also continue to attend scientific and/or veterinary conferences in their areas of expertise to remain current in their knowledge. The Center also consulted with animal scientists in academia; the mastitis addendum to the Technical Assistance Document (TAD) was prepared by a subcommittee of the Research Committee of the National Mastitis Council. As Dr. Sechen explained, "we're free to contact anyone as long as we're not relaying proprietary information." Although the reviewers could not speak specifically about a particular product, it was commonly known that rbGH was under review; "everyone in the dairy science community knew...because the companies had been very public." In Dr. Sechen's view, consultations with the academic community helped to fill gaps in the reviewers' knowledge and to keep them updated on scientific developments:

> While I have a pretty good understanding of all areas of dairy science, my training had been in nutrition and metabolism, and I was not as strong in reproduction and

[18] In order to avoid releasing proprietary information by specifying details of the rbGH case.

> health, so I might call professors that I know in dairy science with expertise in this area and say we are evaluating production drugs in dairy cows and what are the important things we should look for, we're trying to decide what needs to be looked at in these studies.

In judging what kind of trials should be requested, reviewers sought a balance between obtaining scientific information and allowing for experimental ease. "You have to make a happy balance where you're getting the information you need, that will be of practical importance to the users of the drug, but you're also not making the study so complicated that it's impossible to run." Since a number of variables were being examined in each study, reviewers had to ensure that the collection of data on mastitis, for example, would not interfere with the gathering or interpretation of reproduction data or vice versa.

Another consideration was ensuring that the trials reflected "actual dairy practice." So, for example, the FDA might accept data from clinical trials in which extra-label drugs i.e. drugs which are not used in a manner consistent with FDA-approved labelling, if use was not excessive, if records reflected that a veterinarian was directly involved in the decision to use the drug, and if the prescribed extra-label use was considered reasonable for the health condition recorded. At the time that the pivotal studies for Posilac were being conducted, FDA provided regulatory discretion to U.S. veterinarians prescribing extra-label drugs under such careful conditions.[19] Thus, FDA accepted studies for Posilac in which extra-label use of drugs was considered consistent with accepted practices on U.S. commercial dairy farms. The use of prostaglandins and gonadotropins (sex hormones approved by the FDA for use in dairy cattle to regulate reproduction) was permitted in clinical trials, but usually only after a specific waiting period after a cow calved. During the waiting period, a more direct influence of rbST on reproduction could be evaluated. After the waiting period, if these hormones were used, their efficacy while cows were on rbST treatment could be evaluated. According to Dr. Sechen, "we wanted a controlled study but we also wanted to be realistic, to reflect the real world, so this was a way to balance that."

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[19] Furthermore, the 1994 Animal Medicinal Drug Use Clarification Act (AMDUCA) affirmed the FDA's position and legalized such veterinary prescriptions.

Dr. Sechen regarded the evaluation of Posilac as "a learning process" for the FDA, in which the reviewers' ideas might be modified as results came in and were evaluated. This gained knowledge then had an impact on the design of subsequent protocols submitted for future investigational studies for dairy production drugs:

> The FDA and the companies initially didn't have a lot of experience in evaluating dairy production drugs.[20] In particular, deciding how to record and analyze health data, e.g. daily health observations, was challenging because dairy scientists tended to perform less research in this area than for example milk production, nutrition, and reproduction. Also, unprecedented large amounts of data were recorded and needed to be analyzed because pivotal studies evaluating production drugs are usually considerably longer than studies evaluating production drugs for other food-producing animals because of the longer productive life of dairy cows. It was a learning process for us and for the companies at the time.

The companies were able to challenge the reviewers' requirements, and the FDA would accept a company's recommendations if they were scientifically justified and still allowed a valid evaluation of the investigational drug. Company scientists could argue against the FDA's recommendations, or suggest that an aspect of the studies be conducted differently:

> They're the ones doing the research out there, they might be a little more current on things and if they can come in and present a solid argument for doing something differently than we recommend then we'd think about it and if it makes sense we'd accept it. So we learn from the companies as well.

Dr. Sechen expressed this relationship as:

> An exchange of scientific opinions, typical of what occurs in any type of scientific organization. However, the FDA does have the final decision, and so while a company is certainly permitted to argue at length about any of our requirements, if we're not satisfied with their justifications, we don't accept their argument.

The studies evaluated by the FDA's Center for Veterinary Medicine were conducted by Monsanto at two sites in Missouri, and at several land-grant universities[21] in the U.S.: Arizona; Cornell; Florida; and Utah.[22] An efficacy study was also conducted in Idaho, and

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[20] Dr. Sechen added that the FDA has had a lot of experience reviewing production drugs for non-dairy species (e.g. beef, poultry, swine).

[21] A further discussion of the role of land-grant universities can be found in Chapter Two.

[22] Subcutaneous (SC) dose response studies were carried out at four sites: Arizona; Cornell; Florida; and Utah, and the company's site at Dardenne, Missouri. Intra-Muscular (I-M) Single Dose studies took place at Arizona, Cornell, Utah, and Dardenne. The Multi-Lactation Chronic Animal Toxicity Study (TAS), 14-day Drug Tolerance Study, and I-M/SC Bridging Study were conducted at Dardenne, Missouri; and the IM-Dose Titration study at French Village, Missouri. Injection-site reaction studies were conducted at several locations. Injection-site reaction studies at Vermont were elevated to pivotal status.

an injection site reaction study in Vermont. (Studies must be conducted at least three different geographical locations). Once the Investigational New Drug Application has been approved, the company submits a New Animal Drug Application (NADA) and further testing takes place to determine drug safety and efficacy. Studies in support of this application evaluated the company's claim that the drug's use would increase the production of "marketable" or "saleable" milk; that is, milk which does not contain drug residues (such as antibiotic residues) above the FDA-established tolerance level.[23] (FDA 1988)

Animal safety data were compiled from several sources. Traditionally, the FDA required that companies conduct two key studies to determine the safety of an animal drug: an acute toxicity study, a controlled study in which a small number of animals receives up to 25 times - this was later reduced to 10 times - the expected dose for up to 14 or 28 days; and a chronic toxicity study or 1,3,5X in which one, three, and five times the highest expected dose is administered. For Monsanto's product, Posilac, a 14-day Drug Tolerance Study (30X) in which 30 times the expected dose was administered to the animals; and the Multi-Lactation Chronic Animal Toxicity Study in which one, three, or five times the unit dose[24] was administered over two lactation periods (FDA 1988 Section 6b). By giving exaggerated doses of the drug, the 14-day study is intended to highlight any potential safety problems, which can then be investigated further in other safety or efficacy studies. By 1988, the data from the first set of Monsanto safety and efficacy trials had been submitted.[25] In response to the data, the Agency decided that further safety data regarding treated animals' reproductive performance and mastitis incidence should be produced from observations and milk sampling carried out during the efficacy studies (FDA 1988: 1). The protocols for both the efficacy and animal safety studies specified that each animal should

[23]The increase was determined for 3.5% fat-corrected milk (F.C.M.) - that is, for milk which has been standardized to a 3.5% fat content (FDA 1993d: Section 5).

[24] A "unit dose" is 600 mg, or 1.2 times the intended commercial dose of 500 mg (FDA 1993d: Section 6b).

[25] The first Monsanto data submission was made in 1987 (Collier 1997: interview).

be examined every day and any unusual health observations recorded (Sechen 1997: interview). According to Dr. Sechen, the most valuable animal safety data came from the efficacy studies because animals in efficacy studies are managed under conditions more likely to be encountered at commercial dairy farms. Much more animal health data are obtained at doses of the drug likely to be approved because of the larger number of animals used in efficacy studies. As a consequence, the 1,3,5X study is no longer required for production drugs.

The animal health critic, Dr. David Kronfeld, has stated that these methods could not adequately determine the safety of the product. Routine toxicology testing did not identify any specific effects for rbGH; instead, common ailments became more prevalent. The FDA decided to examine health observations recorded during the efficacy trials, but Kronfeld believes that this decision did not enable the Agency to obtain a conclusive result for the effects of the drug on mastitis and reproductive health because efficacy trials were not specifically designed to examine these variables:

> Once the specific toxic effects and the increase in nonspecific adverse effects became known in 1987, the FDA had a choice: to initiate specific safety experiments designed for BST, or to elaborate observations on health obtained in efficacy protocols. The FDA has chosen the latter. (Kronfeld 1994: 116)

The FDA used data from trials testing two routes of administration[26] (FDA 1993d: Section 6c). Animals were blocked separately according to parity. ("Parity" refers to the number of times a cow has calved. At the birth of the first calf, a cow is defined as "primiparous"; with second and later calvings, "multiparous.") Cows were expected to respond differently to the drug according to parity, because cows which have given birth once are still growing and have a different lactation curve than multiparous animals (FDA 1988: 1).

The reviewers had to be particularly careful with the accuracy of the recording, summarization, and analysis of animal health data which were obtained from the animal

[26] This was done after a bridging study was conducted to ensure that the animal's levels of growth hormone were no lower in the studies where the animal was injected into the muscle than the studies where the animal was injected under the skin. On the basis of the I-M study, it was concluded that "the I-M route of administration produced a greater response to circulating somatotropin than did SC administration." (FDA 1993d: Section 6c)

safety and efficacy trials. Dr. Sechen added that the CVM now asks for much more detail in the sections of the protocols describing proper data collection procedures and in the examination of pivotal data because of problems with the authenticity and/or accuracy of data submitted by the companies: "the fact that we are very careful in that section of the protocol...there were reasons for us to be that specific. Maybe it was this company [Monsanto] maybe it was another company. I can't be specific, but it's the fact that we are very careful with that section of the protocol." It would appear that the Center was able to detect when data were not completely accurate. According to Dr. Sechen, "not a lot of people have the knowledge to do it the way we want." Dairy scientists traditionally had conducted less research in the area of general health observations. However, the CVM had designed an approach to summarizing and analyzing health data under categories of major body systems and subsystems. According to Dr. Sechen, this approach allowed the Center a more organized approach to evaluating health effects of the investigational drug and appropriate labelling of the product if it was approved. A veterinarian in the division asked the company to re-analyze the health observation data under eight major categories, e.g. circulatory, respiration, reproduction, digestive, musculo-skeletal - which were then broken down into sub-categories, e.g. particular organs. Results were then analyzed at three levels. For example, if a particular health problem emerged, it would be classified under one of the major categories, a sub-category, and at the level of the observation itself. This type of "grouping" of observations in the analysis allowed both the detection of significant occurrences of individual health effects, as well as whether there were trends for multiple adverse effects occurring with a specific system and/or organ.

Analysis began when data had been submitted. Data from the acute toxicity study, the 1,3,5 X animal safety study, several efficacy studies, and additional pivotal studies formed the animal safety and efficacy package. The combined efficacy trials were regarded as one study at four locations. The first lactation information from the 1,3,5X study was

allowed to be submitted separately in order to draw preliminary conclusions before the second lactation data were submitted.

In order to evaluate the effect of drug treatment on the incidence of clinical mastitis, subclinical mastitis, and somatic cell count (SCC), which measures the leukocytes (white blood cells) in milk[27], the FDA analyzed the data from individual trials, and pooled the data from eight trials.[28] Data were pooled because there were not enough animals in individual trials to draw reliable conclusions from the data. Clinical and subclinical mastitis data from the Utah trials were excluded from the pooled analysis, since the infection was rarely treated at this site, thus confounding the effect of treatment. The long-term animal toxicity study was analyzed separately because of the higher dose administered. Mastitis incidence was analyzed separately according to parity, controlling for parity, or by ignoring parity. When controlling for parity, the FDA found that a treated animal had a relative risk[29] of 1.79 times that of a control animal of showing signs of mastitis. In the *Technical Manual* for Posilac, Monsanto reported that in the eight U.S. studies there were 147 cases of mastitis in treated cows, compared to 64 cases in the control group.[30] (Some animals may

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[27] Somatic cell count is measured as an indication of risk for mastitis; a higher count indicates a greater risk. However, the relationship between SCC and mastitis is not necessarily direct; a high count may indicate that the immune system is protecting itself against mastitic organisms (Burton et al. 1994: 183).

[28] The trials were:
Multi-Lactation Chronic Animal Toxicity Study (TAS)
Multi-Location SC Dose Response Clinical Study (4-Dose SC)
Multi-Location I-M Single Dose Study (Single Dose I-M)
I-M Dose Titration Study (Dose I-M)
I-M/SC Bridging Study
For clinical mastitis, data from the 4-Dose SC, Single Dose I-M, Dose I-M and I-M/SC studies were pooled. Data from the TAS study were excluded because doses higher than the intended commercial dose were used. For sub-clinical mastitis, data from the 4-Dose SC were pooled with the I-M/SC and Dose I-M study. I-M and SC studies were pooled separately for SCC analysis.
Mastitis was detected by forestripping milk onto the floor prior to milking. Observations of abnormal milk were noted, and milk samples taken from the infected animal. Subclinical mastitis was detected in milk samples which were taken and cultured once during the pre-treatment period, and at eight-week intervals during the treatment period. SCC was determined by examination of milk samples taken once a week throughout the study.

[29] Cochran-Mantel-Haenszel (CMH) measures of general association were used to test for association. The case rate was defined as the number of clinical mastitis cases per quarter per cow-day, when a new case could be observed; that is, the number of days in which a cow had an infected quarter (an udder has four quarters). A case was classified as "new" if a new pathogen were identified or if 21 days had elapsed since the last observation of infection (FDA 1993d: Section 6j).

[30] 253 cows were in the treatment group, and 234 in the control group.

have had more than one case of mastitis). In the control group, 17.5% of cows were affected, compared to 29.6% in the treatment group.

The Agency concluded that treatment increased the risk of clinical and subclinical mastitis in both parity groups and increases milk SCC in some herds. It also noted that rbGH cows were treated more frequently with medication, including medication for mastitis. However, when mastitis incidence was examined on a per-milk basis, the effect of the drug was less than the effect of other factors such as season, parity, stage of lactation, and herd-to-herd variation (FDA 1993d: Section 6j). The FDA recorded data on the average duration of cases of mastitis in control and sometribove-treated cows and concluded that the increased total days affected in the treated animals reflected the number of cases of the disease rather than its duration in treated animals (Table 69).

On the basis of data from individual trials, and pooled data, it was concluded that treated cows were less likely to conceive and to calve successfully - that is, to carry a calf to, but not beyond, full term and for the calf to survive for more than seven days after birth, without the mother having to be removed from the herd. The use of the drug was also associated with an increased rate of twinning and incidence of cystic ovaries.[31] The product label stated that treatment "may result in reduced pregnancy rates and an increase in days open [the number of days taken for a cow to conceive after the last full-term pregnancy] for primiparous cows...The labeling recommends the implementation of a comprehensive and ongoing herd reproductive health program preceding use of sometribove." (FDA 1993d: Section 6i)

FDA reviewers had not anticipated that the use of the drug would have any impact on lameness, but reports indicated that this problem needed to be examined. On the basis of studies specifically designed to investigate the issue, the Agency concluded that the drug did not result in increased lameness, but did result in increased foot disorders in multiparous cows and lacerations of the knee.

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[31] In the Post-Approval Monitoring Program no such incidence was found.

The interpretation of the animal health data was complicated by several problems. The animal toxicity tests did not provide a clear conclusion regarding the likely impact of the drug; further data were gathered from observations during efficacy trials, rather than safety studies. Burton et al. have noted that "the long-term (i.e., at least one full lactation) efficacy studies have generally monitored reproduction and health status as secondary observations rather than as primary objectives with intensive sampling and monitoring regimens. Adequate statistical analysis and interpretation of the resulting reproductive and health data have been difficult or impossible due to the small number of cows on individual trials." (Burton et al. 1994: 178) Since a large sample is necessary in order to draw conclusions about the incidence of common ailments such as mastitis, it was difficult to draw conclusions about animal health based on individual trials, and so the data were pooled; however, there was variation between herds (White et al. 1994), whereas pooling would normally be done on homogenous data.

