FDA REGULATION OF BIOTECH/GENOMICS DRUGS: A SCOPING REPORT FOR INNOGEN

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LIST OF ACRONYMS

ADE: Adverse Drug Event

AMA: American Medical Association

BLA: Biologic License Application

CBER: Centre for Biologics Evaluation and Research

CDER: Centre for Drug Evaluation and Research

CDRH: Centre for Devices and Radiological Health

CFR: Code of Federal Regulations

CFSAN: Centre for Food Safety and Applied Nutrition

CGMP: current Good Manufacturing Practice

CVM: Centre for Veterinary Medicine

DDMAC: Division of Drug Marketing, Advertising and Communications

DMA: Division of Monoclonal Antibodies

DRMP: Division of Review Management and Policy

DTBIMP: Division of Therapeutic Biological Internal Medicine Products

DTBOP: Division of Therapeutic Biological Oncology Products

DTP: Division of Therapeutic Proteins
FDA: Food & Drug Administration

FDC Act: Food, Drug & Cosmetic Act

IND: Investigational New Drug Application

IRB: Institutional Review Board

MATTB: Manufacturer’s Assistance and Technical Training Branch

NCTR: National Centre for Toxicological Research

NDA: New Drug Application

OC: Office of the Commissioner

OCTGT: Office for Cells, Tissues and Gene Therapy

OTTR: Office of Therapeutics Research & Review

ORA: Office of Regulatory Affairs

PDUFA: Prescription Drug Users Fee Act

PhRMA: Pharmaceutical Research & Manufacturers of America

PHS Act: Public Health Service Act

SEC: Securities & Exchange Commission

SSK: Sociology of Scientific Knowledge

VGDS: Voluntary Genomic Data Submission
INTRODUCTION

As new life science technologies become increasingly important to the innovative capacity of the pharmaceutical industry, we are beginning to see a complex restructuring of the biopharmaceuticals sector. The changing regulatory framework around biologics is becoming increasingly important to our understanding of the future for pharmaceutical innovation. This scoping report seeks to provide a preliminary literature review and analysis of changes in the Food and Drug Administration’s (FDA) approach to regulation in the age of genomics.

Remit of Report

- Investigate, through a literature review, the way in which biotech/genomics drugs have been defined by relevant regulatory authorities and trade organisations in the United States. Are the new drugs being categorized differently from traditional ones and in what ways, if at all, do organisations such as the FDA, and the pharmaceutical industry more generally, operationalise particular definitional frameworks for regulatory and marketing purposes?

- Document all relevant information concerning how these regulatory initiatives are perceived and responded to by companies.

- Identify and reference all relevant sources (websites, reports, articles, etc) that have dealt specifically with these important issues.

Methodology

To investigate the problem of regulating biotech/genomics drugs, the first source of information used was the United States Food & Drug Administration (FDA) website. Due to liberal freedom of information policies in the United States, this proved to be an invaluable data resource. It allowed for a comprehensive analysis of how the FDA has begun to differentiate ‘biotech drugs’ from ‘traditional drugs’. This report is primarily focused on FDA initiatives in this area.

The second source of information came from industry accounts. These sources were used to identify and understand the biopharmaceutical industry’s perception of emerging FDA initiatives. This ‘stakeholder’ data was mined from the organisation PhRMA, which is the principal lobby group of the pharmaceutical industry, the websites of three major US pharmaceutical companies (Merck, BMS & Pfizer) and annual report filings to the Securities Exchange Commission (SEC). It quickly became apparent, perhaps unsurprisingly, that companies rarely publicize their views and concerns about FDA initiatives, particularly those relating to potentially controversial issues such as biologics. Nevertheless, articles in science journals such as Nature often provided a good secondary source for industry perspectives.

Finally, a review of the literature sought to identify social science and life science journal articles that had discussed the FDA initiatives. Much of this literature is referred to, when appropriate, within this report. Selected articles are also listed in the ‘Literature Search’ section.
EXECUTIVE SUMMARY

Overview Of Findings
The FDA has not yet provided an explicit definition of ‘biotech’ or ‘genomics’ drugs. Nor have they clearly differentiated these new innovative drugs from ‘traditional’ medicines. However, they have made a key distinction between ‘drugs’ and ‘biologics’, with the latter being conceptualized simply as a subset of the former. The FDA has, to an extent, organized itself structurally around this crucial distinction. It is clear that novel FDA initiatives in this area are continuing, as evidenced by the organisation’s draft guidance on the submission of Pharmacogenomic data with approval applications.

Although pharmaceutical companies now routinely use life science technologies in their drug discovery and development process, and are therefore key stakeholders who will be affected by any regulatory changes, few have publicly disseminated their beliefs and concerns about FDA regulation of biologics, or tried to operationalise alternative definitional frameworks. There may be a number of reasons for this.

However, despite the paucity of both explicit and publicly available evidence, a significant finding of this research has been that the pharmaceutical industry has had a significant influence on both the evolution of FDA policy and the technological trajectory of life science-based innovations.

Section 1
The first section of this report focuses on the structure and organization of the Food and Drug Administration (FDA), which is the primary regulatory body for drugs in the United States. A particular focus is on how the FDA has defined and organized itself structurally around biotech/genomics drugs. The first key finding is that the FDA has made a significant distinction between ‘biologic’ products and ‘drug’ products, although the former are, for regulatory purposes, considered a subset of the latter. Essentially, biologic products are distinguished from drug products on the basis of their composition and manufacturing process – biologic products are derived from living systems (e.g. cell lines, blood, viruses etc.) whereas non-biologic drug products are chemically synthesized. Biotech products, when they have been defined, typically refer to monoclonal antibodies and recombinant proteins. They may be considered a subset of biologic products.

The significance of this distinction should not be underestimated, as it has led to biologic products being governed by an additional Code of Federal Regulations (CFR) that does not apply to drug products. Furthermore, the FDA has begun to organise itself structurally around this definition. Traditionally, responsibility for the governance of biologic products lay with the FDA’s Centre for Biologics Evaluation and Research (CBER). In order to demonstrate their ability to adapt to an evolving biotechnological environment, where biologics are becoming increasingly common, the FDA recently transferred regulatory authority for certain biologic products to the Centre for Drug Evaluation and Research (CDER). This involved the transfer of some 200 employees and a $33 million budget.

Despite the different definitions and jurisdiction underlying various CFR laws, drug products and biologic products are generally subject to the same FDA regulatory principles, namely demonstration of safety, efficacy and suitable standards for marketing and manufacturing. Thus, in exploring the criteria for drug approval, the drug approval
processes, manufacturing standards and post marketing requirements, the primary conclusion made is that the FDA assesses each product individually and determines on a case-by-case basis whether or not it should be classified as a biologic product. The key distinctions are operationalised at the level of the CFR laws applied to the product, and the division (and office within the division) that holds primary responsibility for evaluating the product.

Section 2
The present structure, organization and regulatory/legal principles of the FDA only give us a partial picture of its role in the governance of biologic (or biotech/genomics) products. The new and novel initiatives that are currently being considered must also be addressed, because they may give us an insight into the possible regulatory framework that will define the future of biologics, while simultaneously offer an indication of what the FDA currently considers ‘best practice’ for the incorporation of biotechnological advances in its traditional decision-making process.

Of particular interest is the joint CBER/CDER draft guidelines on pharmacogenomic data and drug evaluation. In 2003, the FDA outlined its current thinking about when and how pharmacogenomic data ought to be included in drug applications. It provided a detailed algorithm to assist companies in drafting their submissions. In those cases where the FDA considers pharmacogenomic data to be non-mandatory, the FDA still encourages drug sponsors (e.g. pharmaceutical companies) to submit the data voluntarily. This suggests that the pharmaceutical industry may come to play a key role in shaping FDA regulations regarding validation and utilization of pharmacogenomic data. The fact that the FDA has openly invited ‘stakeholders’ to provide comments on the draft guidelines before they are implemented, provides further evidence of the industry’s increasing role in the design of the regulatory process. Of course, it is still an open question as to whether the FDA will fully consider and take account of industry perspectives.

Other interesting FDA initiatives include the establishment of ‘Team Biologics’, a specialized inspection team with a dual role to ensure FDA consistency in regulatory policy, and inspect biologic manufacturing plants to make sure that they are complying with FDA standards. This initiative indicates the extent to which the FDA considers ‘biologic products’ a unique and increasingly significant regulatory issue. The CBER also provides a training program for manufacturers. This is to ensure that personnel involved in manufacturing have a thorough understanding of FDA policy and guidelines regarding biologics.

Finally, one FDA initiative that is not directly concerned with biologic products, but is still worth mentioning, is the Prescription Drug Users Fee Act (PDUFA). This program allows drug sponsors to pay a special fee to the FDA in return for an agreed timeline for evaluation. The FDA justifies this program on the grounds that the revenues generated can be used to hire additional personnel and improve overall FDA efficiency. However, many consumer groups, as well as academics, have argued that fast tracked drug reviews have lead to an increase in adverse drug events (Olson 2002, Dove 2003). The FDA has denied these claims.

Section 3
This section explores how the pharmaceutical industry has responded to FDA definitions, organization and initiatives as outlined in sections 2 & 3. The
Pharmaceutical Research & Manufacturers of America (PhRMA) is the principal, and indeed largest, industry lobby group in the United States. PhRMA has established a ‘Key Issue Team’ focused on the FDA & Biomedical Research, particularly the regulatory framework around biologics. However, there was no available data on the organization’s activities as related to the issues in sections 2 & 3.

Pharmaceutical companies have also not widely disseminated their views on FDA initiatives. Several reasons may account for this, so the paucity of publicly available information is not necessarily indicative of the commercial sector’s lack of interest in these issues. For example, most pharmaceutical companies have substantial regulatory affairs departments whose personnel continually liaise with FDA officials, as well as relevant colleagues within their firm’s R&D or marketing departments.

Scanning the literature for excerpts from interviews with relevant industry representatives does allow us to access some industry perspectives, although we cannot make broad generalizations from this data. The data collected for this report does suggest, however, that the unification of CBER and CDER has led to the pharmaceutical industry adopting a ‘wait and see’ approach, although it has expressed concerns regarding the loss of key personnel as a result of the transition. The Pharmacogenomics draft guidelines appear to have been generally well received by industry, but there is still palpable concern about how the FDA might eventually use pharmacogenomic data. The PDUFA has largely been welcomed by the industry, although it has recently come under pressure as drug evaluation times have slowed down once again.

The key finding of this report is that the biopharmaceutical industry, which is the principle funder of pharmaceutical R&D and the only sector with the capability to bring innovative drugs to market, constantly interacts with the FDA, which is the principal regulatory body for ensuring drugs in the United States are both safe and effective. The regulatory framework around biologics is therefore mutually shaped by both the FDA and the commercial pharmaceuticals industry.

Avenues for Further Research

Findings in Section raise questions about the effectiveness of the CBER/CDER amalgamation. How smooth and efficient will be the transition of staff and regulatory duties from the CBER to CDER? What impact will this have on drug / biologic product approval times? There is a great deal of concern about the issue of ‘biogenerics’. Will the CDER adopt a different approach from the CBER, which was generally opposed to facilitating biogeneric competition? It would be interesting to map the FDA’s organizational structure and monitor the ongoing regulatory changes, and the rationale behind them.

The findings of Sections 2 & 3 also offer several interesting avenues for further research. One interesting issue worth exploring would be the mutual shaping of FDA policy by both the regulatory authority itself and the broader pharmaceuticals industry. This would require access to representatives from pharmaceutical companies and the FDA. The FDA guidance notes on pharmacogenomics may provide a good basis from which to assess this mutual shaping of regulatory policy.

The PDUFA may also engender a number of interesting questions. However, since this program was first implemented back in 1992, a great deal of research has already been conducted in this area (see Literature Search section). Nevertheless, there are some interesting questions concerning the enrolment of external expert advisors, the impact of
accelerated drug reviews on drug safety, and the influence of the PDUFA on biotechnological innovation.

Finally, although this report does not deal explicitly with the manufacturing of ‘biogenerics’, this is likely to become a critical issue for FDA regulation in the area of biologics. Industry organizations such as BIO, as well as established manufacturers, have a vested interest in preventing the FDA from permitting the manufacturing of generic biologicals. Following the policy dispute and resultant tension on trade (e.g. with India) and politics (e.g. health care spending reform) would be an interesting area to explore.
1. Role of the FDA in Defining and Regulating Biotech Drugs

1.1 An Overview of the FDA

The FDA is the USA's principal regulatory agency for all food and drug related items. According to its mission statement:

‘The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health’

(Source: [http://www.fda.gov/opacom/morechoices/mission.html](http://www.fda.gov/opacom/morechoices/mission.html)).”

The FDA is divided into 8 administrative centres, each with its own specific remit. In relation to pharmaceutical and biotechnology-based drugs, two agencies are particularly relevant – the CDER (Centre for Drug Evaluation and Research) and the CBER (Centre for Biologics Evaluation and Research). The CDER is directly responsible for approving drugs in the USA, although CBER has historically been the gatekeeper for all biological products (such as blood and blood-products, vaccines, protein-based drugs such as monoclonal antibodies and cytokines). (Source: [http://www.fda.gov/opacom/7org.html](http://www.fda.gov/opacom/7org.html)).

The CBER has, since the 1902 Biologics Control Act, effectively enjoyed primary responsibility for the regulation of biologics. However, on October 1, 2003, the FDA transferred some of the biologic-based approval activities of the CBER to the CDER (see Appendix 1). It’s rationale for doing so was explained by commentators as follows:

‘With the rapid growth of the biotechnology industry, and the increasing similarities between the development and marketing of biologics and NCEs, the FDA has now decided to move many of the CBER’s responsibilities – along with the associated funding and staff – to the CDER’ (Dove 2003).

This suggests that the CDER is now the agency with primary responsibility for regulating the approval process for all therapeutics, regardless of whether or not they are defined as biologics. Thus:

The regulatory responsibility, review and continuing oversight for many biologic therapeutic products will be transferred from the Centre for Biologics Evaluation and Research (CBER) to the Centre for Drug Evaluation and Research (CDER). This change in regulatory responsibility will result in the transfer of applications for products belonging to the following product classes:

- Monoclonal antibodies for in-vivo use;
- Cytokines, growth factors, enzymes, immunomodulators; and thrombolytics;
- Proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors)
- Other non-vaccine therapeutic immunotherapies

The following product classes will remain at CBER:
• Viral-vectored gene insertions (i.e., “gene therapy”)
• Products composed of human or animal cells or from physical parts of those cells
• Allergen patch tests
• Allergenics
• Antitoxins, antivenins, and venoms
• In vitro diagnostics
• Vaccines, including therapeutic vaccines
• Toxoids and toxins intended for immunization
• Blood, blood components and related products

(Source: http://www.fda.gov/cber/transfer/transfer.htm)

The significance of this transfer of regulatory responsibility should not be underestimated. It has been reported that the move involved the transfer of 200 employees and a $33 million budget (Dove 2003). However, one poll suggested that up to 90% of the staff would prefer to leave the FDA than transfer from the CBER to the CDER (Ibid.).

In relation to drugs and genomic-based medicine, one other FDA centre is worth mentioning. The NCTR (National Centre for Toxicological Research) has its own biotechnology initiative. They are attempting to understand “the genome and its relationship to disease susceptibility’ (http://fda.gov/nctr/initiatives.htm#Biotechnology). Within this initiative, transgenic animal models, DNA and protein-based technology, and bioinformatics/computational biology are listed as the main program areas.

The remaining FDA centres are not directly relevant to medicine, drug approvals and drug definitions. These include the CDRH (Centre for Devices and Radiological Health), CSFAN (Centre for Food Safety and Applied Nutrition), CVM (Centre for Veterinary Medicine), OC (Office of the Commissioner) and the ORA (Office of Regulatory Affairs). The latter’s name is somewhat misleading, as it is not at all involved in drug regulatory procedures. Instead, it is involved in the inspection of facilities and monitoring of drug companies compliance with FDA standards.

(http://www.fda.gov/opacom/factsheets/justthefacts/7ora.html).

1.2 FDA Definitions of Biotech/Genomic Drugs

1.2.1 CDER and CBER Classification of Drugs and Biologics
The CDER lists general drug categories, under which pharmaceuticals are categorized (see Appendix 2). None of these categories explicitly differentiates biotech and genomics-based drugs from traditional ones; rather, drugs are classified according to their general mode of action. There is no mention within the CDER of a standardized policy for the classification of biotech/genomics drugs. However, the FDA does differentiate more generally between ‘drugs’ and ‘biologics’. Therefore, drugs are not classified on the basis of them being ‘biotech’ or ‘genomic’, per se. CDER’s definition of ‘biologic product’ and ‘drug’ is as follows:
Biologic Product

A biologic product is any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries. Biologic products are a subset of "drug products" distinguished by their manufacturing processes (biological process vs. chemical process). In general, the term "drugs" includes biologic products.