The evaluators of the animal health and efficacy data were aware that determining the drug's mechanism of action was beyond the scope of their mandate, although some knowledge of the mechanism(s), if available, might be helpful in designing studies. Rather, studies are designed to test whether the intended production claim is achieved and to determine if there are any negative animal health impacts associated with the use of the drug. Thus, when requesting studies, reviewers had to ensure that they were not asking for information strictly to determine the drug's mechanism. Although evaluators were not mandated to draw conclusions about the drug's mechanism of action, or the cause of possible health problems, they operated with their own understandings of the cause of physiological changes associated with the hormone. Unlike the critics, Dr. Sechen did not entirely accept that animal health problems such as increased mastitis and metabolic disorders in early lactation could be attributed to negative energy balance per se. "The animal's gone through a huge physiological and hormonal change associated with calving,

the immune system is not functioning as strongly - it's a hard thing to delineate, to control for all those things."

They also needed to distinguish between the "statistical" and "biological" significance of variables affected by treatment of animals with the investigational drug. As with judging what kind of studies would be most appropriate, scientists drew on their background and training to make this distinction. The current literature and the results of their inspections were also important in reaching a decision. Judgements were made collectively. Each reviewer's concerns were discussed by the group. The FDA also consulted with outside experts on the lameness study, and with the USDA on injection site reactions.

Once a conclusion had been made about the biological significance of a reported abnormality, reviewers then decided on whether the problem was severe enough to render the drug unapprovable, or if it could be dealt with by informing the producer through product labelling. Problems which were regarded as "severe," included death; painful conditions; or conditions which were not necessarily painful, but which were increased dramatically compared to controls - "if in control animals it's something you see sporadically, but in treated animals just about every cow has this problem."
Severity was also determined by the novelty of the ailment and was linked to the concept of "management". Since mastitis, for example, was a common disease among dairy cattle, evaluators considered whether this problem could be "managed" by the farmer administering the drug, and the FDA decided in favour of approval. "What we saw didn't suggest that [mastitis cases associated with Posilac use] were harder to treat or that they were [caused by] different types of organisms...so it wouldn't all of a sudden cause a new problem that no-one knows how to handle." Since the difference in mastitis incidence associated with rbGH had been determined as less than the difference between, for example, early and late lactation, it was reckoned that any additional risk could be managed. The management concept also related to farmers' skills in handling health

problems; since it was accepted that farmers were already managing mastitis or reproductive problems associated with high production or environmental factors, it was inferred that any additional risk associated with the drug's use could also be managed. According to Dr. Sechen, "your early lactation cow is the best example. That's when she's most prone to mastitis. Successful dairy farmers are obviously handling that, so in later lactation when they're at less risk for mastitis, you add bST on top of that, they're going to be able to handle it, in our judgement."

The companies were informed of what specific level of increase in mastitis incidence would be of concern to the FDA. Dr. Sechen would not reveal this information because it was a preliminary decision based on dairy production drugs evaluated to date and currently accepted concepts on mastitis incidence in the dairy industry, which could change over time.

After the FDA had reached its decision on the acceptability of the increase in mastitis associated with Posilac use, the mastitis issue was further addressed when it became an issue of public debate. At this point, the FDA summarized the scientific literature to compare the effect of rbST with other factors associated with mastitis to demonstrate further that the increase in mastitis associated with Posilac was manageable.

Reviewers were conscious of the importance of responding to company submissions in a timely manner, "part of our yearly performance evaluation as reviewers is our timeliness." The Center maintains a tracking and reporting system which keeps track of all submissions by companies and their "due date"; the amount of time assigned for review is dependent on the nature of the submission. Reviewers can obtain a listing of their pending reviews in order of due date. "We try to work on things that fall due first. We're definitely very conscious of those things." Protocols gets a short review time - 45 days. "They're given priority because you don't want to hold up a company's opportunity to start a study."

The FDA perceived its "ultimate customer" as the consumer and producer of food. However, the reviewers' second concern is providing the firm with a fair and timely review. Requesting further studies, or not approving a product, may benefit the company as well as customers because it prevents the introduction of unsafe or ineffective drugs; "if something causes serious problems down the line, it will hurt the company's reputation."

After the decision to approve had been made, the FDA needed to consider appropriate product labelling. In accordance with requirements under the Food, Drug and Cosmetic Act, text proposed for use on the label, and in the FOI Summary, is submitted to the FDA by the company. The information which appears in the final version reflects what the FDA felt were not only statistically but *biologically* significant results, in which the effects "were seen consistently and in conjunction with other variables pointing in the same direction," and could, in their judgement, be attributed to use of the drug. The FDA decided that three areas of animal health were clearly affected by rbST: reproduction; mastitis; and nutrition. The reviewers decided that it was important "to let farmers know that the use of Posilac could exacerbate those problems, if you already had problems in those areas. We decided that the best way to express it was to make sure you've got a good management program in place."

3.2. Monsanto's interpretation

The decision to proceed with the product was also influenced by the company's assessment of animal health, which was, in turn, shaped by the conventional knowledge about the product, as described in the literature. The literature indicated that the product would be effective, and would have few, if any, animal health effects. When results from the long-term trials indicated that there were some animal health problems, the scientists viewed these in relation to the production increase the drug induced. Since, they reasoned, high-producing animals tended to exhibit the symptoms shown by treated animals in experimental trials, these symptoms could not be directly attributed to the drug itself. The FDA, however, interpreted the data differently.

Monsanto decided to apply for an New Animal Drug application (NADA) in 1987 after data from the first clinical trials demonstrated that the product was effective (Kowalczyk 1997: interview).

The company believed that it was important to determine the safety and efficacy of the product before submitting a licensing application to the FDA (Collier 1997: interview). The company's aim was that the dairy farmer receive a two-to-one return on his or her investment in the product:

> If you can't produce a 2-1 return, safely, then it's very questionable whether we'd go ahead with the product. You're going to spend very large sums of money when you go to clinical trials, so the place to kill the product is not in the clinical trials, you want to do it before. You don't want the FDA saying sorry you spent ten years and all this money, but it's not approvable. We try to make as many of those determinations as we can ourselves. It's just good business, for one thing. It holds down the cost and if you don't do it, you don't stay in business. It's so tightly regulated. There are too many pitfalls. Typically, it takes ten years to get the product from inception to marketplace. The average person has only one product in their lifetime. Not partial products, but a full product - one in your lifetime. And you're lucky if you get one, because so often they fail. It takes about 25 to get one to regulatory status. You certainly don't want to put out a product that's going to cause health problems: you get negative publicity, you've got human and animal welfare issues, the social impact on the dairy community...that's a nightmare scenario. (Collier 1997: interview)

Existing literature had reported the effectiveness of the pituitary hormone, and short-term trials had demonstrated that recombinant bGH was even more effective (Bauman et al. 1985). The safety of the product could not easily be demonstrated with short-term studies, however; safety problems are more likely to be identified in long-term trials, such as the two-year toxicology study or a set of clinical trials. Therefore, safety determinations could not be made before the start of clinical trials, and estimations about safety were based on scientists' literature reviews. The effect of the product on the incidence of mastitis was considered prior to the clinical trials, but only in relation to milk yield. There was no evidence in the literature that rbGH could change the immune system.

In order to obtain regulatory approval in the U.S., Monsanto conducted its animal trials at several universities in the U.S. and Canada. (The company did not proceed with the formulation used in Canadian trials.) Every two to four weeks, monitors from St. Louis

gathered the university data, entered it in the company's data base, and verified it. A particular study was not analyzed until all the data from that study had been entered and verified. Individual studies, as well as pooled data, were analyzed by company scientists.

The senior research scientist for the rbGH project, Dr. Bob Collier, acknowledged that the pooling of the data presented difficulties for analysis. In examining the incidence of an infectious disease such as mastitis, determining the treatment effect was difficult because analysts had to contend with variability between farms, and differences in parity among the animals. Thus, the data was analyzed separately and was also pooled and analyzed. In an article co-authored with university scientists in the U.S. and Europe, and published in 1994, Monsanto had analyzed data from 15 full-lactation trials in the U.S. and Europe, and 70 short-term studies. Data from the Utah site, which had been excluded from the FDA evaluation, were included. The FDA, on the other hand, had analyzed eight U.S. studies, excluding Utah. In the Monsanto study, the data from the various sites were not normally distributed, nor was variation homogeneous among the sites. Company scientists therefore performed a weighted analysis of variance (ANOVA) on untransformed data.(2252)

Monsanto scientists took milk yield into consideration as a factor that may affect the variability of mastitis. They distinguished between the "direct" and "indirect" effects of the drug. For example, company scientists were aware that there is a relationship between high milk production and mastitis; high-yielding cows tend to have a higher incidence of disease. A higher incidence of the disease in rbGH-treated cows, could, therefore, be attributed to increased production rather than to the direct effects of the drug. In an article co-authored with the principal investigators of the product trials in the U.S. and Europe, they argued that the incidence of mastitis in treated animals was similar to that of the incidence in cows with naturally high levels of milk production. Therefore, when mastitis incidence was examined in relation to milk production, "sometribove had *no effect* on the incidence of clinical mastitis." [my emphasis] (White et al. 1994: 2250) In coming to this conclusion, the researchers reported evidence of higher mastitis rates in cows genetically

selected for milk yield, and observed that this relationship was not altered in treated animals (2256). It was also noted, however, that the association between milk yield and mastitis is small and does not have a major influence on mastitis incidence (2250).

This method of analysis was not acceptable to the FDA, however. Regulatory scientists regarded the cause of the effect as irrelevant. Company scientists believed that the mastitis incidence was accounted for by the increase in milk production, that the effect of the drug was indirect, small, and manageable. According to Bob Collier, the FDA did not accept the indirect effect argument, but "looked at how much milk would be lost, how much would be spent on antibiotics and they determined that it wasn't going to significantly effect profitability on the dairy. So they determined it was approvable. That was before the external review..."

According to Collier, the FDA took an average for the increase in milk production from the whole group, and corrected for that. There were two other factors which, according to company scientists, made it difficult to determine the effect of Posilac. One was that treated cows lactated longer, therefore having more days at risk of contracting mastitis; second, the cows in the treatment groups in the trials Monsanto conducted tended to have a predisposition for mastitis (because their infection levels were higher than control animals in the pre-treatment period). This was a coincidence not expected to occur normally. Therefore, the relative risk of contracting mastitis was lower for Posilac-treated cows. However, in the U.S. studies, 35 of the cows in the control group had mastitis before treatment began compared to 55 of the cows in the treatment group (Monsanto 1994: Section 6.4). But this difference in pre-treatment incidence was not regarded as significant by the FDA (VMAC 1993: 3).

3.3. Interaction between the company and the FDA

Monsanto's interaction with the FDA began when the protocols for the trial were developed and continued until after the drug had been approved and a post-approval

monitoring program (PAMP) had been established. FDA reviewers contacted the company 90 days after the protocol was submitted. Then:

> We set up a meeting with the FDA and we go in to debate the issues - 99% of the time we accept what they're suggesting but sometimes they haven't thought about some of the issues and so they may modify it after they understand why we were asking for that specific parameter.

One example of protocol change was in reproduction; at the company's suggestion, cows could continue to be bred beyond the usual measurement period.[32] Another example was in mastitis measurement - the protocols did not include microbiological sampling in the pre-treatment period until it became apparent that Posilac-treated cows had a higher mastitis incidence, so the company wished to determine whether this was caused by the treatment or whether the treated animals were already predisposed to the disease.

The company submitted its analysis of the data prior to submitting the data package to the FDA. Once the analysis was submitted, the FDA requested that statistical analyses be done according to particular designations. If there was an increase in a particular disorder, the regulators would request further analyses to determine what was affecting the disorder. When the analysis had been completed according to these specifications, it was forwarded to the FDA with the electronic data and files, at which point FDA statisticians re-analyzed the data. If they were not able to duplicate the company's results, company statisticians were contacted to determine whether numbers had been entered incorrectly.

The FDA requested that the animal health data set be reanalyzed by the company. The first data set contained veterinarians' observations as well as barn observations. After this data set had been submitted, however, the FDA wanted the data to be re-analyzed by taking out the veterinarians' observations and re-coding each event by breaking it down systemically - according to the part of the body affected. The re-coding process took a year.

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[32] In the first set of clinical trials, animals were bred up to 150 days in lactation. Since Posilac-treated animals take longer to conceive, the effect of treatment on reproduction was higher than if conception rates were measured after 305 days, which was what occurred after Monsanto suggested that protocol change (Collier 1997: interview).

Monsanto spokespeople regarded successful completion of the trials as critical, not only to obtain approval but in order to beat their competitors:

> Whoever did the best job would get through first. This was the first time that the FDA had a whole new drug with more than one competitor. It was unique for them, not just two, but four companies. It put pressure on us to do the job right, to do it as well as possible. We didn't spare any expense in the amount or quality of the monitoring to make sure that the studies were done correctly. We had a vested interest because at that point, the whole push was to get the biotech. area moving, so we had the advantage of being able to spend 100% of our time doing one thing. The other companies had multiple products, so their people were divided among different things, whereas I knew what my priority was when I came into work. (Kowalczyk 1997: interview)

When the trials were completed, company scientists had "many" conversations with regulators, especially on the mastitis issue. After the initial data review, the FDA had concluded that there was an increase in mastitis incidence; the company then had to determine the extent of the increase, the impact on the dairy herd, and whether the increase was "manageable." The concept of what was "manageable" was based on a concept of the animal health problems already being managed by dairy farmers.

Company scientists were concerned that the warning label that accompanied the product would over-emphasize mastitis, and this issue was discussed with the FDA. The company was happy with the outcome of the discussions and felt that the mastitis issue was "in perspective."

The FDA communicated frequently with the company during the data evaluation and consideration of labelling language. Ultimately, the decision on product approval and labelling is made by the FDA; however, the company is consulted after the data have been evaluated and before the labelling language has been arrived at. Dr. Sechen noted that:

> The FDA allows firms to discuss Agency conclusions. When we review something and draw a conclusion, we relay that to the firm and let them respond. There are certain health factors that we've concluded are significantly affected by the product and should probably be on the label; the company might have an idea that the observation may be related to something else. They may have a better way of expressing it [on a label] to better communicate that to the user. Or they might have a valid reason for suggesting it not be on the label, and if they have a sound, supportable reason not to put it on a label we would consider it and if they can convince us we will accept it. So there is certainly communication with the firm; I don't want to imply that we don't communicate with them a lot.

The FDA and the firm communicated by telephone or face-to-face meetings. Once a data package has been submitted, the initial response is usually in writing; however, if the company wished to discuss a particular issue, a phone conference or meeting would be arranged. Dr. Sechen could not discuss any specific examples of issues on which the FDA and the company communicated. It became clear, however, that the mastitis issue was one issue which was discussed with the firm and the mastitis warning on the labelling was discussed with them. Dr. Sechen added that she could not tell me how much discussion was involved, or what the specifics of the discussion were. The FDA did inform the companies of what level of increase in the incidence of mastitis in treated animals compared with controls would raise concerns.

3.4. The university scientists' interpretation

The principal investigators for the trials tended to share the company scientists' perspective on animal health issues. They did not always begin from a similar perspective, however. A principal investigator at McDonald College of McGill University, Dr. Elliot Block, anticipated different results at the start of the trials. He didn't believe it was possible for treated cows to produce an additional six to eight kilograms of milk per day without suffering from an increased incidence of ketosis, early embryonic deaths and longer calving intervals, reproductive problems, and mastitis, and was surprised to find that only the incidence of reproductive problems increased in treated animals at McGill (1997: interview).