Drug

A drug is defined as:

- a substance recognized by an official pharmacopoeia or formulary.
- a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- a substance (other than food) intended to affect the structure or any function of the body.
- a substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.

Biologic products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process vs. biological process.)

(Source: http://www.fda.gov/cder/drugsatfda/glossary.htm)

Two other reports reinforce this interpretation. According to the CBER (before it transferred evaluative responsibilities to the CDER):

In contrast to most drugs that are chemically synthesized and their structure is known, biologics are derived from living sources, such as humans, animals, plants and microorganisms. Therefore, CBER is responsible for regulating products as diverse as blood, blood components and their derivatives, allergenics, vaccines, biotechnology-derived products such as monoclonal antibodies and cytokines and growth factors, and somatic cell and gene therapy.

Most biologics are complex mixtures that are not easily identified or characterized; they, include those manufactured by biotechnology, tend to be heat sensitive and susceptible to microbial contamination. (Source: http://www.fda.gov/cber/faq.htm)

Furthermore, the USA’s Code of Federal Regulations, Part 600.3 of Title 21 (21 CFR 600.3) gives perhaps the definitive definition of a biological product:

'(h) Biological product means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man:

(1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.

(2) A therapeutic serum is a product obtained from blood by removing the clot or clot components and the blood cells.

(3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced
therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.

(4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.

(5) A product is analogous

(i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum.

(iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process'.

Source: Code of Federal Regulations; Title 21, Volume 7;(Revised as of April 1, 2003). From the U.S. Government Printing Office via GPO Access (available from: http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/cfr_2003/aprqtr/21cfr600.3.htm)

A key distinction between biologic and non-biologic drugs relates to the manufacturing process. Non-biologic (‘traditional’) drugs are manufactured via chemical processes, whereas biologics are produced through biological processes, such as, for example, the production of recombinant proteins in animal cell lines. In other words, biologics are products based on or derived from living systems (e.g. blood, viruses, proteins, toxins) whereas non-biologic drugs consist of chemical compounds.

1.2.2 Note on Consistency of Term Usage

It should be noted that the terms ‘biotechnology-derived’, ‘biotechnological product’, and ‘biotechnology product’, have all been used by the CBER and CDER in various documents. For example, in issuing guidance on a program for industry entitled ‘Independent Consultants for Biotechnology Clinical Protocols’, the CBER explicitly refer to ‘biotechnology-derived’ products:


However, in almost every case, the term biotechnology-derived, biotechnological product or biotechnology product is accompanied by the term ‘biological’. However, in reviewing the documents (available from http://www.fda.gov/cber/guidelines.htm), despite the variety of terms used, their usage was consonant with definitions for ‘biologic’, as described in section 1.2.1.

1.3 Criteria for Approval of Drugs and Biologics

The CDER is responsible for the approval and registration of both non-biologic and biologic drugs. Generally speaking, the clinical trials procedure applies equally to both ‘biologics’ and ‘drugs’ (which exclude biologics), although different terminology is often used. For example, when initiating a clinical study in humans, an NDA (new drug
application) is filed for drugs, whereas a BLA (biologic license application) is filed for biologics. However, different legal statutes govern the approval of drugs and biologics.

‘Drugs’ are governed by section 505 (b)(1) of the FDC act, which states:

(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.

‘(b)(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (F) specimens of the labeling proposed to be used for such drug. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A)’.


‘Biologics’, on the other hand, are governed by section 351 of the PHS (Public Health Service Act), which states:

(ii) The Secretary shall approve a biologics license application -

(i) on the basis of a demonstration that -

(I) the biological product that is the subject of the application is safe, pure, and potent; and

(II) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent; and

(ii) if the applicant (or other appropriate person) consents to the inspection of the facility that is the subject of the application, in accordance with subsection (c) of this section.


Despite being governed by different laws, the approval process for both drugs and biologics is quite similar. There is a legal mandate for this. Under the FDA Modernization Act of 1997 (section 123 f), ‘congress...directed the agency to take measures to “minimize differences in the review and approval” of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505 (b)(1) of the FDC act.’ (Source: Guidance for Industry
Both drugs and biologics must demonstrate safety and ‘substantial evidence’ of efficacy. In the case of biologics, this is phrased as ‘safe, pure and potent’ (PHS, 351, 2(b)(iii)). Drugs and biologics must demonstrate that clinical studies used to demonstrate the efficacy of these products are ‘adequate and well-controlled’. (21 CFR 314.126: see Appendix 3 for full definition). However, with regards to biologics, this contingency may be waived if:

‘…not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantial effectiveness (21 CFR 601.25 (d) (2)). One such adequate alternative was identified to be serological response data where a previously accepted correlation with clinical efficacy exists. (Ibid., p.7)’

Furthermore, it should be noted that the CDER typically requires more than one clinical study before making an approval decision. However, approval on the basis of a single clinical study is possible if, in the case of drugs:

‘a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds. (Ibid. p. 6)’

‘The FDA has also approved biological products that have been able to demonstrate single, multicenter studies with strong results (Ibid., p. 7)’.

The critical message to be learned from the FDA’s amalgamation of biological products into the CDER’s regulatory sphere is:

1) The same principles for drug approval apply to both drugs and biologics

2) For both drugs and biologicals, evaluation and approval decisions are made on a case by case basis rather than by a standard set of procedures:

‘From a scientific standpoint…it is recognized that the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the claim. Therefore, the Agency is able to accept different levels of documentation of data quality, as long as the adequacy of the scientific evidence can be assured.’ (Ibid., 19)

In providing examples of the types of data that might influence regulatory approval decisions, the FDA has stated explicitly that far more important than simply whether or not a product is a biologic or a drug, is that evidence in support of efficacy is consistent with FDA principles:

‘This guidance is not intended to give a complete listing of the circumstances in which existing efficacy data may provide independent substantiation of related claims; rather, it provides examples of the reasoning that might be employed. The examples are applicable whether the claim arises in the original filing of an NDA or BLA…’ (Ibid., 9)

Therefore, the approval of both ‘biologic’ and ‘non-biologic’ drugs is based upon clinical trial data, which is assessed by the CDER and must conform to their interpretation of ‘validity’. This, in turn, is determined on a case-by-case basis – variables such as the specific drug, disease, clinical trial design, history of the drug and degree of medical need etc., are always taken into account.
1.4 Approval/Regulation of Biologics and Non-Biologics

1.4.1 Drug Review Process

The Public Health Services Act requires all manufacturers of biologics to hold a special license granted by either the CDER or CBER, who oversee the drug approval process. According to the FDA, the drug approval process involves a number of sequential stages, which can be summarized as follows:

Drug Review Stages

1. Pre-clinical (animal) testing.
3. Phase 1 studies (typically involves 20 to 80 people).
4. Phase 2 studies (typically involves a few dozen to about 300 people).
5. Phase 3 studies (typically involves several hundred to about 3,000 people).
6. The pre-NDA period, just before a new drug application (NDA) is submitted. A common time for the FDA and drug sponsors to meet.
7. Submission of a new drug application is the formal step that requests the FDA to consider a drug for marketing approval.
8. After an NDA is received, the FDA has 60 days in which to decide whether to file and review it.
9. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's data regarding the drug's safety and effectiveness.
10. The FDA reviews information that goes on a drug's professional labeling, guidance on how to use the drug.
11. The FDA inspects the facilities where the drug will be manufactured as part of the approval process.
12. FDA reviewers will approve the drug or find it either "approvable" or "not approvable."


This process is similar for biologics:

“Licensing of biologic products under the PHS Act is very similar to the new drug approval process for human drugs. Following initial laboratory and animal testing, a biological product is studied in clinical trials in humans under an investigational new drug application (IND). If the data generated by the studies demonstrate that the product is safe and effective for its intended use, the data are submitted to CBER as part of a biologics license application for review and approval for marketing.

(Source: http://www.fda.gov/cber/faq.htm)
An IND (Investigational new drug application) is required in order to begin clinical trials for humans. INDs are reviewed by both the relevant FDA agency as well as by institutional review boards (IRBs). Formally, the IND form (Form FDA 1571) is:

‘A request for Food and Drug Administration (FDA) authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved new drug application’.