Block anticipated a number of problems would result from using the drug, but the only problems he was seriously concerned about, or which he felt would justify refusing to license the product in Canada, were irreversible problems such as reproductive failure and abortions. He viewed other problems, such as mastitis, as self-limiting; if a farmer experiences mastitis after using the drug, he or she would stop using it; however, reproductive or teratological problems (birth defects) would not become apparent immediately, and the damage to the herd would be permanent.

University scientists distinguished between "catastrophic" and "subtle" effects on animal health.[33] They argued that no evidence of catastrophic effects had been produced during the rbGH trials, and the evaluation of subtle health effects required "large numbers of cows studies under a range of environmental and management conditions." (White et al. 1994: 2250; see also Burton et al. 1994: 178; Bauman 1992: 3442) The limited number of cows at each site made it difficult for researchers to draw conclusions about disease incidence based on clinical observation, particularly if blood profiles were not taken, nor specific pathogens identified (Block 1996: interview).

American principal investigators co-authored an article on the relationship between milk yield and mastitis incidence which was primarily written by Monsanto personnel (and reviewed by the principal investigators), which was published after the FDA's approval of Posilac (Collier 1997: interview). Canadian animal scientists wrote a review article which came to similar conclusions. Mastitis was classified as a subtle effect which needed to be analyzed from a pooled data set. Mastitis incidence was perceived in terms of its relationship to milk yield. White et al. (1994) argued that the correlation between disease incidence and milk production in genetically high-producing cows corresponded to the incidence in treated animals, concluding that "the results provide evidence that increased incidence of clinical mastitis in sometribove-treated cows primarily reflects their higher average yield relative to untreated controls" (2258). This article examined the incidence of infection in relation to units of milk produced as well as cases per cow. Bauman explained that mastitis incidence was evaluated from a number of perspectives; examining it in relation to milk production was most meaningful for evaluating food safety:

> In terms of food safety issues, the concern about mastitis isn't per cow, it's per unit of food produced. So the reason why we looked at it that way has to do with the food safety issue. If I've got a cow that only has one case of mastitis but gives 20 pounds of milk, and another one that gives 10 times that and has two cases of mastitis, the chances that the drug could lead to contamination of the milk by

[33] Bauman defined "catastrophic" health effects as: ketosis; fatty liver, chronic wasting, crippling lameness, milk fever, mastitis, infertility, heat intolerance, sickness, suffering, and death. Mastitis was classified, therefore, as both a "catastrophic" and a "subtle" effect (1992: 3441).

> antibiotic residues are very low...any risk factors are related to cases per unit of milk. (Bauman 1997: interview)

He added that :

> If herd A averages one case of mastitis and 12,000 kg of milk per cow per year while herd B averages the same incidence of mastitis per cow but only half as much milk per cow, the risk from inappropriate drug use (e.g. antibiotic residue) is less per unit of milk in herd A.

Other animal health parameters were also viewed in terms of their relation to milk production. Bauman (1992) cites studies which relate the decrease in pregnancy rate to increased milk yield (3437). This perspective was shared by Canadian animal scientists:

> With any of the safety parameters we were measuring, whenever you increase milk production in an animal, you risk other things going wrong. Reproduction is usually the first, because animals are losing a lot of body weight at the beginning of the lactation. During that period, they don't cycle normally. I can increase milk production by changing the cow's diet; by changing her environment; or by giving her somatotropin. So it's very hard to tell whether somatotropin is doing something by itself or if it's just the increase in milk production. (Block 1996: interview)

One scientist believed that the experiments should have compared high-producing and treated cows:

> The real trials that should have been done, never were done. What should have been done was to take a group of cows that makes X amount of milk per year, and another group of cows that makes the same amount with somatotropin, so you have two groups where the only difference is somatotropin. And then you can start looking at safety factors, and if something goes wrong you can attribute it to somatotropin. (Block 1996: interview)

Burton, the principal investigator at Guelph, found it "impossible" to determine whether the incidence of mastitis was directly attributable to the drug, or to increased milk production. However, he, and his counterparts, believed that the relationship was relevant.

McGuire and Bauman have also argued that the well-being of treated cows is indicated by their improved milk performance; sick cows are unable to produce milk at their usual level (1996: 2). Bauman has added that:

> ...cows that are stressed or sick use nutrients less efficiently and produce less milk. Use of bST has consistently demonstrated an increase in the efficiency of nutrient use. (Bauman 1998: personal correspondence)

Prior to working with Monsanto's recombinant product, Dr. Bauman, Professor of Animal Science at Cornell University, had investigated the effects of growth hormone on

the regulation of the animal metabolism. Bauman's early investigations were motivated by curiosity about the biological basis for high milk production: "the national priorities in my country were to understand the biology of what makes some animals more efficient." He has reported that his research on animal physiology was an important component of the Monsanto trials (1998: personal correspondence). In an interview, Bauman explained that he had proved the existence of two types of regulation: homeostasis, in which a physiological equilibrium is maintained through metabolic adjustments; and homeorhesis, in which metabolism is coordinated to support a change in physiology, such as pregnancy or lactation (Bauman and Currie 1980: 1515). Bauman stated that "these concepts have been proven by studies conducted by scientists throughout the world and verified by use of bST in 15 countries. It was a concept when it was first proposed in 1980 but is proven to this day" (Bauman 1998: personal correspondence). During homeorhesis, nutrients are supplied to meet the additional requirements for fetal growth during pregnancy, or milk production during lactation. Bauman has shown that higher-level homeorhetic controls accommodate the need for homeostatic regulation; that is, metabolic processes may be altered to support lactation or pregnancy without detriment to the animal's basic physiological state.[34] (McGuire and Bauman 1996: 6) Bauman applied these concepts to rbGH: "treatment with bST both increases the rate of milk synthesis within the mammary gland and orchestrates other body processes in a manner to provide the necessary nutrients to support this enhanced rate of milk synthesis." (7) The concepts of homeorhesis and homeostasis demonstrate why human growth hormone is effective in the treatment of patients recovering from surgery, burns, cancer, or infection (1996: 5).

> Not only does somatotropin not cause disease, it has these coordinating effects on other tissues which minimize disease. Somatotropin is presently being given

[34] In contrast, Bauman and Currie's 1980 article, written prior to the confirmation of the role of growth hormone in the coordination of metabolic activities, pointed out that pregnancy and lactation make tremendous demands upon the animal:
The inability to adjust metabolism quickly enough to meet these needs frequently results in acute and subclinical metabolic disorders in farm animals. Nature has accorded a high priority to the functions of pregnancy and milk secretion, allowing them to proceed at the expense of other metabolic processes even to the point that a disease state is created (1514).

> experimentally to minimize the incidence of metabolic diseases. Human somatotropin is also being used experimentally in humans post-surgery. (Bauman 1997: interview)

3.5. The critics' interpretation

Critics, however, have contested the FDA's conclusions on several grounds. The most outspoken animal health critic has been Dr. David Kronfeld, Professor of Agriculture and of Veterinary Medicine at Virginia Polytechnic Institute and State University. Kronfeld's perspectives on growth hormone was informed by evidence from trials with the pituitary hormone in the 1950s. As a veterinary student in Queensland, Australia he saw photographs from Sweden which showed a widening of horses' bones as a result of hormone treatment. Kronfeld associated the growth hormone with both high production and negative metabolic effects:

> It struck me that we were selecting horses for precocious speed and precocious growth and maybe we're selecting them for too much growth hormone, and that was widening the physis (the growth plate in the horse's knee). A few months later we started a study of ketosis in highly producing cows and the same idea came up again, that we were selecting cows for really high production, selecting them for growth hormone, and they'll tend to mobilize their own body tissue to make more milk, and one sign of that would be ketosis. [Ketosis is a metabolic disorder which occurs when production of ketones - an organic compound produced in the metabolism of fats - exceeds the ability of the body to use them. It occurs when the need for glucose exceeds the production of glucose.]

In 1957, Kronfeld began an academic appointment at the University of California, Davis, and later was appointed to the University of Pennsylvania. He conducted a small trial with growth hormone in which cows suffered from a condition he referred to as "subclinical ketosis," which he argued would predispose cows to a number of diseases. He has not conducted long-term trials with rbGH.

According to Kronfeld, in 1963 he was invited to give two seminars at Monsanto. He suggested that they attempt to synthesize growth hormone chemically. Almost twenty years later, when Monsanto bought the rights to the recombinant bacteria from Genentech, he and his colleagues at the University of Pennsylvania were delighted because they felt that they were well-connected with Monsanto and would therefore have a good chance of acquiring the contract for undertaking the animal effectiveness and safety trials. The initial

agreement was that Monsanto would contract with the University of Pennsylvania, and Cornell University. Kronfeld had "grave misgivings" about the contract signed with Monsanto; he wished to conduct further examinations of animal safety than required under the Monsanto protocol. He went overseas on leave. On his return, the Monsanto contract had been terminated, and two of his colleagues had been employed by the company. Kronfeld and another colleague then "went after Cyanamid" to try to obtain the contract to conduct that company's studies. After four months, Kronfeld claims, the colleague told Kronfeld that Cyanamid regarded him as a risk because he was too interested in the drug's side effects, and that they would agree to have the research conducted at the University of Pennsylvania only if Kronfeld were excluded from involvement with the trials. At this point, Kronfeld was moved into administration. He then moved to Virginia Polytechnic.

He had conducted one short-term experiment with the Cyanamid product, in which protected fat was fed to the animals during rbGH treatment, to determine whether this would prevent the cow from using her own body tissue and help protect against infertility and infectious disease. In Kronfeld's view, the experiment was successful from the perspective of animal science, but not from preventive medicine; protected fat enabled the cow to increase milk production even further, but did not prevent disease incidence.

Kronfeld has claimed that the negative effects of rbGH have not been promptly and accurately reported by the university researchers conducting safety and efficacy trials:

> In 1987, I wrote a paper examining the first nine long term trials and pointed out that there had been adverse effects in seven of them but they weren't being reported openly and this paper put me on the outside of people who were getting money from the companies and put me on the outside of people in the companies.

Kronfeld claims that in conversations with friends and former colleagues who are now with Monsanto, he has been told that because of competition between the companies, they did not release data during the approval process: "they felt that as long as in the long run they made all the data available...that would make good business sense and is acceptable business ethics." In Kronfeld's view, the publication of data which did not mention

adverse animal health impacts increased pressure on regulatory agencies to approve the drug:

> The USDA said in 1987 that the drug should be approved as soon as possible to help American farmers compete in a global economy. Then we had a piece by the OTA which said how marvellous this drug was, again that there are no side effects, and I think this virtually ensured that the drug would have to be approved.

Kronfeld has also argued that the influence of the published data was compounded by the prevalence of animal scientists on the FDA evaluation team. Although veterinarians were also involved in the review of the animal health data, in Kronfeld's view, "the political climate was such that the veterinarians who did know more about epidemiology didn't bother to blow the whistle on it." According to Kronfeld, Posilac approval was justified within the FDA in spite of the increase in mastitis incidence because of an article which compared this increase with variation in incidence induced by other factors.

Kronfeld has also disagreed with the argument that all of bST's metabolic effects are coordinated during lactation, arguing that health effects are dependent on lactational stage: "milk production and feed intake are obviously not coordinated. Peak milk production comes in three to six days, whereas peak feed intake doesn't come until six to twelve weeks later." (1997: interview). He has acknowledged that there is some evidence that the hormone may have positive, as well as negative, effects, possibly accelerating cellular functions associated with immunity (1994: 126). However, whether the administration of the drug is positive or negative overall depends on the lactational stage at which it is administered. Kronfeld explains the mastitis incidence by comparing physiological changes induced by the administration of bST to those induced by early lactation. The incidence of mastitis is highest in the first 8 to 12 weeks of lactation, which Kronfeld refers to as the catabolic phase, in which the animal cannot consume enough energy to support milk production, and begins to break down her own tissue. During the catabolic phase, which lasts approximately eight weeks, animals tend to experience a higher incidence of disease, including mastitis. Since the cow uses more energy than she can get from feed, this phase is also known as "negative energy balance." Kronfeld has argued

that the use of sometribove extends the catabolic phase for another two months, extending the period in which the animal is likely to succumb to disease by a concomitant period (Kronfeld 1993: 3). Metabolic processes are more likely to be adequately coordinated in the second phase of lactation than in the first (1994: 120). He has claimed that the pooling of data has obscured the inconsistency of responses across herds and temporal sequence of health responses during drug treatment (Kronfeld 1993; 1994).

Kronfeld has relied on studies conducted at Cornell and Vermont, the White et al. report on clinical mastitis, and a report by Thomas et al. reviewing data from 15 U.S. herds. He has acknowledged that an increased mastitis frequency has not been observed in all herds, but in "1 of every 2 or 3 BST-treated herds" (1994: 123). However, his major criticism has been that pooling of the data obscures the severity of mastitis incidence in certain herds, and that improved management of those herds will not necessarily address the problem. Although the increase in mastitis incidence in treated animals may not represent a threat to human health because of milk monitoring for antibiotics, Kronfeld has argued this does not mean that the disease itself is "manageable" in treated animals. For Kronfeld, this is an animal welfare issue; regardless of whether mastitis is an indirect human health problem, it is a painful disease for animals which is already difficult to manage and prevent, and the introduction of a drug that increases its risk is unjustifiable. In Kronfeld's view, the FDA-Monsanto judgement that bST-induced mastitis is manageable by current methods is not supported by the data and, indeed, is inconsistent with the high incidence in the bST-group and low incidence in the control group at Cornell University, the University of Vermont and Monsanto's own dairy.

Kronfeld has questioned the validity of the FDA's claim that the incidence of mastitis due to treatment is less than that from other factors such as season, parity, and herd. He objects to this conclusion for two reasons. First, the treatment group should be compared to the control group rather than to the whole population of dairy cattle. If the Agency wished to compare the effects of the drug with a variety of environment conditions,

trials should have been conducted under those conditions. Second, the FDA compared factors which are not easily controllable - such as the season - to one which is controllable, the introduction of a drug (Kronfeld 1993). According to Kronfeld, preventive medicine distinguishes between controllable and uncontrollable disease factors; it is therefore inappropriate to compare the incidence of mastitis associated with rbGH usage to that associated with uncontrollable sources of herd variation.

He has rejected the company's argument that the increase in the mastitis incidence of treated cows is related to increased milk production: "from an epidemiological point of view, it doesn't matter to identify an intervening factor, it does not diminish the influence of the risk factor, in this case, the drug. In any case...the only people who could evaluate it were the FDA because they broke it down into individual cow data, but they've never published that data, and they rejected [the idea that mastitis incidence can be explained by milk production increases.]" (1997: interview)

He has also criticized the FDA's conclusion that the average duration of mastitis incidence was similar in both the control and treatment groups. He drew on evidence from the University of Vermont - a study which was not included in the FDA's analysis - which indicated that the duration of antibiotic therapy was approximately six times longer in the treatment group (Kronfeld 1993: 5, reviewing Pell, 1992); and on a study by Thomas et al. (1991) which indicated an increase in therapy duration in seven out of 15 herds.

The former FDA veterinarian, Dr. Richard Burroughs, has also alleged that mastitis and reproductive problems had been found by the FDA when limited trials were run to list possible toxic responses. According to Dr. Burroughs, these trials were not followed up adequately by the FDA; instead, the manufacturers went on to efficacy and on-farm studies (Burroughs, 1994: 13-14).

3.6. The NIH Review

The NIH Technology Assessment Conference of 1991 also addressed the animal health issue. In a draft of its report, the panel noted that "[a]dditional effects of rBST on the

health of the dairy cow appear to be minimal." It then modified the draft to include the proviso "on the basis of data reviewed by the panel," before this clause. (NIH 1991: 11) However, the panel did not have sufficient evidence to draw any conclusions about the incidence of mastitis. Its final conclusion was that milk and meat from treated cows was as safe as that from untreated animals. The panel did suggest several areas in which more research was needed on the effects of rbGH. With regard to animal health, the committee suggested continued study on the long-term effects of the hormone, particularly on reproduction, and evaluation of clinical and subclinical mastitis and the relationship of mastitis to milk production.