(Source: http://www.fda.gov/cder/forms/1571-1572-help.html)

This form is sent either to the CDER or CBER for approval. With regards to the difference between biologic and non-biologic drugs, whether or not the IND is filed to the CBER or CDER depends on the type of product. Effective from October 1, 2003, as previously noted (in 1.1), an important development has been the transfer of authority for the regulation of certain biologics from the CBER to the CDER: The therapeutic biological products now under CDER's review include:

- Monoclonal antibodies for in-vivo use
- Cytokines, growth factors, enzymes, immunomodulators; and thrombolytics
- Proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors)
- Other non-vaccine therapeutic immunotherapies

(Source: http://www.fda.gov/cder/biologics/default.htm)

The following product classes will remain at CBER:

- Viral-vectored gene insertions (i.e., “gene therapy”)
- Products composed of human or animal cells or from physical parts of those cells
- Allergen patch tests
- Allergenics
- Antitoxins, antivenins, and venoms
- In vitro diagnostics
- Vaccines, including therapeutic vaccines
- Toxoids and toxins intended for immunization
- Blood, blood components and related products

(Source: http://www.fda.gov/cber/transfer/transfer.htm)
The product class determines whether firms submit Form FDA 1571 to the CDER or CBER and, therefore, which agency is responsible for regulating the product. (source: http://www.fda.gov/cder/forms/1571-1572-help.html).

If investigators decide that the clinical trial data is sufficient, they file Form 356H. This form, entitled ‘Application to Market a New Drug, Biologic, or an Antibiotic drug for Human Use’, specifies whether the application is an NDA or BLA. The FDA agency responsible for evaluating the product (CDER or CBER) subsequently decides whether to review the NDA or BLA and, if so, whether or not the drug is ‘approvable’.

Title 21, section 601.2 of the CFR describes the general provisions relating to biologics licenses (Appendix 5). (It should be noted that Title 21, section 601.2 is likely to be amended, because the procedure still calls for all BLAs to be filed at the CBER.) The key message is that biologics must demonstrate ‘safety, purity and potency’; all clinical and non-clinical data relating to the product should be submitted; a full description of the manufacturing process should be included in the BLA; and, finally:

Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products. Applicable requirements for the maintenance of establishments for the manufacture of a product subject to this section shall include but not be limited to the good manufacturing practice requirements set forth in parts 210, 211, 600, 606, and 820 of this chapter. (Source: http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/cfr_2003/aprqtr/21cfr601.2.htm)

The drug approval process applies to both biologics and non-biologics. Basically, the same set of procedures are involved and the process is guided by the same principles in both cases – drugs must demonstrate safety and efficacy before gaining licensure. As noted, the CDER and CBER are responsible for issuing drug licenses, depending on the type of product. It is therefore useful to explore in greater depth the division of labor between the CBER and CDER.

1.4.2 Role of CDER Concerning Biologics

In order to review the biologic products under its control, the CDER has established two new offices. Under the Office of New Drugs, the Office of Drug Evaluation VI was established. It has three divisions: the Division of Therapeutic Biological Oncology Products (DTBOP), the Division of Therapeutic Biological Internal Medicine Products (DTBIMP) and the Division of Review Management and Policy (DRMP).

Under the Office of Pharmaceutical Science, the Office of Biotechnology Products was created. This Office has two divisions: the Division of Monoclonal Antibodies (DMA) and the Division of Therapeutic Proteins (DTP).

(Source: http://www.fda.gov/cder/biologics/default.htm)

Review of IND filings and NDA filings requires co-ordination between multiple offices, each with responsibilities for specific activities, such as reviewing statistical, pharmacological, chemistry-related or medical-related data (Appendix 4 - Figures 1, 2, 3).

Generally speaking, the CDER can be viewed as the primary FDA centre for the approval and licensure of drugs, including biologics. However, the biologics that it
reviews are those with proven track records, such as monoclonal antibodies, cytokines and recombinant proteins. More experimental biologic products, such as therapeutic vaccines or stem cells, fall under the jurisdiction of the CBER.

1.4.3 Role of CBER Concerning Biologics

The CBER no longer has extensive involvement in regulating several classes of biologics. Its Office of Therapeutics Research and Review (OTTR), which was responsible for the evaluation of biologic drugs, has now been transferred to the CDER. Nevertheless, therapeutic products falling under the CBER’s control would still need to follow the procedure outlined in 1.4.1, and continue to be licensed by the CBER.

The CBER recently established a new office; the Office for Cells, Tissues and Gene Therapy (OCTGT), indicating its recognition of an increase in regulatory activities in the areas of cellular and tissue-based products, gene therapies, and all forms of stem cell transplantation. (http://www.fda.gov/cber/summaries/gmp082503me.htm)(Figure 1)

More specifically, the OCTGT will have regulatory and review responsibilities for tissues, cellular and tissue-based products, gene therapies, xenotransplantation, unique assisted reproduction (such as ooplasm transfer) and combination products containing both living cells / tissues and medical devices. (Ibid)

The establishment of the OCTGT is consistent with the CBER’s emphasis on novel biotechnologies. As the press release announcing the transfer of some CBER duties to the CDER reported:

‘This consolidation provides greater opportunities to further develop and coordinate scientific and regulatory activities between CBER and CDER, leading to a more efficient, effective, and consistent review program for human drugs and biologics. FDA believes that as more drug and biological products are developed for a broader range of illnesses, such interaction is necessary for both efficient and consistent agency action.’(Source: http://www.fda.gov/cder/biologics/default.htm)

Therefore, products falling under the CBER’s jurisdiction must adhere to the FDA drug approval procedure outlined in 1.4.1. Furthermore, there is a trend towards greater coordination between CBER and CDER activities.
Figure 1: Organization of CBER (OTTR transferred to CDER effective October 1, 2003). (source: http://www.fda.gov/cber/summaries/gmp082503me.htm)

1.4.3.1 New Biotechnologies and the CBER
The experimental nature of many of the innovative products now falling under the CBER’s jurisdiction is particularly interesting. The CBER recently disseminated its current thinking on genomics and proteomics, and their potential implications for regulatory activities. It stated that these technologies were a:

- Critical component of safe and effective drug development
- Basis for new drug discovery, biomarkers and surrogate endpoints for toxicity and efficacy monitoring
- Means to detect and assess chemical and biological terrorist agents

(Source: http://www.fda.gov/cber/summaries/gmp082503me.htm)

The CBER considered that these technologies had the potential to have a significant regulatory impact on several aspects of drug safety and efficacy assessment:
- Vaccine assessment/potency
- Surrogate endpoints- efficacy/toxicity
- Quality control/quality assurance for product production
- New Bioassays
- Biomarkers for early detection
- Toxicity detection and prediction
- Discovery of new therapeutics targets
- Risk of disease recurrence
- Patient-tailored therapy. Prospective selection
- New paradigm in disease classification/characterization
- Proteomic-based epidemiology

(Source: http://www.fda.gov/cber/summaries/gmp082503me.htm

Despite these potential impacts, CBER decided that no formal, sweeping changes to the drug approval process would be made. However, it is expected that, in time, additional information derived from genetic/proteomic technologies will be included in firms’ IND and/or BLA/NDA filings for drug approval. This will be further addressed in Section 2.2.

1.5 Regulation of Manufacturing

Drugs and biologics produced for clinical trials, and then market distribution after approval, are subject to FDA manufacturing standards. NDA or BLA approval, as well as final marketing authorization, is only granted if the production process adheres to FDA standards. Since the processes for synthesizing drugs and biologics are quite different, it is necessary to consider the manufacturing regulations.

As with other aspects of the drug regulatory process, ‘manufacturing’ is mandated by different sections of the CFR. FDA guidelines for current Good Manufacturing Practice (CGMP) of (non-biologic) drugs are outlined in 21 CFR 210 and 21 CFR 211; for biologics, 21 CFR 600 and 21 CFR 610 are most relevant (http://www.fda.gov/cber/ind/ind.htm). However, there are stipulations in CFR 210.2 (a) that regulatory considerations for both drugs and biologics may in certain circumstances supplement each other. This further indicates the inter-dependency between the regulatory philosophies underpinning drugs and biologics.

‘The regulations in this part and in Parts 211 through 226 of this chapter as they may pertain to a drug and in Parts 600 through 680 of this chapter as they may pertain to a biological product for human use, shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the drug in question shall supersede the more general.’

(Source: http://www.fda.gov/cder/dmpq/cgmpregs.htm#210.2)

1.5.1 Drugs

Appendix 6 lists the parameters outlined by CFR 21 211 that detail the standards that manufacturers must meet in order to adhere to CGMP. Many of the details are not
particularly enlightening. However, it is interesting to consider the scope of the regulatory requirements that must be adhered to. These include specifications on the type and training of personnel; buildings and facilities; equipment; drug product containers; production and processes; packaging and labelling; procedures for holding and distributing the product; guidelines for appropriate reporting and recording; and restrictions on drug product salvaging and returning. Guidelines concerning product contamination, tests for batch consistency and testing stability are also included.

The guidelines list various procedures that need to be followed, but, interestingly, exclude such things as storage temperatures and maximum storage durations. The focus is very much on providing guidance on how to make potency or yield calculations and ensure the facility is sterile.

1.5.2 Biologics

The manufacturing of biologics is inherently more complex than synthesized chemicals, and this is reflected in the guidelines issued by 21 CFR 600 and 21 CFR 610. It might also explain the intense involvement of the CBER (and increasingly the CDER offices) in biological production:

- ‘After a license application is approved for a biological product, the product may also be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by CBER, the manufacturer submits samples of each lot of product to CBER together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer’s tests performed on the lot. CBER may also perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, CBER conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

(Source: http://www.fda.gov/cber/faq.htm)

Appendices 7 & 8 list the CFR standards for biological production. What most differentiates these guidelines from those of non-biological drugs is that they are far more normative and numerous. For example, there are requirements for the maximum level of aluminium permitted in biological samples. Furthermore, since many biological manufacturing processes are cell-based, there are specific instructions relating to the cell lines (identity, origin, contamination, etc.) and the serums used in the production of recombinant proteins. A number of other stringent conditions exist, as detailed in the appendices. The important point is that the FDA has imposed very different manufacturing standards for the producers of non-biologics and biologics respectively.

1.6 Post-marketing regulation

1.6.1 Post-marketing studies & reporting

In certain cases, the FDA can require that, after product licensure, certain additional studies be undertaken. In the FDA’s guidance to industry (guidance is not legally binding but simply outlines the FDA’s current thinking on important issues), the FDA notes:

‘Postmarketing studies are those performed by you, a drug or biologics applicant, after FDA has granted approval to market its product. Such studies are used to gather additional

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information about product safety, efficacy, or optimal use. Postmarketing studies are also used to evaluate chemistry, manufacturing, and control (CMC) issues, which are important for ensuring consistency and reliability in drug production.'

(Source: http://www.fda.gov/cber/gdlns/post040401.htm#i)

'The FDA also describes the sort of studies that might be undertaken:

Such studies might include evaluating a drug's effect on:

- Survival or long-term morbidity;
- Effectiveness in a different disease, or in a different phase of the same disease; or in a different population (e.g., children or elderly); or
- How pharmacokinetics are altered in special populations, such as the elderly or renally impaired …
- How interactions with other drugs or foods affect safety or effectiveness; or
- Humans or animals to determine if long-term administration causes serious adverse events'.

The decision as to whether a product must be subject to postmarketing studies is evaluated on a case-by-case basis. Particularly relevant to this report is that the requirements for both drugs and biologics are similar. However, the key difference comes with the agency to which the results from the postmarketing studies must be submitted (CBER or CDER), and the laws under which the postmarketing studies are regulated. For drugs, reporting of postmarketing studies (if required) is mandated by Title 21, Section 314.8 of the CFR. For biologics, this is mandated by Title 21, Section 601.70.

Another important area is the mandatory reporting of ADEs (Adverse Drug Experiences). For drugs, this is mandated by 21 CFR 310.305, 21 CFR 314.80 and 21 CFR 314.98. It stipulates that 'any person whose name appears on the label of a marketed drug as its manufacturer, packer or distributor has reporting responsibilities, as does the individual or corporate entity that holds an approved new drug application (NDA).' For biologics, reporting of ADEs is also mandated, in this case by 21 CFR 600.80 and 21 CFR 600.81. It addition, it stipulates that 'any person whose name appears on the label of a licensed biological product as its manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing has postmarketing safety reporting responsibilities.' (Source: Guidance for Industry, 'Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines', available from: http://www.fda.gov/medwatch/report/mfg.htm#regs).

The similar reporting requirements for both drugs and biologics, and the inclusion in the guidance documents of clauses that apply to both, reveals further the parallel nature of approval and regulation for drugs and biologics.

1.6.2 Regulation of Labelling and Marketing

The FDA is also involved in regulating the labelling and marketing of drugs and biologics. Regulations stipulate the types and presentations of claims made of a drug's safety, efficacy, usage and storage, etc. This applies to claims made both on the drug label as well as in promotional material. Labelling and promotional regulation is specifically outlined in 21 CFR, sections 99, 200.5, 200.7, 200.200, 201.10, 201.100,
201.200; further, 21CFR 202 refers specifically to prescription drug advertising. (Source: http://www.fda.gov/cder/ddmac/lawsregs.htm). For biologics, 21 CFR 602.12 and 21 CFR 610.60-610.65 detail the most appropriate regulations.

In general, biologic and non-biologic drugs are treated in a similar fashion. For biologic drugs regulated by the CDER, the Office of Medical Policy’s Division of Drug Marketing, Advertising and Communications (DDMAC) is in charge. This division is organized according to drug class. Biologics are considered to fall within one of these drug classes. Therefore, biologics that fall under the CDER’s jurisdiction would be subject to the same regulations on labelling and promotion as are non-biologic drugs. Appendix 9 explains the CDER review process for promotional material. (http://www.fda.gov/cder/ddmac/contacts2.htm).

The CBER follows a similar process, using personnel from its ‘Advertising and Promotional Labeling Staff (APLS). In this process, applicants submit form FDA-2567, which ‘is to be used for all introductory advertising and promotional labelling, all materials following approval, as well as any submission for a request for review and comment.’ (Source: Office of Establishment Licensing and Product Surveillance Advertising and Promotional Labeling Staff, Procedural Guidance Document, 1994, from www.FDA.gov). The CBER reviews this form and ensures that the criteria for acceptable communication are met.

It is interesting to note that the Prescription Drug Marketing Act also regulates the commercialisation and distribution of drugs in the USA. Its key focus is the distribution of drugs:

The PDMA, as amended by the Prescription Drug Amendments, modified sections 301, 303, 503, and 801 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 331, 333, 353, and 381) to:

1. Ban the sale, purchase, or trade of, or the offer to sell, purchase, or trade, drug samples and drug coupons.
2. Restrict re-importation of prescription drugs to the manufacturer of the drug product or for emergency medical care.
3. Establish requirements for drug sample distribution and the storage and handling of drug samples.
4. Require a wholesale distributor of prescription drugs to be State licensed, and require FDA to establish minimum requirements for State licensing.
5. Establish requirements for wholesale distribution of prescription drugs by unauthorized distributors.
6. Prohibit, with certain exceptions, the sale, purchase, or trade of (or the offer to sell, purchase, or trade) prescription drugs that were purchased by hospitals or other health care entities, or donated or supplied at a reduced price to charities.
7. Establish criminal and civil penalties for PDMA violations.

1.7 Conclusions & Avenues for Further Research

In this section, the organization and structure of the FDA has been documented. Regarding ‘biotech/genomics’ drugs, the key distinction made by the FDA has been between drugs and biologics - the latter have been considered to be a subset of the former. There has often been separate, but nevertheless similar, legislation dictating the many aspects of biologic and drug regulation, ranging from clinical trials, CGMP and approval, to labelling and promotional materials.

It is clear that the FDA has undergone extensive re-organization as a consequence of the emergence of biotech/genomics products. Not only is there a separate division focused on biologics (CBER), but also, more recently, certain responsibilities have been transferred to the CDER. The magnitude of this re-organization (200 employees, $33 million in budget transferred) suggests several avenues for research. How smooth will this transition be? What will be the impact on drug/biologic product approval times? It should be pointed out that in 1982, the FDA attempted to consolidate these two centres. It abandoned the project 6 years later (Bouchie 2002).