3.7. Health Canada's interpretation

The implications of the animal health data were interpreted differently than the human health data. Dr. Drennan, the former Chief of the division responsible for evaluating rbGH, stated that there were problems with the data itself, and that the evidence of animal health problems was unacceptable to Health Canada. Without full knowledge of what was submitted to the Bureau, and how it differed from the package submitted to the FDA, it is difficult to know whether both submissions were flawed, and how these flaws were dealt with by the FDA. It would appear from the FDA interviews that reviewers were aware that problems had appeared in the data and that the Agency needed to be "very clear" about the requirements for the protocol. Even if these issues were resolved by the FDA before approval, and not resolved at Health Canada before 1996, Dr. Drennan's interpretation of the evidence still differed from the FDA's. An animal health risk which was regarded as acceptable by the FDA was not acceptable to Health Canada.

Dr. Drennan did not feel that the animal health data submitted by Monsanto justified approval, in spite of his awareness of the economic consequences for the company of not approving the drug, and his inclination, if possible, to give the company the benefit of the doubt:

> You've got a company that's put a lot of money into this and you're going to cut their throat. If there's anything there that's acceptable that could be salvaged, you have to give them the benefit of the doubt....

Dr. Drennan claimed, however, that the data submitted by Monsanto did not conform to the company's protocols, and this caused him to question the acceptability of the data.

When making animal health decisions, Dr. Drennan claimed, "there's nothing cut in stone" because health concerns vary depending on the nature of the drug. For example, reviewers examining data submitted for the licensing of a reproductive drug would be concerned about conception rates and effects on the offspring. Those evaluating the data on an injectable product would consider how quickly the product is assimilated into the animal's system, whether it interfered with its movement, and whether there was a site reaction. Although the Bureau makes general guidelines available to companies, the approach will necessarily vary from product to product.

Decisions on animal safety are at the discretion of the reviewer, and involve judgements about what the farmer needs to know about the product. Most of the Bureau's reviewers have a background in veterinary medicine, rather than animal science. According to Dr. Drennan, all but two of the Bureau's scientists had a veterinary background. Reviewers also have access to other scientists, such as statisticians, within Health Canada, and discussed the review process with one another, since there are only 13 evaluators in the Bureau.

Health Canada's approach to protocol submission was similar to that of the FDA before changes introduced with the 1996 Animal Drug Availability Act. If a company wished to present a protocol to their Bureau, they were welcome to do so. As in the United States, this is voluntary; in Canada, however, Monsanto did not submit its protocols to the Bureau prior to its data submission, although it did submit them in the U.S.. At the Senate hearings, Ray Mowling from Monsanto stated that protocols had been submitted to the Bureau (Senate of Canada 1998).

According to Dr. Drennan, data were first submitted to the Bureau in the mid-1980s. The company submitted data from sites in the northern U.S. since it had not proceeded with the product formulation which had been tested in Canada. Health Canada will accept data from U.S. sites, provided that husbandry and feeding practices, and climatic conditions, are similar to those in Canada. As in the U.S., the Bureau then has 180 days in which to respond to the manufacturer in writing by either issuing a Notice of Compliance (NOC), refusing to issue it, or requesting further information. According to Dr. Drennan, the company was notified by phone and in writing:

> When there's a problem with information, the reviewer, or his Chief, would ring and say we don't know what's going on here. Would you please explain? And you would always follow that up with a letter so that it was in writing and they had something recorded as to what you said to them on the phone. (Drennan 1997: interview)

Prior to receiving the data from Monsanto, the Bureau's evaluators came up with a list of basic requirements they expected to see addressed by the data. They had also been reading articles from refereed journals regarding experimentation in other countries, and may have added requirements based on that knowledge.

When Dr. Drennan received the data, his main concern was determining whether the data conformed with the original protocol which was included in the data package. Dr. Drennan commented that:

> One of the first things I did was to read the protocol, to find out if they had actually followed it. Did they do what they said they were going to do? Now, I won't go into the details, but the bottom line is that they did not. And what they did not do I won't discuss with you. Basic science tells, if you didn't follow the protocol, why not? Where was the explanation? This was not provided. There was a real concern with the company with regards to the [animal] safety...and I discussed this with the company, both in meetings and by letter.

He was disturbed by the company's failure to conform to its own protocols:

> There were things happening in those experiments that were just horrendous. Now I can't get into that because that's privy information, but in my opinion, it was very bad experimentation. I had a real concern that those experiments were not done as they should have been done. I corresponded with them about this and they said fine, we'll come in and talk to you, and get this straightened out. Well, it never did get straightened out.

He was also concerned that the data showed evidence of animal health problems:

> Too many things were going wrong. A lot of the animals were not well. There were a lot of incidences of mastitis, reproductive problems, lameness...that's common knowledge.

Dr. Drennan's definition of the concept of "safety" was more stringent that that of the FDA reviewers. If around half, or more than half, of the treated animals showed signs of illness, Dr. Drennan regarded this as highly problematic. If fewer than half the animals were ill, he would want to obtain further evidence that this level would not increase:

> Suppose with bST in less than 1% of the cases you see a certain type of mastitis. Well, that's not enough to say we can't market this drug. Statistically that's very low, and you make that statement on the label....If you've got 50% or more, that's an automatic no. With 50% or less, if say 48% are getting mastitis, you say to the company you want more studies done to show that it remains at 48%, or perhaps that it's going to drop. If it stays up there it's no.

Dr. Sechen at the FDA indicated that a similar conversation may have taken place in the United States, outlining what mastitis level was "approvable." Since she did not reveal what that level was, I cannot determine whether it was higher - or lower - than Health Canada's cut-off point.

The nature of the illness, as well as the proportion of animals affected, was also taken into account when making judgements about whether a license should be issued or denied. If, for example, all treated animals had injection-site reactions, but swelling diminished within several hours, this effect could appear on the label. Dr. Drennan regarded mastitis as a serious issue, however; even a 10% incidence in treated animals would cause him some concern. He also viewed the mastitis issue in the light of Canada's supply management system. If a farmer has to throw out milk because of high somatic cell counts, or antibiotic residues, he or she would have to buy milk to make up the quota, or pay a fine.

Dr. Drennan regarded the labelling issue differently from his American counterparts. Canadian animal drugs have a warning label to protect human safety, and a cautionary label to indicate animal safety problems. For example an anti-parasitic drug for cattle contains a label to indicate that people applying the drug need a mask and gloves to

protect themselves. The cautionary statement indicates any animal health problems which do *not* justify the refusal of a Canadian license. In his view, the reproductive problems, mastitis and other "major issues" were too significant to be dealt with on a cautionary label:

> Our system says you have to demonstrate that it's safe and effective, and that means that you can't come out with a label that says you can use this, but beware of all these things that could happen. That's not right, in my view.

He did not regard the U.S. approach of labelling to indicate potential animal health problems as acceptable in Canada, but could not give a detailed response to the FOI Summary.

According to Dr. Drennan, Monsanto agreed with his criticisms of the data. He reported that he had discussed the Health Canada decision with Monsanto representatives at a meeting in the fall of 1995. Five Monsanto representatives, mainly from the U.S. parent company, were present at the meeting, along with the Assistant Deputy Minister of Health Canada, the Director General, and the Director of the Bureau's Human Safety Division. According to Dr. Drennan, the company representatives agreed with the Bureau's analysis of the data. "When we finally sat down with them and said, this is wrong, they agreed...I don't know how many of the people who agreed with me are still with the company." Dr. Drennan retired from the Bureau several months after this meeting, and does not know what conversations have taken place with Monsanto officials since then.

Although Dr. Drennan had conversations with organizations and individuals outside the Bureau, he argued that the review was "strictly a Health Canada decision." He had spoken to FDA representatives, and to principal investigators at university sites within the U.S., but claimed that these conversations did not influence his view of the data submitted. Nor, in his view, did the 1994 House of Commons hearings have any effect on the review process.

During the review, he kept abreast of the literature, particularly in the Journal of Dairy Science, which he regarded as a reputable source of information. However, he

differentiated between the results reported in the literature and those he had seen in the Monsanto submission:

> If you read something, you don't automatically believe it. You file it in the back of your head and you think well, [this scientist] had these results, someone else had other results, and we're looking at a set of data that maybe contains both sets of results, but they [the company] didn't follow the protocol...You come to a conclusion based on what the company has done, not what somebody else has done...They have to be able to demonstrate to me based on what they did that it's safe and effective, not what Joe Blow did in South Carolina.

Dr. Drennan asked for raw data from the sites to compare with the company's summary reports, and was not satisfied with his investigations; "I didn't have to go very far through all these sheets ...before something told me this is not good."

Company scientists presented a different picture of the review process in Canada. They perceived it as either unduly influenced by political concerns, or merely delayed because Health Canada had fewer resources to devote to the evaluation than the FDA Monsanto's Director of Regulatory Affairs, Dr. Dave Kowalczyk, described the Health Canada decision-making process as similar to the FDA:

> Basically, it's the same in so far as they base all their decisions on science, like the FDA. The outside pressures can slow things down, but at the end of the day, they don't change the science - the [FDA] decision was based on science and that's true in Canada too. I've been interacting with Canada since 1985. Just letting them know what the requirements were. They were a little further behind in what should be required for this kind of product. As a company, we really focused on the U.S. to get approval. We did do some work up in Canada, but it was for a product form we didn't go forward with. One of things that's different is they have fewer people to work on it and I think they were overwhelmed with the amount of material and being able to manage that.

In fact, Dr. Kowalczyk indicated that the process was not taking any longer in Canada than in the United States, because the Canadian submission was made about three years after the American submission:

> We're still at the same point in Canada similar to the time it took to get through the FDA. All our effort was to get U.S. approval. It's the key approval, to help you get approvals in other parts of the world. U.S., Canada and Europe - if you get any of those approvals it helps you anywhere else in the world, in South America, South East Asia. When we had the issues in Europe we put all our focus on the U.S. to get approval first. We didn't put the resources in Canada. It's just taking a longer period of time. The FDA has a lot more depth. They re-analyzed all the data, they had computer know-how and power to do that, where Canada has not had that, and resources to physically look at the files.

Both Dr. Drennan and Monsanto, regarded the request for a voluntary moratorium as irrelevant to the review process. According to both Monsanto representatives, the company knew that approval was unlikely during the next twelve months, so the moratorium made no difference to their strategy. Dr. Kowalczyk commented that:

> We weren't expecting approval at all. They wanted to set up a Task Force and didn't want approval before the Task Force was finished. We weren't expecting approval anyway. That was an artificial date of a year's time so they could complete the work - it wasn't unexpected.

A former Monsanto biochemist and sales manager, Dr. Rick Ryan, who had been involved in the international marketing of bST between 1993 and 1995, had a different perception of the company's interactions with Health Canada. Dr. Ryan stated that Monsanto was extremely frustrated when approval was not announced when it was over:

> At the end of that it became clear also that there wasn't going to be any serious intent by Health Canada to approve the product. So we basically withdrew and weren't going to spend resources on it any more....We no longer have an office for this product in Canada. The registration's still active, but I can't comment on that, I haven't been with the company for nine months. We pulled our people out of the office there and decided we weren't going to spend additional resources the way we did before because it was not viable to do so. We were given no assurances at all that people [at Health Canada] were working in good faith.

Dr. Ryan emphasized that since he was no longer with the company, he was not aware of the current situation. However, he felt that, as in Europe, socio-political influences rather than science-based arguments influenced the process in Canada.

According to Dr. Kowalczyk, on the other hand, Monsanto had decreased its commitment to obtaining Canadian approval in order to concentrate its resources on the U.S. process. Dr. Kowalczyk also indicated that Monsanto had encouraged interaction between the two regulatory agencies:

> We have tried to interface the two agencies because there's NAFTA. It doesn't make sense - both the CVM [the FDA's Center for Veterinary Medicine] and the BVD [Health Canada's Bureau of Veterinary Drugs] are being cut back, why are they duplicating this work? We're trying to get them to interface and use each other's knowledge. There were two people from the BVD at both VMAC meetings and we've given authorization so there are no confidentiality problems between regulatory groups. They have access to either set of files.

Dr. Drennan acknowledged that he had had conversations with officials in the U.S., but would not divulge the content of those discussions.

In Canada, rbGH would only be approved under condition that it was prescribed by a vet. This does not necessarily pose a difficulty for Monsanto; in the U.S., a farmer's first drug purchase came with a $150 voucher to pay for a veterinarian to examine the herd prior to starting rbGH treatment.

> I think it's one thing we've learned from market research is that the number one person the farmer relies on is the vet, so that's why we want to get the vet involved early on. So that's why we went with vouchers, to get the vet to come out there, to do herd health, to make sure all their management is in place. We paid that for the farmer - free management advice. That will happen [visit by the vet] automatically in Canada, which will be helpful.

3.8. Animal health as a public health issue

The possibility that increased rates of mastitis would result in increased antibiotic residue in milk, and antibiotic resistance in the general population, was first raised by Epstein in 1989. It became controversial as a public health issue when the General Accounting Office released a report arguing that the FDA had not considered this potential indirect risk to public health from antibiotic residues in milk (GAO 1992b). Two years earlier, the GAO had questioned the FDA's effectiveness in monitoring the milk supply for antibiotic residues. It claimed that the survey methodologies used by the FDA were not adequate for determining the level of antibiotic residue because the surveys were not statistically valid, nor did they test for drugs not approved for use by the Agency, but which were none the less believed to be commonly used by the dairy industry. (Ordinarily, drugs must be used in accordance with the guidelines on the label; for example, a drug for a horse cannot normally be used in treating a cow. Under an "extra-label" use policy, however, the FDA permits drugs to be used in ways which do not conform to the label instructions, provided that the drug is prescribed by a veterinarian and that more orthodox treatments have been tried, or judged to be ineffective in the particular case.) (GAO 1990: 4) In 1992, the GAO noted that milk monitoring had improved, but was still not adequate

to ensure public health. In April 1991 the FDA agreed to expand the number of drugs to be screened and to recommend new methods the states and industry might use for screening them. However, by July the following year these changes had not yet been implemented. The Agency also began its own testing program to screen for twelve, rather than four, drugs; however, the GAO stated that there were 82 animal drugs which could leave residues in milk, 64 of which are either commonly used, or may present a health risk when consumed (GAO 1992b: 3).

In response to the GAO, the FDA had tentatively concluded that the indirect public health risk was insignificant (Guest, 1993: 2); however, it convened a one-day public meeting of its Veterinary Medicine Advisory Committee (VMAC) to address the issue. The FDA asked the committee to consider the following questions:

> 1) Does the use of sometribove result in a meaningful biological effect on incidence of mastitis?
> 2) Does the increase in mastitis cases due to use of sometribove, as compared to other influences on mastitis, exceed an acceptable threshold? (i.e. will the dairy farmer and his/her veterinarian be able to manage the problem and assure proper drug use?)
> 3) and finally, depending on the answer to #1 and #2 above, whether the incidence of mastitis due to Monsanto's BST will contribute a significant amount of illegal drug residues in milk and meat reaching the public. (i.e. is there danger of toxicity, hypersensitivity, or selection for drug resistant organisms?) (Guest, 1993: 4)

The questions were framed in such a way that the answer was determined by the question. Question two asked the committee to determine whether the mastitis increase exceeded "an acceptable threshold," but the previous phrase proscribed how that threshold would be determined; in relation to other factors identified by the FDA. It was the validity of this comparison which had been questioned by the critics. In order to reach a different conclusion from the FDA, one had to dispute the comparative method of analysis. For the Center, the relevant questions were whether the increase was "meaningful", and whether it was "manageable" in two senses - could the animal health risk be managed by farmers without becoming an unacceptable practical or economic burden, and could the risk to public health be managed by the existing system for monitoring milk drug residues?