Industry concerns about the CBER/CDER consolidation have appeared in relation to the issue of ‘biogenerics’. Several firms believe that biogenerics should not be permitted even after patents have expired, due to the high complexities of the bio-manufacturing process (Bouchie 2002). The question is whether the CDER will respond to this issue differently than the CBER, which was generally opposed to the facilitation of biogenerics?

In addition to the structural and legislative re-organization of the FDA around the distinction between biologics and non-biologics, the FDA, particularly the CBER division, has focused their attention on the implications of the new technologies for drug development. Section 2 will focus on some of the most interesting of these initiatives in order to provide further insight into how the FDA has adapted to advances in modern biotechnology.
2. FDA Initiatives Related to Biologics

2.1 Introduction
Section 1 outlined the organization and general procedures defined by the FDA (CDER & CBER). In Section 2, focus will be on some of the recent FDA initiatives designed as a response to advances in genomic technologies and their implications for drug development.

2.2 Guidance on Pharmacogenomics

2.2.1 Rationale for the Guidance on Pharmacogenomics
One way in which the FDA has outlined its foresight on issues related to emerging technologies has been through the issuance of guidance documents:

‘FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations…’

(e.g. http://www.fda.gov/bbs/topics/NEWS/2003/NEW00969.html)

On November 3, 2003, the FDA issued its draft guidance on pharmacogenomics, which reflected its ‘great promise to shed scientific light on the often risky and costly process of drug development, and to provide greater confidence about the risks and benefits of drugs in specific populations’ (see Appendix 10) The FDA claimed it would enable interested stakeholders to comment on its draft guidance (closing date Feb 2, 2004), before issuing a final guidance document. (Ibid.) The FDA has also hosted several open workshops with the pharmaceutical industry to discuss the draft guidance, the latest being on November 14, 2003, in Washington, where 500 representatives from the pharmaceutical industry and government agencies were in attendance. (Savage 2003).

Interestingly, the FDA does not yet have an established policy on pharmacogenomics data and its regulation. Therefore, this consultation exercise reflects more an acknowledgement of the anticipated importance of pharmacogenomics and the FDA’s desire to remain ‘relevant’. The press release announcing the guidance stated:

‘This is FDA’s first step towards integration of this new field into the process of demonstrating that new drugs are safe and effective, and thus the regulatory guidance is intended to facilitate this integration. This guidance is intended to ensure that evolving regulatory policies and study designs are based on the best science; provide public confidence in this new field where scientifically appropriate; facilitate the use of such tests during drug development; and clarify for industry what types of pharmacogenomic data to submit to FDA.’ (Ibid.)

The actual report, entitled ‘Guidance for Industry: Pharmacogenomic Submissions’ was issued as a draft by the CBER, CDER and CDRH. It detailed the FDA’s views on the use of pharmacogenomic data in drug development as related to IND, NDA and BLA submissions, provided an algorithm to determine whether or not pharmacogenomic data ought to be submitted for a given drug, and also provided information about the process for submitting such data. The rationale for the document emerged from the fact that because FDA requirements for submitting data were developed before the advent of pharmacogenomics, they did not address the type of data that should be included. The document was necessary because it:
‘...clarifies how the FDA currently intends to use such data in regulatory decision making, when it will be considered sufficiently reliable to serve as the basis for regulatory decision making, when it will be considered only supportive to a decision, and when the data will not be used in regulatory decision making.’ (Guidance for Industry: Pharmacogenomic Submissions, 2003, p.3.)

However, this statement does not reveal the full picture. One could interpret the FDA’s decision to issue guidance on pharmacogenomics as an attempt (arguably a very reasonable one) to remain relevant whilst also gaining public trust. The FDA has stated:

‘It is important for the FDA to have a role in the evaluation of pharmacogenomic tests, both to ensure that evolving FDA policies are based on the best science and to provide public confidence in the field. It is also important that FDA policy facilitate, not impede, the use of pharmacogenomic tests during drug development and, to the extent possible, encourage open and public sharing of data and information on pharmacogenomic test results.’ (Ibid., p3).

2.2.2 Role of the FDA in shaping the trajectory of pharmacogenomics

Owing to the novelty of the field of pharmacogenomics, and the FDA’s central role in the regulation of data submissions and drug approvals, it is not surprising that the FDA have a vested interest in the future of pharmacogenomic developments. The FDA has itself claimed:

‘The policies and processes outlined in this draft guidance are intended to…assist in advancing the field in a manner that will benefit both drug development programs and public health.’ (Ibid.)

This statement helps us to contextualize several interesting issues. Firstly, because pharmacogenomics is an emerging field, there is no well established evidence-base for judging the validity of experimental results and incorporating them into regulatory decision-making. According to the FDA, laboratory procedures, interpretative scientific frameworks, the ability to extrapolate data across species or different study populations and the processing of data from microarray technology, is not yet ‘suitable for regulatory decision making.’ (Ibid. 2) However, tests such as those for drug metabolism are ‘currently being integrated into drug development decision making and clinical practice.’ (Ibid., 3)

Therefore, the FDA will play a key role in determining test validity as the technologies develop:

‘This guidance...makes a distinction between pharmacogenomic tests that may be considered valid biomarkers appropriate for regulatory decision making, and other less well-developed tests...Undoubtedly, the distinction between what tests are appropriate for regulatory decision making and those that are not will change over time as the science evolves.’ (Ibid., 4)

Another area of interest is the current FDA guidance on whether or not companies must submit data derived from pharmacogenomic research. Currently, the FDA is encouraging voluntary submission of data via Voluntary Genomic Data Submissions (VGDSs). However, in certain circumstances the FDA is requiring such data be submitted. The guidance document presents a series of algorithms to help drug sponsors (i.e. pharmaceutical and biotechnology companies) determine whether or not they must submit data. These are divided into algorithms for IND filings, unapproved NDAs and BLAs and approved NDAs and BLAs (Ibid; Appendix A, B, C). The specifics of these algorithms are beyond the scope of this report. Perhaps of most interest is the FDAs position on the utility of VGDS reports:
'The purpose of the VGDS process is to provide the FDA access to emerging pharmacogenomic data so that a foundation can be built for developing scientifically sound regulatory policies. The Agency intends to gain experience and to develop an aggregate genomic knowledge database from multiple VGDSs that could be used to rationally facilitate the use of pharmacogenomics in drug development and to share what general knowledge is learned from the data repositories, where appropriate.' (Ibid., p10).

The position of the FDA essentially permits drug companies to submit only that pharmacogenomic data that supports their drug application. Companies are unlikely to submit data that undermines their application. Therefore, the pharmaceutical industry itself appears to have a degree of control over the regulatory framework around pharmacogenomics. Within the industry there is a great deal of ambivalence towards the submission of pharmacogenomic data. (Savage 2003).

In general, the FDA guidance notes on pharmacogenomics offers interesting insights into the regulator’s current thinking on the role of genetic knowledge in drug development. As it is still a relatively new and unproven area, several interesting areas for further investigation emerge. These will be elaborated in section 2.2.3.

2.2.3 Avenues for further research

Hedgecoe and Martin (2003) have identified two dominant ‘visions’ of pharmacogenetics that are currently shaping its development. One is focused on the elimination of undesirable side effects; the other is focused on developing medicines tailored to individuals’ genetic make-up. Considering the important role ‘visions’ play in framing a technology’s development, in combination with the social factors that are instrumental in shaping new technologies (Pinch & Bijker 1984, Bijker 1995), the FDA’s guidance on pharmacogenetics yields a number of interesting questions and avenues for further research.

1) How will FDA guidance affect industry decision-making around pharmacogenomic data submissions and vice versa? If, for example, a pharmacogenomic test were not expected to yield promising information, or even demonstrate that a drug would not be efficacious in a subset of patients, would a sponsor conduct and/or submit such research? In other words, might sponsors focus on pharmacogenomic research biased towards positive drug approvals (e.g. used to prevent ADE’s but not to test efficacy) but not negative drug approvals? How will drug sponsors (i.e. industry) use pharmacogenomics in a way that enhances the chances of getting drugs approved but will not shrink their markets?

2) How is the process of pharmacogenomic test validation developing, and what is shaping the definitional framework? Since the FDA determines the kind of data necessary for drug approval, it would be interesting to analyse the processes through which pharmacogenomic data become labelled as ‘valid’.

3) Because the FDA has only issued guidance notes at this stage, it will be interesting to see if and how they will become mandated through legislation, and assess the extent to which formal legislation is mutually shaped by both the regulators and industry.

2.3 Team Biologics

Together with the ORA (Office for Regulatory Affairs), the CBER has established ‘Team Biologics’. This remit of this team will be to ensure the quality and safety of marketed biologic products. (http://www.fda.gov/cber/genadmin/teambio.htm; see Appendix 11).
In general, the underlying rationale is to develop a team of dedicated employees, with skills and competencies relating to biologics and biologic manufacturing, to inspect authorized producers of biologics. The concept is designed to ensure that there are no inconsistencies between the regulatory activities of different FDA divisions. According to the FDA, this partnership between ORA and CBER will:

‘... use the diverse skills and knowledge of both ORA and CBER staffs to focus resources on inspectional and compliance issues in the biologics area. Team Biologics will bring FDA's regulatory approach for the biologics industry in line with other FDA Centers. The goal of Team Biologics will ensure the quality and safety of biologic products and quickly resolve inconsistencies and bring products into compliance.’

Oversight reviews have identified the following goals for more effective and efficient regulation of biological products:

- Assure a comprehensive regulatory posture among all product lines.
- Promote uniformity between CBER and the field and among FDA field components associated with inspections, policy implementation, and current good manufacturing practice (cGMP) interpretation.
- Develop and maintain a highly trained and professional work force.
- Design an organized approach to inspections with clearly defined ORA and CBER roles.
- Design a rapid and effective process for resolving ORA/CBER differences.
- Focus on an operational and policy approach that fits within FDA's existing structures and systems.
- Provide for oversight and assurances of consistent quality of work products, decisions, and actions.
- Bring about maximum efficiency of operations.

Evaluate new methods of implementing the biologics inspection and enforcement programs.

(Source: http://www.fda.gov/cber/genadmin/teambio.htm)

Team Biologics, as of June 16, 2003, currently evaluates fractionated products, licensed in vitro diagnostics, biotechnology products (i.e. monoclonal antibodies and recombinant DNA-derived proteins), allergenic products and vaccines. Although it is not stated officially on the FDA’s website, one might assume that Team Biologics will co-ordinate extensively with the CBER following the re-organization of biologics regulation within the regulatory agency.

2.4 Manufacturer’s Assistance

In line with its objective of ensuring compliance with the manufacturing of biologics guidelines, the CBER has established a manufacturer’s assistance program, via its Manufacturer’s Assistance and Technical Training Branch (MATTB):

The Centre for Biologics Evaluation and Research (CBER) has established a manufacturers assistance program to provide assistance and training to industry, including large and small manufacturers and trade associations, and to respond to requests for information regarding CBER policies and procedures.
Manufacturers assistance is available in numerous areas including: clinical investigator information, adverse event reporting procedures, electronic submissions guidance and requirements, and information on how to submit an investigational new drug application to administer an investigational product to humans. This assistance extends to facilitating effective development of all products regulated by CBER including products to diagnose, treat or prevent outbreaks from exposure to the pathogens that have been identified as bioterrorist agents.

The Manufacturers Assistance and Technical Training Branch (MATTB) inform industry and trade associations of the status of CBER policies and initiatives through regular information dissemination and training. MATTB also serves as the CBER focal point for industry and trade associations to provide meeting support, and coordinates external meetings with other FDA Centers.

(Source: http://www.fda.gov/cber/manufacturer.htm)

2.5 Prescription Drug User Fee Act (PDUFA)

2.5.1 Introducing PDUFA

The PDUFA is an FDA initiative concerned with the processes relating to improved speed to market of drug products. The FDA launched this Act in 1992, which requires biotechnology and pharmaceutical companies to pay a user fee to the FDA in exchange for accelerated drug approval times. The FDA puts this money back into the drug evaluation process.

‘Previously, taxpayers alone paid for product reviews through budgets provided by Congress. In the new program, industry provides the funding in exchange for FDA agreement to meet drug-review performance goals, which emphasize timeliness.’

(Source: http://www.fda.gov/oc/PDUFA/overview.html)

The PDUFA was originally given a 5 year lifespan. However, owing to the success of the program, the PDUFA has been renewed three times. PDUFA III will be valid until 2007. By 2002, the PDUFA fees collected ‘permitted FDA to spend an additional $161.8 million per year for the drug evaluation process.’ (http://www.fda.gov/oc/pdufa3plan/default.htm)

Furthermore, the planned fee collections (from industry) for the period 2003-2007 exceed $1.25 billion (Ibid.). A notice issued by the FDA specifies the type of fees charged by the FDA:

This notice establishes fee rates for FY 2004 for application fees ($573,500 for an application requiring clinical data, and $286,750 for an application not requiring clinical data or a supplement requiring clinical data), establishment fees ($226,800), and product fees ($36,080). These fees are effective on October 1, 2003, and will remain in effect through September 30, 2004

(Source: http://www.fda.gov/OHRMS/DOCKETS/98fr/03-19654.htm)

Both the CBER and CDER participate in PDUFA III. Both benefit from the program by gaining revenues, which lead to increased staff:

Planned increases from 2002 staffing levels by component are:

- CDER—a net increase of 293 staff years by the end of 5 years
- CBER—a net increase of 59 staff years by the end of 5 years
Furthermore, each submitted detailed plans concerning additional staff and training, development of risk management capacities and hiring independent expert consultants etc. Interestingly, consistent with its addition of certain ‘biotech’ drugs (i.e. monoclonal antibodies and recombinant proteins), the CDER stated:

CDER plans to retain independent expert consultants to assist in review of clinical protocols expected to serve as the basis for approval for new biotechnology drugs. CDER will engage these consultants on an ad hoc basis in response to requests from applicants. CDER has developed draft guidance on how this program will be implemented and will work to finalize the guidance. The estimate for FY 2003 is $56,000.

There are several interesting issues around the PDUFA, although many of these fall outside the scope of this report. In general, the FDA, through the PDUFA, has committed itself to approving drugs within limited timeframes in exchange for revenues from drug sponsors.

2.5.2 Avenues for Further Research

a) The CDER’s increased commitment to the review of biologicals is implied by its submitted PDUFA action plan, which refers to hiring of independent expert consultants to assist in the drug review process. This raises an interesting question about the approval process around biologics: how will these experts be engaged? If applicants request them, will they be biased towards approving the drugs in question?

b) What is the impact of accelerated drug evaluation processes? Is there an impact on the quality of the drugs reaching market? A text on the FDA’s website indicates:

Some FDA stakeholders, and recently the General Accounting Office2 (GAO) have expressed concerns about the number of drugs approved under PDUFA that have been withdrawn for safety reasons. However, an analysis of the rate of withdrawal for safety reasons of New Molecular Entities approved prior to PDUFA compared to those approved under the PDUFA program shows no significant difference (2.7% for drugs approved pre-PDUFA and 2.5% for drugs approved under PDUFA3. While FDA’s standards for safety have not changed under PDUFA, the total number of drug and biologic products on the U.S. market has increased substantially, and many of these products are being approved first in the U.S. As a result of this heightened awareness, the importance of rigorous post-market surveillance of recently approved products has increased under PDUFA.

However, many have contested this. Olson (2002) and consumer activists (Dove 2003), suggest that reductions in drug review times may be associated with an increase in ADEs requiring hospitalization.

c) What is the impact of the PDUFA on biotechnological innovation? If user fees are the same for all companies, regardless of their size, this might be considered to give Big pharma an unfair, competitive advantage. Smaller firms may become even more reliant on establishing partnerships with the larger companies.
2.6 Biogenerics

The CDER/CBER amalgamation might have implications for biogenerics. The CBER has traditionally tried not to facilitate a biogenerics market, but the CDER is far more committed to promoting biogeneric competition. As reported in Nature Biotechnology:

‘Debate is already underway between firms producing generic drugs and the biotech industry as to whether regulatory agencies should ease the approval process for generic biologics; the biotech lobby maintains that even small differences in how a biologic is manufactured can significantly affect its safety and efficacy, and thus biogeneric products should be regulated as stringently as the original biologic. Currently, biogenerics must pass through at least abbreviated clinical trials to show bioequivalence.’ (Nat. Biotechnology Vol. 19 (2001) p.117).

However, some CDER officials have reportedly claimed that the FDA has given them the authority to approve generic versions of biologics that are regulated as drugs, such as human insulin. Although the FDA has stated that its current policy on generic biologics will not be affected by its decision to restructure, Hutt [an attorney and former chief counsel of the FDA] says, “Once you bring the two organizations together, the potential for blurring these lines increases.”(Bouchie 2002)

2.7 Conclusions

This section has outlined the some of the interesting FDA initiatives relating to both biological products as well as drug approval times.