In the FDA's view, since the risk of antibiotic residues entering the milk supply was being successfully managed by a national and state system of milk monitoring, the risk associated with rbST could also be managed by that system. Since the difference in mastitis incidence associated with rbST had been determined to be less than the difference between, for example, early and late lactation, it was reckoned that any additional risk could be managed. The management concept also related to farmers' skills in handling animal health problems; since it was accepted that farmers were already managing mastitis or reproductive problems associated with high production or environmental factor, it was inferred that any additional risk associated with the drug's use could also be managed. According to Dr. Sechen, "your early lactation cow is the best example, that's when she's most prone to mastitis; successful dairy farmers are obviously handling that, so in later lactation when they're at less risk for mastitis, you add bST on top of that, they're going to be able to handle it, in our judgement."

At this meeting, FDA officials emphasized recent steps taken to improve drug residue monitoring. The most commonly used drugs in the treatment of mastitis were beta-lactam antibiotics, which may cause allergic reactions in people who are already sensitized to penicillin. However, the FDA argued, the dairy industry had been required to test every milk tank for beta-lactams since 1992. Even if the residues were not detected, ingestion of residues in allergic individuals tended to result in a skin rash, and was not a serious enough reaction to pose a significant health risk (Mitchell 1993: 7). Dr. Mitchell did not discuss the potential for increased bacterial resistance to antibiotic drugs as a result of rbGH introduction.

Company representatives stressed the relationship between mastitis levels and production, positing that the level of mastitis per unit of milk produced would actually decrease with sometribove (Collier 1993: 3). However, the FDA representatives noted that "mastitis cases increased on a per unit of milk basis, but less than on a per animal basis"; that is, that although milk production did increase in line with the incidence of disease,

individual animals still suffered from higher rates of disease. The points raised by the FDA were repeated by company spokespeople. The issue of whether the ingestion of residues could increase the level of bacterial resistance to antibiotics was also addressed, and it was concluded that there was no evidence to support this. Monsanto's Vice-President Dr. Virginia Weldon pointed out that only 10% of antibiotics given to animals are used for therapeutic purposes; the other 90% are administered at subtherapeutic levels in animal feed to encourage growth. There was no conclusive proof that subtherapeutic doses of antibiotics presented any risk to human health[35]; therefore, the use of rbGH would also not represent a risk (Weldon 1993).

The American Medical Association raised an issue which had been discounted by the company: that of the effects of treatment on the animal's immune system. However, it was argued that this was a manageable problem which did not pose a risk to public health:

> Resistance to infection apparently is decreased in lactating cattle treated with somatotropin, as a direct consequence of the somatotropin-induced shift in homeorhesis that stimulates lactogenesis. The resulting negative energy and protein balances slightly impair immune function. However, it has been shown repeatedly that in order for the use of somatotropin to become economically profitable, the implementation of high-level, state-of-the-art animal management techniques is necessary. With such a management program in place, the incidence of the nutritional and environmental conditions that encourage mammary infections will be reduced. Those dairy operations efficiently integrating somatotropin into their total quality control practices may well experience no increase in mastitis incidence (Skelton 1993: 3-4).

The Consumers' Union, represented at the hearings by research associate Dr. Michael Hansen, expressed concern about the potential for the spread of antibiotic resistance and antibiotic-resistant food-borne infections, particularly given that antibiotics were used illegally in Monsanto trials.[36] Essentially, the Consumers' Union - and other

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[35] Recent studies suggest that the antibiotic avoparcin, used to treat animals in subtherapeutic doses, is at least partly responsible for the development of vancomycin-resistant enterococci in humans. Subtherapeutic use of animal antibiotics has been regulated in the UK since the 1970s (Hawkey 1998: 1298). In July of 1998, a U.S. National Academy of Sciences panel stated that there was a risk of humans contracting antibiotic resistant infections from food-producing animals, but that the risk from eating meat or poultry had not been determined (Leary 1998: A7).

[36] In support of this statement, Hansen quoted a 1988 letter to Monsanto from the FDA, which stated that the company "should address the use of gentamicin and tetracycline which are not approved for the treatment of mastitis in dairy cattle." Since this letter was dated 1988, it probably referred to trials administering the I-M, rather than the S-C, formulation (Hansen 1993: 5).

opponents - were not prepared to accept any risk associated with the approval of rbGH because the drug itself was not perceived to confer any benefits which would make any potential adverse consequences worth bearing. Hansen stated that:

> This drug admittedly increases disease rates. So what are its benefits? It increases output of an agricultural product that is already in surplus and has been for at least a decade. We see absolutely no justification for tolerating an increase in disease rates for a drug that increases milk production, and that the FDA cannot possibly determine to be safe (1993: 2).

Statements such as this were repeated at every rbGH advisory committee hearing, and in media reports and trade journal correspondence. (See for example Wilson 1993: Sanders 1993: Rifkin 1986).

In response to evidence presented at the meeting, the committee concluded that the product was approvable; that is, that "there is no risk, or the risk is insignificant." One of the VMAC committee members expressed that view that "we would have to wait 20 to 30 years to have good drug resistance data." (FDA 1993d: 5)

3.9. Summary

It has been recognized that the use of Monsanto's rbGH product is associated with an increased incidence of mastitis, reproductive problems, and foot and leg disorders. What this means in terms of the drug's approvability has not been resolved across institutions. From the company perspective, when mastitis is viewed in terms of production, it is no longer a problem; there is, according to company scientists, less mastitis when viewed in relation to the amount of milk produced. For the FDA, the production perspective was not regarded as relevant, but the problem was regarded as manageable. In Canada, however, the problem was regarded as severe. For critics, this is an ethical and animal welfare issue; given that the current level of mastitis incidence is difficult to manage, an increase is unacceptable.

In Canada, the related human health issue of antibiotic residue was not considered significant because of stringent testing. However, in the U.S., mechanisms available to Congress and the critics ensured that this question was publicly debated by the FDA

advisory committee. The committee heard less evidence, however, on the question of antibiotic resistance, and the potential for increased food-borne illness. In Canada, on the other hand, these latter questions have preoccupied the dissenting scientists within the Bureau of Veterinary Drugs. Unlike the Bureau's human health reviewers, the authors of the internal "gaps analysis" report have considered animal health as a human health issue.

4. The Public Relations War: the Role of University Scientists and Health Professionals

The story Monsanto's scientists tell about the company's investment in rbGH is a story about the journey from innocence to experience; from an "age of innocence" in which negative response to the technology was completely unexpected, to a "new paradigm" in which the company was well aware of the need to change its public relations approach, obtain the support of respected scientific bodies, and enlist third parties to transmit information to consumers. The company learned that the public no longer welcomes technological breakthroughs wholeheartedly. In response to this realization, it has decided not to release information about products in the pipeline until they have been approved by regulatory agencies. Although "revolutionary" language was important in inspiring the fist wave of biotechnology investment, and recent reports seem to suggest its continued importance, such rhetoric inhibited public acceptance; new technologies are now to be positioned as "evolutionary not revolutionary" (Kowalczyk 1997: interview).

When speaking about the length of the process, the Public Affairs Director perceived the delay as political:

> All the researchers had no doubt it would be approved, because it worked. There was no problem with efficacy. What we were getting back was very positive. What we were unrealistic about was how long it was going to take when you have an innovative product. The FDA underestimated that too. (Kowalczyk 1997: interview)

Authoritative science was regarded as necessary, but not sufficient, for the product's success. "When you've got the science behind you, that you've got a safe and effective product, there's just nothing going on," said Kowalczyk. However, the science itself was

not enough; it also had to be communicated to the public, and third parties, rather than the company, were better placed to undertake that role.

The company regarded the negative publicity as a problem of education; opposition would die once consumers were informed about the product. This required an internal, as well as an external, information campaign to inform Monsanto employees about why the company was proceeding with the product. According to Bob Collier, "we had just as much internal debate as external..." (Collier 1997: interview)

The company regarded the National Institutes of Health (NIH) conference, and the Veterinary Medicine Advisory Committee (VMAC) meetings as helpful to the communications effort. It is not unusual for an advisory committee to review the safety and efficacy data for a human drug prior to approval; however, rbGH was the first animal drug to be reviewed by an advisory committee. The FDA's decision to institute a committee review process was made after the GAO released a report suggesting that increased levels of mastitis could represent a human health risk. A Monsanto spokesperson believed that "since that was a public report, I think Kessler was pretty smart saying let's have this aired...[the VMAC meeting] addressed all the concerns that came out of the report which was very beneficial" (Kowalczyk 1997: interview). Authoritative science was regarded as necessary, but not sufficient, for the product's success. However, the science also had to be communicated to the public, and third parties, rather than the company, were better placed to undertake that role. The company recognized that favourable assessments by committees such as VMAC, or Codex, were not useful unless consumers were aware of their content. "The average person doesn't know about the expert committee of Codex." Materials were distributed to academics, the university extension services, dairy organizations, and dairy processors. (Kowalczyk 1997: interview)

University scientists at land-grant universities in the U.S. have a role in extension services, which have traditionally been responsible for transferring knowledge from the academy to the state's farmers. At Cornell, Barbano regarded food processors and

consumers as the food scientists' constituency; animal scientists provided extension services to local farmers. There was a network of people at Cornell producing information on rbGH for distribution to consumers, food processors, and health professionals. Barbano understood his role as enabling consumers to make an informed choice; "our job is not to promote or to detract, but to allow people to choose. We do a lot of that in extension - how to choose." The level of publicity generated by the extension services was proportional to public controversy about the product. "The number of questions you get fuels the activity level. If there's a newspaper article about a product...there are a lot of questions to be answered" (1997: interview).

Questions were generally answered in the form of fact sheets. Dr. Barbano also coooperated with Dale Bauman and scientists from the University of Illinois, Michigan State, and the University of California to produce a news release for the Council for Agricultural Science and Technology, CAST.[37] The news release responded to each of the critics' claims, not only on human and animal health issues, but economic and environmental concerns. Barbano also co-authored an article for the Journal of the American Medical Association (JAMA).

Powell and Leiss (1996) have argued that risk decisions must be communicated to the public in order to avoid controversy and to dispel misinformation, and have criticized Canadian scientists' silence on rbGH. By entering the fray, however, scientists were subjected to pressure from two directions. Salter (1988) contends one of the characteristics which defines mandated science as a distinct form of intellectual work is the requirement that its practitioners make their work intelligible to both the public and to the scientific community. In the case of rbGH, this pressure was intensified because the controversy began before the product's evaluation was complete. Although the academic scientists could speak about the results of their own trials, the "safety" of the product could only be adequately judged by an assessment of multiple trials: data which they could not have

[37] Jack Doyle has noted that approximately 57% CAST's operating budget comes from 200 agribusiness corporations and trade associations (Doyle 1985: 368).

access to until all the trials had been completed and analyzed. Second, the academic scientists were not only expected to express their opinion to the public and the rest of the scientific community, but were also expected to maintain the confidentiality of the data. Since the company viewed the university scientist as playing an important role in the debate, the scientists' public education function cannot, in this instance, be clearly distinguished from their function in directing controversy away from the company. Academics' function as risk communicators was inevitably complicated by their constituents' knowledge of their relationship to the company. Block felt:

> Caught between a rock and a hard place. You have on one side, the public, including the farmers, who don't trust you because you're under the auspices of the company. The company paid for this research. They also for some reason are attacking us for things that are illogical; how can I say that they're not going to get an increase in mastitis? I can't. I don't know if your cows are going to respond. Then on the other side you have the companies, who say don't raise any questions, when you're giving a talk to somebody. Don't stand up there and say you should look a bit more at IGF-I, yes, IGF-I does increase a bit more in milk, don't say that. Well, why shouldn't I say that, that's what there is! (1996: Interview)

In a 1994 review article, Block and others did raise questions about IGF-I. They indicated that IGF-I concentration rises in milk from treated cows (Burton et al. 1994: 189) and questioned Juskevich and Guyer's conclusion that ingested IGF-I is orally inactive.[38] (190) This was a compromise between the position advocated by Block, who believed that although IGF-I "has to have oral activity," the amounts in milk were too small to raise health concerns, and McBride from Guelph, who believed that the increase in IGF-I levels obliged researchers to investigate further before approving the product. Block's contention

[38] They suggested that further experiments should be conducted, including:
1) the full characterization of hormones and bioactive substances in milk from rbGH-treated cows, including compounds such as prostaglandins, erythropoietin, progesterone, prolactin, thyroid hormones, gonadotropin-releasing hormone, thyrotropin-releasing hormone, growth hormone releasing factor, vasoactive intestinal peptide, epidermal growth factor, estrogens, relaxin, plasmin, interleukins, tumor necrosis factor, insulin, IGF-I, IGF-II, and GH;
2) the feeding of milk from rbGH-treated cows to neonatal primates to determine the effects on gastrointestinal tract development, absorption, and function; and
3) the effects of consumption of milk from rbGH-treated cows on immune recognition and subsequent immune function in the gut (Burton et.al. 1994: 190).

was that it should be investigated, but the approval process should not hinge on the outcome (Block 1996: interview).

In its public-relations battle, Monsanto also garnered the support of various professional groups, including the American Medical Association, the American Dietetic Association, and the American Pediatric Association. The support of third parties became even more critical after the FDA directed Monsanto to stop promotional campaigns, including those by the trade association, the Animal Health Institute (AHI) which had co-ordinated the manufacturers' public relations management. (Kowalczyk 1997: interview) In 1991, the Center for Veterinary Medicine (CVM) wrote to Monsanto warning the company against improper promotion of the drug in the pre-approval period.[39] (*Chemical and Engineering News*, 1994: 8) This was a turning point for the industry; Monsanto recognized that information would need to be distributed indirectly, through third parties. In their communications with industry, academia, and the medical profession, company managers stressed that rbGH was a protein hormone, and is digested like any other protein; that bovine growth hormone was already present in milk and levels did not increase after treatment with the recombinant product; and that it is not biologically active in humans. (Kowalczyk 1997: interview) Professional bodies were willing to participate in the effort to assuage public fears about rbGH:

> Even without us prompting, people were so outraged that they said if you can't go out there and talk, I'm going to. So you had people...who said this isn't right, these people [opposition groups] are polluting science and scaremongering and I want to speak out. Well, a university professor standing up and talking about something has a lot more credibility than Monsanto, or any company coming out and saying "believe us." So it actually worked in a much more beneficial way by having these third party people standing up and talking about it. (Kowalczyk 1997: interview)

In March, the AMA's Council of Scientific Affairs published a report on agricultural biotechnology, which had been adopted at the AMA's 1990 General Meeting. The aim of the report was to "promote the education of the medical community, and dispel

[39] Monsanto was later criticized by the Inspector-General for the Department of Health and Human Services for continuing promotional activities after the FDA warning. See *Chemical and Engineering News* (1994) and Department of Health and Human Services, Office of Inspector General, 1991.

public misconceptions." Since physicians were the scientific resource most readily available to the public, the Council argued, they should be informed about the safety of the product in order to be able to alleviate consumers' concerns (AMA Council on Scientific Affairs 1991: 1429).

A spokesperson for the American Medical Association was motivated to speak because he feared that criticism from animal rights and anti-biotechnology groups posed a threat to science. He believed that biotechnology held enormous potential for medicine; "we are right on the wave of the greatest scientific revolution that has ever occurred in the history of mankind" (Image Base, 1993) and was dismayed at the prospect that this revolution might be defeated by anti-biotech groups.

> Our feeling was that this particular biotech product was going to be the most well-researched product there is and if you couldn't win the public relations battle to accept milk from bST-treated cows you didn't have a ghost of a chance to get the public to accept other things in the scientific pipeline. It was a test case, and we felt it was a must-win case because the company had already invested a lot of money in R&D by the time it became a public issue. (Schwarz 1997: interview)

Dr Schwarz also trusted the ethical, and scientific, judgement of Monsanto's CEO, Richard Mahoney, and the company's Vice-President for Public Affairs, pediatrician Dr. Virginia Weldon:

> [Monsanto's] CEO is a very bright intellectual with very high ethical standards. He didn't like to lose. He wasn't going to lose for any reason except the science was no good. We had quite a bit of interaction with them. (1997: interview)

He believed that Mr. Mahoney's fortitude led to the eventual marketing of bST:

> If you didn't have a CEO like the CEO of Monsanto at the time, and a company with enough resources, they would have given up on the product long before it came to be marketed.

On the evidence reviewed by the AMA on bST:

> We reviewed every scrap of paper that had been published in the scientific literature. We also had ongoing conversations with Monsanto, and followed the kinds of experiments that were done there; we also had conversations with the FDA. We also had public and private debates with [opponents of the drug].

Although the support of the associations was advantageous to Monsanto, association representatives did not mention contact with the company as providing the impetus for their actions:

> Of course Monsanto was very pleased that we were doing this, and they were pleased with the outcome of our evaluations, but we never had a formal relationship with Monsanto. We didn't do the evaluation for them nor did we get paid for it.

Both the ADA and AMA have committees which are responsible for producing position statements on controversial issues of relevance to their members. The AMA's Council on Scientific Affairs produces between 15 and 20 reports each year dealing with issues of concern to the medical community. Both organizations' statements are reviewed by their House of Delegates before the final draft is produced. The AMA also sends out a draft of the paper for comment to the relevant medical societies, or recommended experts; these comments are incorporated into the draft before it is submitted to the House of Delegates (Schwarz 1997: interview).

Internal opposition was overcome by communication within the organization. Within the AMA:

> If we did have a group that was uncertain or wavering, or moderately hostile to the use of bST, we'd go see them and describe everything from what the substance is to what it isn't and what tests have been done, and as I recall without exception these audiences came behind us and the position we'd taken.

The Association agreed to endorse the FDA's approval of bST because:

> Their conclusion was consistent with our conclusions. Second, because we knew it would be controversial and we wanted to weigh in on the controversy. Third, we wanted to advise the public of what our scientific process was. And I'm sure there was probably a call from Monsanto saying are you people going to say anything. Since the FDA's decision agreed with our report, it was quite easy to put out a statement of support (Schwarz 1997: interview).

Representatives from the American Dietetic Association (ADA) and its Canadian counterpart also trusted the judgement of their colleagues who were engaged in biotech. research. Dr. Beth Kunkel of the ADA was persuaded by her colleagues' position that biotechnology was not qualitatively different from traditional plant or animal breeding techniques, but merely accelerated the pace of genetic change (1997: interview). Dr.

Gougeon of the McGill Nutrition and Food Science Centre had confidence in the abilities of her colleagues who were researching rbGH at McGill, and her statements were informed by conversations with them, as well as by her review of the literature at that time.

Both organizations were aware of their role as a resource for consumers; the ADA noted that "[d]ietetics professionals are perceived by the consumer as reliable providers of food and nutrition information and services" (Kunkel 1993: 189). The education of other professionals also motivated the organizations' stance. The AMA's Council of Scientific Affairs report on agricultural biotechnology stated its aim: "to promote the education of the medical community, and dispel public misconceptions." Since physicians were the scientific resource most readily available to the public, the Council argued, they should be informed about the safety of the product in order to be able to alleviate consumers' concerns (1991: 1429). Monsanto was not unaware of the organizations' public role and regarded their support as critical to the success of their public relations strategy. The support of the professional associations enabled the company to reach greater numbers of people and to diffuse controversy. In the words of Monsanto's Public Affairs director, "we realized there's no way we could go to every consumer in the country, most of them don't care anyway, we need to get all the scientific communities out there and people who would potentially be called upon to know about it" (Kowalczyk 1997: interview). Later comments by Monsanto representatives highlighted the usefulness of this resource; the Dairy Research Director, Robert J. Collier, said that "when the approval came...consumers did call. They went to these professionals, and it ended there" (Collier 1994).

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[40] The ADA defines an Association Position as "a statement of the Association's stance on an issue which impacts the nutritional status of the public, is derived from pertinent facts and data, and is germane to the mission, vision, philosophy an values of The American Dietetic Association." (ADA 1997)

The AMA's Council on Scientific Affairs produces between 15 and 20 reports each year dealing with issues of concern to the medical community. The ADA also has a mechanism for establishing positions on controversial issues. The ADA's position paper was written in response to a debate at the House of Delegates meeting at which criticisms of biotechnology had been voiced. Dr. Kunkel wanted to "argue for a more balanced paper...to look at the potential benefits as well as the risks". (Kunkel 1997: interview) Both organizations' statements are reviewed by their House of Delegates before the final draft is produced. The AMA also sends out a draft of the paper for comment to the relevant medical societies, or recommended experts; these comments are incorporated into the draft before it is submitted to the House of Delegates. (ADA 1997; Schwarz 1997: interview; Kunkel 1997: interview)

Internal opposition was overcome by communication within the organization. Within the AMA:

> If we did have a group that was uncertain or wavering, or moderately hostile to the use of bST, we'd go see them and describe everything from what the substance is to what it isn't and what tests have been done, and as I recall without exception these audiences came behind us and the position we'd taken. (Schwarz 1997: interview)

The companies created a list of medical professionals and academics who could be called upon to speak in place of Monsanto representatives. As a result of this strategy:

> A couple of things happened; first of all, the issue usually died away, and there was no controversy because having an activist and an academic person in an exchange doesn't elicit that much news. Whereas as soon as we step in the place, or another company does, it makes big news. That's part of the lesson we learned on how you can really force communication. (Kowalczyk 1997: interview)

The articles and fact sheets were geared toward their target audience; it was assumed that consumers, for example, were not aware of the difference between steroid and protein hormones, so this was emphasized in consumer communications. Doctors, however, were assumed to understand the difference between the two and would automatically be aware that protein hormones are digested. The food industry was another group targeted by extension services. Factory managers were given information on rbGH safety in the event that consumers called their local cheese factory with questions.

Monsanto has used a similar strategy with its other biotechnology products. The company now distributes information to scientific bodies early in the development process, so that these organizations can defend the technologies. After rbGH, the company intends to "let the regulatory process proceed before publicizing the benefits"; that is, that information about a product will not be publicly released until it has been approved by regulatory agencies.

5. The Post-Approval Monitoring Program

After the drug was approved for commercial use in the U.S., the company began a two-year program to monitor adverse health reports from the drug. The program was also designed to check whether label directions were adequate, and whether antibiotic use would be managed under commercial conditions. The company therefore sought out adverse drug reports; conducted a 28-herd study to evaluate drug use; and tracked the amount of milk discarded due to contamination with antibiotics residue before, and after, the drug's introduction. There was no difference in the amount of milk discarded for violative residues in post-approval period. The incidence of mastitis had increased for treated cows in the 28-herd study, and use of drugs to treat the disease had also increased; however, the increase was not as high as in the pre-approval studies, and was taken to be in line with the label guidelines. Clinical mastitis incidence was not monitored as intensively as in the pre-approval studies, since under commercial conditions, it was not viable to do clinical culturing every 60 days (39). Overall, the effects observed on commercial herds were similar to those reported in pre-approval studies, with the exception that the incidence of twinning, cystic ovaries, and abortions was not significant in the post-approval data set.

At the end of November, 1996 the Veterinary Medicine Advisory Committee heard the final report on the findings from the Post-Approval Monitoring Program (PAMP). FDA officials stated that there was no increase in the amount of milk discarded due to antibiotic residues since the start of rbGH sales. The evaluation of 28 commercial herds concluded that the experience with the drug reflected the most of the predictions on the label: mastitis

was increased; feet and leg injuries were higher, as was the use of medications increased. Some of the reproductive problems in the pre-treatment studies were not found in the commercial herds, and the incidence of mastitis was lower than originally determined; however, the regime for assessing mastitis incidence was less rigorous than in the university studies (VMAC 1996).

The FDA said that it had inspected farms in New York and Florida - presumably those that had been reported in the media as having significant animal health problems as a result of the drug - and discovered that the problems "related more to farm management practices than to the use of Posilac" (VMAC 1996: 29). Kronfeld argued that these kind of judgements actually inhibited the reporting of adverse drug experiences:

> This has worked a bit against reporting because, when a farmer reports that he's got a mastitis problem and Monsanto approaches him and they have an animal scientist and veterinarian and told him to look at the label, the FDA agrees with us, it's management, it's not the drug itself, which is responsible for the mastitis. This must be very discouraging for the farmer, and, in fact, I've had a number of farmers call me and I've talked with other people who have said that farmers are being discouraged from reporting adverse effects by this vigorous, enthusiastic, proactive program which will try to pin the disease on the farmer's management rather than on the drug (VMAC 1996: 112).

6. Conclusion

In the rbGH debate, there was a surprising degree of consensus regarding what the evidence showed. It was agreed that the recombinant hormone itself was not biologically active; that there was evidence to support the hypothesis that IGF-I was not orally active; and that there was an increase in mastitis and other animal health problems. However, the theory behind each other these conclusions was complex, and the data inevitably also included counterinstances which conflicted with the overall conclusion. There was therefore disagreement about what action should be taken under these circumstances. Did contrary evidence regarding IGF-I warrant further investigation, or could it be adequately accounted for by established scientific knowledge? Could increased mastitis be managed, or was the management concept itself flawed? These questions were answered differently by individual scientists within institutions, and by the institutions themselves.

There were differences in institutions' criteria for acceptability. These criteria related to judgements about the acceptability of existing dairy practices, and the changes in those practices the drug's introduction would effect. The FDA and the companies believed that the existing dairy practices were sufficient for managing animal health problems, and protecting any resulting public health risk. They also believed that the milk monitoring system was adequate for the protection of public health; critics had less faith in the system's capacity to fulfill the goal of public health protection.

The progagation of scientific information was not only about informing the public, but unavoidably also about maintaining the legitimacy of corporate, academic, and regulatory institutions, and ultimately ensuring the product's commercial success. The profitability of a product can no longer be ensured by its contribution to agricultural, or industrial, efficiency; its safety is also essential for its commercial value. The endorsement of a product's safety is therefore simultaneously an endorsement of its marketability. This was not the driving force behind the endorsements of professional associations and university scientists; their interest was in correcting misinformation and protecting the future application of recombinant technology in biomedical science. However, the public/private distinction in agricultural and biomedical research has become blurred, such that both commercial and public institutions have a stake in the future commercial potential of biotechnology.

Chapter Six

Conclusion

1. The interpretation of the evidence

In assessing the scientific evidence regarding the safety and effectiveness of the product, scientists within the company, the FDA, Health Canada, and the universities operated on the basis of existing scientific knowledge when assessing both animal and human health. The approval of the drug in the United States can best be explained as the result of a regulatory system in which the studies requested, and the interpretation of the data, were derived from a conventional scientific framework. I am using the term "conventional" here in Thomas Kuhn's sense to refer to science which has been accepted by an established scientific community, which he also terms "normal" science. Kuhn attributes the success of the sciences in solving puzzles about the natural world to the existence of such frameworks or paradigms, which enable the existence of certain kinds of entities and relationships to be taken for granted, and indicate which areas need still to be explored. Paradigms are necessary not only for the progression of scientific knowledge, but for the formation of any coherent thought about the natural world. It is only within a particular framework that scientists are able to determine the relevance of their data, and to distinguish anomalous instances from overall patterns.

In this case, conventional science included the literature on human studies conducted with natural bGH in the 1950s, and, since rbGH was a protein hormone, the literature on protein digestion and absorption. Conventional science constructed reviewers' expectations about the likely result of safety studies, enabled them to decide what kinds of studies should therefore be requested, and influenced their interpretation of the data. Initially, the reviewers' consideration of the human health implications of hormone use focused on the biological activity of rbGH. The bGH studies of the 1950s had demonstrated that the pituitary growth hormone was not active in humans; it was therefore

expected that the recombinant version would not be biologically active either. Experiments on rats were undertaken to test this hypothesis, and the data confirmed reviewers' expectations. The decision to allow milk from investigational herds into the food supply was based on this data.

Further examination of the literature suggested that another protein, insulin-like growth factor I (IGF-I), mediated the effects of growth hormone. Reviewers' initial expectations about the effects of IGF-I were formed by their understanding of conventional scientific knowledge about the substance itself, and the class of compounds it belonged to (proteins). Based on scientists' knowledge of conventional science, however, it was not expected that the ingestion of IGF-I in milk from treated cows would have any effect on human health, and IGF-I studies were regarded by scientists as unnecessary. Controversy about the drug led the FDA to request studies in spite of the reviewers' convictions about the unlikelihood of risk. The study parameters were also determined by reviewers' expectations. The length of the IGF-I studies was set according to the length of time one would normally expect to see an effect from administration of a protein.

Generally, the resulting data confirmed scientists' expectations, although anomalous results were reported. Anomalies were only apparent in contrast to an expected pattern which had already been established by earlier studies. In instances where such anomalies did appear, they were also viewed through the conventional paradigm in order to decide what effects could reliably be attributed to the drug itself. Regulators distinguished between *statistical* and *biological* significance. That is, they did not assume that a statistically-significant difference between the treated and control groups could automatically be attributed the drug, but considered whether the changes were consistent, and whether they made sense in terms of existing scientific knowledge about its potential effects. So, for example, when female rats displayed effects not shown in male rats, this was not attributed to the drug, since nothing in the literature indicated that the effects of IGF-I were sex-specific.

Conventional science formed the knowledge base for academic and corporate as well as regulatory scientists. However, the pressures under which regulatory scientists operate tend to make them more reliant on conventional knowledge than their counterparts whose work does not perform a specific public policy function. In order to determine which studies were most appropriate, and in order to interpret the data from those studies, regulatory scientists employed the assumptions and beliefs which were prevalent in their own training and accepted by the established community of which they were a part. Regulatory scientists relied on conventional science, particularly as it was expressed in the literature, because their mandate precludes basic research, and requires that they reach a conclusion which can be justified to the drug sponsors within a given period of time. This conclusion, as Salter (1988) has pointed out, will also eventually be subject to public scrutiny, but the immediate recipient is the sponsoring company.

There are several dimensions to the time limitation. Scientists in both the U.S. and Canada have 180 days in which to review the data package submitted to them by the drug sponsor and to decide whether to approve the drug, deny approval, or request further information. The time limitation does not compel a reviewer to approve a product he or she believes to be "unsafe." However, reviewers were conscious of the importance of timeliness in terms of its impact on their own career prospects, (timeliness was one of the criteria by which they were assessed at yearly performance reviews), and on the sponsoring company. There was an awareness that a request for further studies imposed costs on the company, both because of the resources expended on the study itself, and because the additional time would delay market release. When competition between companies was fierce - as in the rbGH case - the cost of delay was particularly high.

Reviewers would not violate their own definitions of safety in order to approve a product; however their definition of safety was bounded by notions of what they could reasonably ask a company to perform which was, in turn, dependent on the distinction between conventional and unconventional science. Human health evaluators regarded it as

reasonable to request further information, in spite of the financial burden this implied, provided that there were good scientific grounds for such a request. Given that scientists' expectations, and their interpretation of anomalous data, were largely determined by conventional science, I would contend that "reasonable" requests must therefore remain within the boundaries of normal science, and the investigation of anomalies which would not be regarded as problematic within the established framework would not necessarily be regarded as reasonable and therefore as placing an unnecessary burden on drug companies.

The system in which companies, academics, and regulators operate is not merely external to them, exerting its pressures from without, but becomes incorporated into their conceptions of reasonableness, timeliness, and therefore of safety. This is not to suggest that reviewers are automatons, uniformly reproducing their mandate. Individuals have a high degree of latitude in deciding whether a product is "safe"; in both Canada and the U.S. the decision regarding crucial elements of the human health review was made by a single reviewer, and supported by his or her superiors. In forming their decisions, however, scientists work with an internalized understanding of their role within the institution in which they operate, and the consequences of their actions for those affected by them.

The reliance on conventional knowledge was problematic for a product as controversial as rbGH. Critics believed that the anomalies could not be explained by the existing paradigm. In the absence of any other forum for questioning the appropriateness of agricultural biotechnology in general and rbGH in particular, critics seized on reports from scientists outside the debate whose conclusions represented a challenge to the conclusions of academic, corporate, and regulatory scientists who contributed to the decision-making process about the drug. Not all scientists approved of the use of their work by the drug's opponents. The conclusions these scientists reached, however, would seem to confirm some of Kuhn's propositions regarding the difference between conventional and unconventional science. The work which presented a challenge to conventional views about protein breakdown was conducted by researchers who were not specialists in the field, and

who had investigated it as a consequence of other research they were pursuing, rather than in their normal line of work or in response to the rbGH debate.

Viewed from the perspective of this research, the anomalies in the studies submitted to the FDA warranted further investigation. Critics wanted the FDA to review its human health decision in the light of more recent research. Although reviewers recognized that the critics' concerns could not be ruled out completely, within the understandings of normal science, the critics' inferences were nonsensical and could not justify the expenditure of further resources to explore what they believed had been adequately investigated within the paradigm. Once a conclusion had been reached with which the reviewers were satisfied, their role, and their own sense of self, required that they stand by that decision. From their understandings of existing science, the likelihood of a human health risk was virtually non-existent. From the critics' perspective, however, even a low risk was not acceptable when the drug itself was perceived as offering few benefits against which the attendant risks could be weighed.

In Canada, the IGF-I issue created controversy within the regulatory agency as well as outside it. The Chief of the Human Health Division of the Bureau of Veterinary Drugs, Dr. Man-Sen Yong, decided that the use of rbGH did not represent a risk to human health. Reviewers within the Bureau dissented from Dr. Yong's interpretation, and objected to a decision having been made unilaterally. The human health decision in Canada was interlinked with questions of the Bureau's decision-making processes and degree of autonomy from corporate pressure. Although the IGF-I issue was not specifically linked with concerns about pressure on the Bureau from corporate agents, the dispute about the interpretation of evidence occurred in an environment in which reviewers alleged that their decision had been overturned by managers who had been pressured by drug sponsors.

The critics also raised questions which had not been considered within the regulatory process and which were linked to broader questions about the consequences for human health of perceived health risks, and the potential to aggravate latent risks in the

food system. For the critics, the health and safety questions could not easily be separated from concerns about economic risks. Farmers feared that the perception of a human health risk would cause milk consumption to drop, further threatening livelihoods which were at risk due to increased production. Consumer and food policy groups noted that there were not only economic, but health, consequences for reduced milk consumption. These kinds of secondary questions, however, could not be addressed through existing regulatory mechanisms, nor did individuals working with the relevant institutions think they needed to be addressed.

The FDA's human health decision was based not only on conventional scientific knowledge, but on what I have called "contextual" knowledge - adapted from Helen Longino's definition of contextual values, judgements about the way things are or ought to be. In order to decide whether differences in IGF-I levels between treated and untreated cows in investigational trials meant that treatment posed a risk to human health, reviewers considered such factors as the level of the growth factor in saliva, human breast milk, and in pasteurized milk and infant formula. The scope of contextual knowledge was expanded by the GAO's investigations, which pushed the FDA to debate the use of antibiotics on dairy farms and the effectiveness of the institutions in place for ensuring that these practices did not lead to the contamination of the milk supply with antibiotic residues. The GAO advised that the product should not be approved until this issue was resolved. The FDA opened this issue to its advisory committee for consideration. At the meeting, it contended that public health would be protected by the existing state and federal monitoring system, which had been strengthened by recent reforms. These reforms had been instituted, however, as a result of previous GAO criticism of the system's failure to test for a wide enough range of antibiotics. A more recent GAO report suggested that although the FDA had expanded testing, the Agency had failed to keep up with antibiotic use, and there were still many drugs which were not being detected. In the judgement of company and FDA scientists, the institutions currently in place could protect public health.

With regard to animal health, the data were more ambiguous, and the animal health decision cannot be detached from understandings about the nature of the existing system of dairy production. Contextual knowledge, therefore, played an important role in the animal health decision. The data from these trials was difficult to interpret because rbGH did not induce any specific toxicological effects, but resulted in an increase of common animal health problems. The extent of the increase could not clearly be determined by studies specifically designed to test safety, which involved a small number of animals, and so it was decided that health variables would also be measured during the efficacy trials, which involved larger numbers of animals. Even these trials were not sufficiently large to base a conclusion on individual trials, so the data were pooled; however, the incidence varied from herd to herd, complicating data pooling. Under these conditions, the animal health data indicated that there was an increase in the incidence of mastitis, and of various reproductive problems, associated with rbGH use. Reviewers had to decide, therefore, not only what level of disease incidence was associated with rbGH use, but what level was acceptable. As with the human health data, reviewers tried to determine the *biological* significance of *statistically* significant increases in these variables. In order to draw conclusions regarding biological significance, reviewers compared the disease incidence in treated animals not only with the control group, but with the general population under a range of conditions. They also considered whether the increase was *subtle* or *catastrophic*. A subtle increase was acceptable, whereas a catastrophic increase, clearly, was not. They also assessed whether the increase were *manageable*. "Manageability" had slightly different meanings in human than animal health. The human health impact was partly determined by an assessment of the capacity of existing institutions to monitor, and prevent, antibiotic contamination of milk. With regard to animal health, an increase in disease incidence could be regarded as "manageable" if the *existing* situation were assumed to be acceptable, and if the increase did not exceed a certain threshold amount. These calculations were contextual in the sense that they relied on an assessment of the

acceptability of existing dairy practices; farmers' abilities to cope with current, and potentially increased, disease levels; and the point at which such increases would no longer be "manageable." These judgements could be contested, but not definitively answered, on the basis of strictly "scientific" evidence. Although corporate and regulatory scientists disagreed about the cause and extent of animal health problems, they agreed that an increase in disease incidence would be "manageable". This conclusion was based on the premise that existing levels of disease were acceptable.

Existing dairy practice was reflected in both the trial protocols and the analysis of the data. Guidelines were developed by the FDA and its consultants for the recording of mastitis data after trials indicated that the disease was problematic. These guidelines attempted to balance the requirement for clear scientific information with the need for the trials to replicate "real-world" conditions, which involved the use of antibiotics to treat mastitis and other infectious disease, and of hormonal treatment for the regulation of reproduction. The use of these medications was therefore permitted on the trials.

When interpreting the data, FDA deliberated about what level of disease increase farmers could manage. Their deliberations were based on their own experience of dairy farming and their training, as well as a reading of the literature, attendance at conferences, and their interaction with the companies. Ideas of manageability were based on comparisons with notions about what a "successful" farmer was currently managing. Although this was not stated by the reviewers I interviewed at the FDA, their deliberations about the manageability of the problem must, in my view, have entailed an assessment of the economic impact of the drug. Mastitis is the most costly disease for the farmer because milk from mastitic cows must be discarded. Reproductive disorders also involve an economic cost to the farmer. I would take the reference to a "successful" farmer to mean *economically* successful, and that the calculations about drug safety therefore involved considerations about the extent to which farmers would be affected economically if they adopted the product. An academic consultant claimed that the FDA assessed the impact of

mastitis by comparing the expected increase in milk production with expected milk loss due to the disease, and concluded that the productivity increase would outweigh the loss. I have not had this confirmed by the FDA.

Critics were skeptical about the concept of manageability, which appeared to them as an arbitrary distinction. At the interviews I conducted, "manageability" initially seemed as if it were a difficult concept to articulate because it was based on reviewers' tacit knowledge from their own experience and training. However, the FDA did come to a conclusion about what level of mastitis was acceptable, and informed the company of what the "threshold" was. This limit was not expressed to the critics, however, who remained confused about its basis.

The critics also contested the statistical methods used by the FDA and the company to reach their conclusions about the extent of the increase. The differences in methodology are less important as a cause of controversy than the background assumptions motivating them. From the FDA's perspective, the increase, when compared with existing conditions, was acceptable. The critics disputed this conclusion and the comparative method underpinning it, but they also disputed the assumption that existing conditions were acceptable. rbGH was introduced during a period of rural crisis, in which the number of farm closures, loss of income, and social breakdown in rural areas had reached proportions not seen since the 1930s, when forms of income support and import protection were first introduced to compensate for the devastating effects of the Great Depression. As that system began to buckle under the strain of farm debt and overproduction in the 1970s, farmers questioned the application of technology which had contributed to vastly increased productivity which, in the context of farm support, had led to the overproduction crisis.

The contrast with the Canadian example serves to highlight the potential for different interpretations of the data and the extent to which judgements about acceptability were dependent on contextual knowledge. In the Canadian case, the Division Chief primarily responsible for the animal health review prior to 1996 believed that the data raised

serious animal health concerns. It is possible that in the initial stages of the review, the FDA shared similar concerns. However, the former Health Canada reviewer did not agree with the FDA's conclusions and operated with very different conceptions of what constituted a "subtle" versus a catastrophic effect. The threshold of acceptability would appear to have been much lower in Canada.

Monsanto, and the university researchers who acted as principal investigators on product trials at land-grant universities in the U.S. and agricultural colleges in Canada had also concluded that the drug was safe, but the reasons for their conclusion differed from the FDA's. University and Monsanto scientists attributed the increase in mastitis associated with the drug to increased production levels and to the higher pre-treatment incidence in treated animals compared to controls. Although some Canadian scientists were concerned that the attribution of mastitis to high levels of production rather than to the drug had not been sufficiently well-established, they did accept the relevance of the relationship. The FDA, however, did not accept this as relevant.

The FDA did consult with the company during the review process, however, and when deciding on the wording of the accompanying product label. It is difficult to determine what effect these consultations had on the FDA's conclusions. The company was able to obtain changes to the protocol which appear relatively minor, but which did enable the company to provide evidence for its contentions about mastitis incidence in the treatment groups. By ensuring that the protocols measured disease incidence before treatment, the company was able to argue that this was an explanatory factor.

Although there were differences between the company's and the FDA's interpretation of the animal health data, ultimately both groups of scientists agreed that the risk involved was acceptable. This conclusion was rejected by groups for whom the existing situation was not acceptable. The animal health decision, and the reaction against rbGH, needs to be placed in the context of the 1980s farm crisis. The political economy of agriculture literature has explained the crisis as the result of a crisis in the industrial model

of production into which agriculture has been integrated. The model consisted in a system of mass production and consumption, and relied on a complementary system of regulation. In the post-World War Two era, the use of industrial inputs in agriculture, which had commenced in the 1920s and 1930s, expanded further, and was accompanied by the transformation of farm production into industrial inputs for processing by food conglomerates. The advancement of these two trends meant that agriculture was no longer a discrete sector, but had become a subordinate part of the industrial production system. These trends, however, had initially been facilitated by nationally-based farm support programs introduced in the 1930s to protect farmers from the vagaries of the international market place and to reduce the disparity between urban and rural incomes. The deployment of state price-support programs in the U.S., and the adoption by other Western countries of similar programs modelled on the U.S. system, constituted one aspect of what Harriet Friedmann has termed the "food regime," an implicit framework of rules governing the regulation of food production on a global scale. Although policies aimed at domestic protection, they also facilitated the integration of food production across national lines. This combination of domestic protection and transnational production characterized the "surplus regime", in which overproduction of wheat, soybeans, and cheap oils was disposed of through food aid programs and export of feed grain for cattle, as meat consumption expanded. In the early 1970s, however, this regime collapsed with the export of massive quantities of wheat to the Soviet Union (the surplus regime had previously excluded the socialist bloc), the breakdown of the Bretton Woods monetary and trade regimes, and the oil price hike. Although the transformation of agriculture into a segment of global, industrial production was predicated on government support programs, transnational production has since become decoupled from domestic regulation. New systems of regulation are gradually emerging. For the first time since negotiations began, agriculture was included in the Uruguay Round of GATT negotiations, with the U.S. aiming to reduce agricultural protection schemes worldwide.

The introduction of rbGH, and resistance to it, needs to be placed in the context of the breakdown of the surplus regime, with its component systems of national regulation, and the extension of the transnational restructuring of food production and diets, coordinated by transnational agri-food corporations rather than by national governments. In this context, technological innovation could facilitate competitiveness in a globalized marketplace. Agricultural biotechnology could promote the productivity and competitiveness of American crops in world markets, a theme that was reiterated repeatedly by rbGH proponents at successive Congressional and advisory committee hearings in the United States. With global competitiveness as the goal of the early 1980s, agricultural economists suggested that rather than banning the technology in order to preserve the U.S. price support system, or, in Canada, the supply management system, these programs should be eliminated in order to facilitate the application of the technology and the increased productivity of North American agriculture. The solution to the overproduction crises which resurfaced in the 1980s was not the blocking of productivity-enhancing technology, but the elimination of programs which distorted market mechanisms. Most rbGH proponents accepted, however reluctantly, that the level of government support for agriculture would gradually decline, and that the trend toward greater efficiency, fewer cows, and fewer farms would continue. Under these conditions, rbGH represented a logical means to increase the productive efficiency of American agriculture and its capacity to compete in world markets. The drug's manufacturers viewed technological applications as just as essential to the continued economic competitiveness of agriculture as to other industries. Corporate developers believed that the decline of American industry could be attributed to its failure to invest in new technologies, and that agriculture was similarly doomed if it resisted the advent of biotechnology.

From the perspective of the political economy of agriculture literature, however, the analogy between agriculture and industry is false. Unlike the production of industrial goods, the growing of food is dependent on ecological cycles. The application of

technology has occurred without regard for agriculture's ecological distinctiveness and cultural importance, and resulted in environmental and social problems. Industrialization, which was facilitated by the institution of social protections under the surplus regime, has continued in the wake of the regime's collapse. The enhancing of global competitiveness through the application of agricultural biotechnologies represents an extension of, rather than an alternative to, industrialized agriculture. The abandonment of social protections in an industrialized system will not provide long-term solutions to the problems which emerged during the surplus regime, and alternatives to this system must be sought.

Monsanto persisted with drug development, in spite of the resistance to its introduction, because of the company's belief that its future profitability depended on investment in biotechnology, and rbGH was the first biotech. product in the pipeline. The company's interest in developing some form of bGH dated back to the 1960s, when scientists had attempted to synthesize a chemical version of the hormone. The advent of recombinant technology enabled this project to be fulfilled. By the 1980s, however, the use of recombinant technology to produce this specific product was less significant than the creation of the technology itself. rbGH was chosen because it was one of the first molecules to become available; had the technology initially been applied to another molecule, Monsanto would have pursued another line of development. Monsanto, like other chemical firms, turned to biotechnology in order to offset declining profitability in chemicals. In the 1970s, leading chemical, oil and pharmaceutical firms turned to biotechnologies as part of a dual strategy to revitalize profits by diversifying production, and extending demand for their agricultural chemicals. In Monsanto's case, agricultural biotechnology fulfilled both goals. As early as the 1960s, the company sought ways to extend the market for its top-selling herbicide, "Roundup", and to develop alternative products. In the 1980s, the company used plant biotechnology to create Roundup-resistant cotton and soybean seeds. In 1997 the company divested its chemical enterprises, renamed

"Solutia", in order to focus on the application of biotechnology, or "life sciences", in agriculture and pharmaceuticals.

The belief in the significance of the biotechnology revolution was the overwhelming force behind the development of rbGH. The company proceeded with the drug, and resisted protest against it, because of the strength of this belief. The commercialization of the drug required that decisions be made at a number of stages, and, at each stage, the company persisted with the product in spite of regulatory and political conflicts. The company made its own assessment of the product's safety and efficacy before submitting an application for regulatory approval. This assessment was based on existing scientific knowledge, and the results from short-term trials. Decisions were also made based on assessments about the drug's marketability and acceptability, but failed to anticipate certain regulatory requirements as well as opposition from farm, consumer, and food policy groups. The initial product route of administration was based on marketing considerations. The marketing department believed that farmers would only accept a product which could be administered like antibiotics, but this affected meat quality, and hence was not acceptable to the FDA. When Monsanto began developing rbGH, company scientists and managers believed that the product would appeal to farmers because they assumed farmers shared the goal of increasing efficiency. Farmers, however, particularly in the main dairying states of Wisconsin and Vermont in the United States and in Canada, were far more ambivalent about the utility of efficiency in a period of record milk surpluses. In the U.S., farmers questioned the wisdom of enhancing productivity not only because they doubted the need for further milk increases, but because they had begun to question the appropriateness of earlier technological innovations which had resulted in vastly increased productivity and a corresponding reduction in farm numbers. Monsanto was surprised by the reaction, particularly from small farmers, since unlike earlier dairy technologies, rbGH did not require a large capital investment and therefore was equally available to holders of small and large farms alike. Company scientists believed that since the technology did not require

a huge capital investment, it was "scale-neutral" and did not represent a threat to small farmers. Protest against its introduction, however, was not based on perceptions of its inaccessibility, but the net effects of its application on the dairy surplus and consequently on dairy support programs.

The company continued to hold that the drug could be beneficial to all dairy producers and, upon the drug's approval, provided incentives which did not discriminate between large and small farms in order to encourage the adoption of the drug among farmers with smaller holdings. Scientists and managers were surprised by the reaction to their message, rather than the reaction to the product itself. The company believed that resistance could be overcome through the dissemination of information. Monsanto needed to convince its own employees, as well as those outside the organization, of the wisdom of introducing rbGH. It also needed to reach consumers to convince them of the safety of the product. Consumer acceptance of the product's safety was important to its marketability. Without it, farmers may not have been willing to purchase rbGH. In order to reach those outside the company, it enlisted the support of medical associations, who also engaged in a process of convincing their own members to back the association's position on rbGH, and biotechnology in general. Questions and uncertainties about biotechnology were expressed within the American Medical Association and the American Dietetic Association before the development of position statements on these issues. By the time the statement had been produced, dissent had been quelled and the entire membership was prepared to back a position originally articulated by an individual or small number of individuals within the group.

The universities also were involved in the debate. University scientists assumed a dual role - as evaluators, and endorsers, of the drug's safety. They contributed to public policy not only through their work, but through their active involvement in the debate about the product's safety. Scientists with responsibilities in extension services as well as in teaching and research informed their constituents about the safety of rbGH, forming

networks across disciplines in order to be able to refer questions to the appropriate expert. The extension role, particularly in the U.S., became more important as the controversy surrounding the product intensified; indeed, it was determined by the extent of the controversy. This role fulfilled several functions for the companies. In 1991, the companies were forbidden from directly promoting the product's safety. The involvement of third parties in the debate meant that support for the product could still be articulated. It also diffused controversy and enabled the company to reach consumers more directly. The researchers, however, did not perceive anything problematic in their role, but regarded it as a contribution to public education which enabled farmers, processors, and consumers to make an informed choice about the product. The scientists' perception reflects the diminution of public research to the extent that the distinction between "public" and "private" goods has been blurred.

In their extension role, university scientists were expected to articulate their position on the drug's safety, although their information was based mainly on their experience from trials conducted at their institution which may, or may not, have reflected the overall situation. Unlike the FDA or the companies, the university scientists did not have the pooled data at their disposal. The individual trials were generally conducted with too small a sample of animals to draw firm conclusions about product safety. In the U.S., however, university scientists co-authored a paper published jointly with Monsanto scientists which analyzed data pooled from 15 trials in America and Europe. This article was published after the product had been approved by the FDA. The scientists were also aware of that the company data was proprietary, and of the competition between companies in the race to get the product to market first.

The relationship between the universities and the company was complex. Both parties gained from the relationship. University studies could be more carefully conducted, and the data more accurately recorded, than field studies. University studies also had greater legitimacy than those conducted at company sites. Companies were able to draw on

the skills and resources from a number of different disciplines within a single institution, and to economize by linking the research performed in each area. For example, food scientists could test the nutritional quality of milk from cows in investigational herds being tested by animal scientists within the same institution. In return, the scientists were able to pursue their own research interests by piggybacking on the company studies. The company provided an amount of additional funding which paid for technicians and materials and thereby allowed university researchers to examine questions they were interested in. In Canada, such financing enabled scientists to apply for matching government funding.

Not only were professional associations and university scientists involved in the rbGH debate, but the FDA itself was involved in responding to queries and answering critics. My analysis here relates closely to Liora Salter's (1988) discussion of mandated science, that is, science which serves a public policy purpose. One of the pressures which mandated science experiences, in contradistinction to normal science, is the pressure to both meet the requirement of public openness while simultaneously addressing the scientific community and maintaining data confidentiality. Only an idealized science, Salter contends, could fulfill these conflicting goals. In the rbGH case, this pressure was experienced by scientists very early in the evaluation process, prior to their evaluation of the animal safety data. The companies and universities conducting contract research publicized the results of their studies very early in the review process, with the result that public alarm about the impact of the drug was raised early, and the conclusions about human and animal health were anxiously anticipated. To allay public fears, the FDA took the unprecedented step of publishing a summary of the human health data in the respected journal *Science*. It also presented some data for review by the National Institutes of Health, and opened its decisions regarding the potential indirect public health risks, and product labelling, to its advisory committees, another unprecedented move for an animal drug. The FDA also publicly endorsed the product's safety, in an effort to defend its own credibility as well as to ensure that time limitations were not exceeded. When inquiries from the public

began to affect reviewers capacities to complete their evaluation in a timely manner, they defended the human health decision publicly. The legitimation process in the case of rbGH, then, was not merely through the act of regulation itself, but through the reviewers performing the dual role of evaluating the product and legimitizing their decision to the public.

The form of "progress" represented by agricultural biotechnology was highly contested during the investigational trials. The creation of the Coordinated Framework for the regulation of biotechnology in 1986, and the Congressional hearings on the ethics of transgenic animal patents in 1987, put biotechnology back on the agenda of public debate. In public discussions, FDA officials tried to distinguish food derived from rbST-treated cattle from "transgenic" products. Biotechnology policy was based on the distinction between "process" and "product", however. When discussing the Coordinated Framework, FDA scientists observed that the Framework was not relevant to the rbGH issue because the product was not "biotech"; however, it was the Framework which promulgated a definition of biotechnology which excluded rbGH from this category. Policy makers distinguished between the *process* and the *product*; the product could be regulated through the existing system; the process was not inherently harmful, and did not, therefore, require separate legislative action. (See Jasanoff 1995) This distinction was ironic given the other discourses about the significance of biotechnology. On the one hand, the belief in the capacity of technology to revitalize the American economy motivated the changes in American patent and tax law, and facilitated the commercialization of biotechnology. The economic implications of this new development were regarded as so profound that proponents warned regulatory restrictions would kill investment and put the U.S. at a comparative *dis*advantage. On the other hand, the techniques themselves were not regarded as revolutionary, but as a mere extension of traditional means of genetic selection. (See Kessler et al. 1992)

The FDA evaluators attributed the start of the controversy to the actions of a few individuals who were more motivated by concerns about biotechnology and milk over-production than the drug's human health implications. They also believed that the symbolic value of the product inflated the sense of public danger. Dr. Sechen is surely right in identifying that public anxiety is more likely to be aroused by a perceived danger from milk than from other products. Protest groups were well aware that the manufacturers' choice of biotechnology product did not help their case. However, the image of milk purity was one which had been heavily promoted by the industry itself; public alarm at the prospect of its adulteration is at least partly a reaction to past idealization.

However, although the Agency spoke out about the portions of the data it had evaluated, much of it remained confidential. Confidentiality created problems, particularly in Vermont, where the authenticity of the data was challenged by rural advocacy groups and Congressional representatives. Scientists outside the debate, whose results conflicted with those of the FDA, wished to see data which indicated how the experiments were performed. They may indeed have been performed to their satisfaction; however, without a description of the methodology, they were not prepared to accept the conclusions reached.

The second characteristic of mandated science identified by Salter - the interconnectedness of legal and scientific considerations - is less evident in the rbGH debate, although legal considerations were apparent in the FDA's decision on product labelling. The repeated statement that milk from treated cows was the "same" as milk from cows not administered the drug had legal as well as scientific connotations; if the two kinds of milk were the same, there were no grounds on which a mandatory labelling law could be justified.

The difference between purely scientific debates, and those centred around public policy issues - another factor identified by Salter - was particularly apparent in the rbGH case. The language in which it was expressed emphasized the public policy conclusion rather than the anomalies in the data. Scientists outside the debate, on the other hand,

tended to emphasize the experimental constraints under which their work was conducted and the difficulty of extrapolating from it. Finally, as Salter emphasizes in her fourth point, rbGH science, particularly in its estimation of the animal health data, could not be easily extricated from considerations of the drug's impact.

Once a decision on the drug's safety had been reached, the FDA also considered whether milk from treated cows should be labelled as such. Critics, on the other hand, wished consumers to be informed through the mandatory labelling on dairy products from treated cows. They had hoped that, if the drug was authorized for sale, those who opposed its use could effectively mobilize against it by voting with their wallets and refusing to buy milk from treated. This goal could only be easily achieved if the FDA mandated the labelling of milk from treated cows. The FDA was aware of its legal obligations and constraints with regard to labelling policy, however. Although the Agency recognized consumers' right to know about the content of the food they were consuming, it also recognized that the "right to know" had not been broadly construed. Under existing guidelines, labelling could not be required unless consumers were deemed to have a material interest in the product label; that is, if the milk presented a human health risk, or unless its organoleptic qualities (taste, smell, texture) differed from milk from untreated cows. The Agency was aware that by going beyond these guidelines, it risked imposing a greater obligation on the company than was required by the statute, and that such a labelling requirement could be regarded as false and misleading if it implied that the milk from treated cows was inferior to that from untreated animals. The F.D.A. did recognize a consumer interest in product labelling by permitting voluntary labelling of milk from untreated animals. In order to avoid the implication of inferior quality, the guidelines stipulated that any label noting that a product was rbGH-free must also state that there was no significant difference between milk from treated and untreated cows. The scope of labelling, therefore, was largely determined by the health decision, although critics had hoped that it would provide a way of resisting the decision that had been made.

Voluntary labelling created a number of problems. It is the farmer who is *not* using the product who has to demonstrate that his or her product is rbGH-free. Soon after the product was approved, Monsanto threatened two companies who were labelling their product rbGH-free with legal action, although their label also included the "no significant difference" disclaimer. Conflict erupted between states when guidelines in one state, which outlawed any mention of rbGH on product labels, resulted in the disposal of products from another state which had instituted labelling guidelines. Voluntary guidelines were regarded as insufficient by states which had campaigned hardest against rbGH labelling laws, but their attempts to introduce mandatory labelling were overturned by the courts, who did not recognize the relevance of consumer interest. In Canada, labelling has been ruled out because of the cost of creating a dual-supply system to separate milk from treated and untreated cows.

2. Conclusion

This thesis has argued that the problems in the science policy relationship arise at the point at which judgements are made about the implications of the data. In this case, although there was a consensus about what the data showed, interpretations varied between contexts, the US/ Canadian contrast being the most obvious example of this.

The science and public policy literature provides valuable insights into the nature of the relationship, but does not adequately explain the rbGH case. The risk communication literature highlights the problems which may result when the nature of risks are not adequately expressed. Lack of communication cannot explain the Canadian case, however, because there was not a consensus to be communicated. Although the literature may explain this anomaly in terms of communication problems within the department itself, this would not account for the reservations about the animal health data held by reviewers responsible for the evaluation. The communication of risks is problematic when there are not adequate mechanisms to ensure that public concerns may have an impact on the risk assessment

process. Also, in the case of the animal health data, judgements could only be made in terms of contextual knowledge about the practices which were so controversial.

Salter's concept of mandated science is useful for understanding the pressures under which regulatory science is conducted, but does not explain the difference in outcome between the Canadian and American case. The difference in the cases highlights the need to examine other factors which influence the science and policy relationship.

Studies which examine science policy from a comparative framework claim that the differences between jurisdictions can be explained in terms of the policy process within each country. Authors such as Jasanoff have argued that the open, adversarial nature of the American political system explains differences in process and outcome between Canada and Europe. This does not explain the rbGH case, however, in which not only have the outcomes been different, but the American policy process has been considerably shorter than the Canadian.

A framework based on Longino's concept of contextual knowledge best explains the rbGH case. Although Longino argues that we make sense of empirical evidence in relation to the background assumptions we bring to it, she does not deny the relevance of the evidence, nor the importance of the scientific enterprise. In the rbGH case, there was a surprising degree of consensus about the evidence, even among the critics. The hypothesis to which this evidence was related was ultimately, however, a social one. A conclusion about safety can only be informed by data, not determined by it, and it was this conclusion which was the source of dispute.

The conventional knowledge which informed scientists' construction of guidelines and interpretation of data interpretation can also be seen in Longino's terms as forming the basis for background assumptions. The extent to which scientists departed from this depended on their institutional affiliation and, in some cases, their specific discipline. Although this did not necessarily determine their answers to "safety" questions, it did influence answers to the various parts of the argument needed to reach this conclusion.

Background assumptions were also related, in the animal health case and its potential human health consequences, to the context into which the drug was to be introduced. Given that the animal safety debate was conducted in terms of questions of production and management, there is no way to disconnect it from contextual considerations.

The safety debate about rbGH/rbST ultimately relates to our expectations of the regulatory system, and the agricultural system. At the time of the U.S. approval, the data generated did not indicate potential human harm. Alternative hypotheses did not indicate a public health risk, but suggested that certain premises on which human safety conclusions were based warranted further exploration. This was beyond the scope of regulatory science in its existing form. When issues regarding the application of biotechnology have not been resolved socially, the demand for them to be resolved scientifically will further increase the pressure on regulatory bodies. The development, and approval, of rbGH in the U.S. was the outcome of a series of decisions at the regulatory, academic, and corporate levels which fostered the rise of the biotechnology industry and limited regulation of its products to a technical evaluation of health and safety under existing law. Concerns about rbGH's social and economic impact, and long-term human health effects, could not be identified within a framework which excluded that former considerations, and evaluated the latter in terms of the conventional scientific framework.

Although there was no evidence of human harm, there was evidence of adverse animal effects. These effects were regarded as manageable, and therefore acceptable, in the U.S., but not in Canada. If we do consider the drug as a management, or production, tool, which can increase efficiency in conjunction with the application of other skills, the question of its acceptability comes down to the kind of production system we wish to have. The related human health questions can not be extricated from this question. The U.S. conclusions regarding this issue were based on the unlikelihood of animal drug residues in milk representing a public health risk. Other questions regarding antibiotic resistance and

food-borne illness could not be answered within this framework, and rbST itself would only be a factor here in a broader set of practices. Compared, for example, with the use of antibiotics in animal feed at subtherapeutic doses, or in treatment of animals at unapproved doses, the increase in medication associated with rbGH use is not regarded as problematic. As those practices themselves become subject to further examination, particularly in the wake of bovine spongiform encepalopathy ("mad cow" disease), spreading antibiotic resistance, and outbreaks of food-borne illness in locations across North America - the demands on regulatory, and other, forms of science will grow unless we also develop alternative methods of considering these questions.

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