Most significantly, the CDER/CBER guidance on pharmacogenomic data and the drug approval process clearly demonstrates the FDA’s increased awareness of the importance of biotechnology. Since this is a new initiative aimed at collaborating with industry (e.g. by encouraging voluntary submissions), it offers an opportunity to study the mutual shaping of FDA policy and drug industry strategies.

Other FDA initiatives geared at biologics include the establishment of Team Biologics, which will combine personnel from the CBER, ORA and CDER. This team will be focused on inspecting and ensuring manufacturer’s compliance with FDA standards. This is to ensure safety and efficacy of marketed biological products.

The CBER has issued a set of manufacturer’s assistance programs, designed to help drug sponsors understand and adhere to CBER policies.

The PDUFA is a major initiative launched by the FDA. It has been designed to gain user fees from drug sponsors’ drug applications. These fees are translated into additional staff and a commitment to reduce drug evaluation times. This program leads to interesting questions, such as how the agency contracts ‘independent experts’ (specifically the CDER for review of biotechnology drugs) when requested by drug sponsors; and what implications reduced drug evaluation times have for the safety of marketed drug products.

Finally, the CDER/CBER consolidation signals the potential for change in legislation in the regulation of biogenerics, an area in which industry has a strong, vested interest.
3. Industry Perceptions on FDA Initiatives

3.1 – PhRMA

3.1.1 Lobbying Power of the PhRMA

The Pharmaceutical Research & Manufacturers of America (PhRMA) is an organization dedicated to protect the interests of the pharmaceutical and biotechnology industry (excluding producers of generic medicines) in the United States. The pharmaceutical industry is one of the biggest and most active lobby groups in the United States.

‘In 2001, the drug industry’s army of lobbyists easily outnumbered all 535 members of Congress as pharmaceutical companies employed 623 different hired guns…Four companies and PhRMA employed more than 50 different lobbyists each in 2001. Pfizer and PhRMA employed the most (each hired 82 lobbyists), followed by Bristol-Myers Squibb (76 lobbyists). Eli Lilly and Amgen each fielded 58 lobbyists.’

(Source: http://www.citizen.org/pressroom/release.cfm?ID=1130)

Michael Heaney, a doctoral student at the University of Chicago, published an article in 2003 stating that the PhRMA has more lobbying power over healthcare policy than even the AMA (American Medical Association):

‘The most notable finding is that the Pharmaceutical Research and Manufacturers of America (PhRMA) sits at the top of the list of most influential groups. That position represents a change from previous studies that identified the American Medical Association (AMA) as the undisputed heavyweight in health and medicine.’


The PhRMA is considered to have played a central role in influencing US trade policy on international patent laws (TRIPS), which demonstrates the power that the organization wields. The Guardian newspaper has claimed:

‘… no industry wields as much power as the Pharmaceutical Research and Manufacturers Association (PhRMA), a pressure group breathtaking for its deep pockets and aggression, even by the standards of US politics.

(Source: http://www.guardian.co.uk/international/story/0,3604,437212,00.html)

3.1.2 Mission & Focus of the PhRMA

The PhRMA is a representative organization that seeks to protect the various interests of the pharmaceutical industry. It describes itself as follows:

‘The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country’s leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. The industry invested an estimated $33.2 billion in 2003 in discovering and developing new medicines. PhRMA companies are leading the way in the search for new cures.

Mission Statement

Johnathan Suk
The PhRMA represents the leading research-based pharmaceutical and biotechnology companies in the United States.

PhRMA companies are devoted to discovering and developing new medicines that will enable patients to live longer, healthier and more productive lives. In 2002 the companies invested more that $32 billion in discovering and developing new medicines, marking the 32nd straight year the industry has increased its investment in R&D.

PhRMA’s mission is to conduct effective advocacy for public policies that encourage discovery of important new medicines for patients by pharmaceutical/biotechnology research companies.

(Source: http://www.phrma.org/whoweare/)

The PhRMA annual report (2003-2004) lists the organization’s Key Issue Teams. The teams include: Federal Healthcare Legislation; FDA & Biomedical Research; Canada Key Issue Team; Intellectual Property; State Health Care Reform; and Task Force on Emergency Preparedness. (source: PhRMA Annual Report, 2003-04

However, despite there being a Key Issue Team for FDA & Biomedical research, little information about it was available. On the PhRMA website (www.phrma.org), there was a number of press releases about FDA-related and genomics-related issues, but these were generally focused on such things as incentives for patent protection, counterfeit drugs and the imports of discounted drugs from Canada, etc. No comments could be found on either the reorganization of the CBER and CDER, and their respective responsibilities, nor on the PhRMA’s response to the pharmacogenomics guidance issued by the CBER or CDER.

However, the PhRMA has commented, through its website, on a number of general issues concerning the FDA. The focus has been predominantly on the short-term economic issues affecting the pharmaceutical industry, such as protection of patents, cost-benefit analysis of pharmaceuticals and healthcare, and even the construction and maintenance of barriers to entry (through emphasizing high quality standards). The latter is exemplified in the organization’s response to FDA manufacturing guidelines:

A statement by John T. Kelly, M.D., PhD, PhRMA’s Senior Vice President for Scientific and Regulatory Affairs, in support of the Food and Drug Administrations (FDA) initiative on pharmaceutical manufacturing practices expressed the view that:

The decision of the FDA to reassess the agency’s current approach to pharmaceutical “Good Manufacturing Practices,” or GMPs, will help ensure that patients continue to benefit from timely access to high-quality pharmaceutical products manufactured according to state-of-the-art, science-based standards.

PhRMA and its member companies are fully committed to working with FDA to assure that appropriate GMP standards are in place to maintain optimum pharmaceutical manufacturing practices for the benefit of patients. The pharmaceutical industry and FDA have a wealth of experience and scientific knowledge to keep improving current manufacturing processes. We applaud the FDA’s initiative to develop new regulatory standards and processes for GMP compliance.

3.1.3 – Conclusions
The PhRMA is a large and powerful lobby group for the pharmaceutical industry. It has recognized the importance of the FDA, as well as novel biomedical technologies, for the industry as a whole. This is confirmed by the presence of a Key Issue Team dedicated to these issues. However, there is little information available from the PhRMA website to reveal the organization’s views on FDA initiatives such as the reorganization of the CBER/CDER, or on the issuance of pharmacogenomics guidance. One possible explanation might be that the FDA has not yet published its final document.

3.2 Pharmaceutical Companies & the FDA

The following sections will explore the responses of three leading US-based pharmaceutical companies (Merck, Pfizer & Bristol-Myers Squibb) to the regulatory initiatives of the FDA and the emergence of new biotech/genomics drugs. Data were collected from the companies’ websites and from financial reporting to the Securities & Exchange Commission (SEC).

There was little information on the company websites relating to the FDA initiatives and company responses to them. This is not to say, however, that such companies do not pay significant attention to regulatory initiatives – they do. Pharmaceutical companies have large regulatory affairs divisions that scrutinize each FDA publication and ensure that their companies’ operations, from GMP manufacturing to product labelling, are in line with FDA regulations. However, this is a continuous process – rarely, if ever, would FDA guidelines be so radical that a company would be forced to drastically alter the way in which it operated.

It is important to note that regulatory affairs departments work in close contact with FDA officials. There is therefore significant scope for regulatory affairs officers to influence FDA initiatives. FDA initiatives, such as the new guidelines on pharmacogenomics, typically encourage responses from ‘stakeholders’ (e.g. drug sponsors) on draft documents before guidelines are finalized.

Each of the three companies spend billions of dollars per year on R&D, and establish a number of strategic alliances with biotechnology companies and academic laboratories. Each of the companies is heavily involved in employing and exploring a wide range of new life-science-based technologies, from cloning and stem cell research to pharmacogenomics and proteomics. Therefore, these companies are in many ways driving the technological trajectory. In this context, the FDA and the pharmaceutical industry enjoy an inter-dependent relationship. These relationships shape both FDA policies and pharmaceutical companies’ R&D strategies.

3.3 Merck & Co.

3.3.1 Website
Merck’s website offers little insight into the ways in which FDAs initiatives have influenced its drug development process. Their focus is typically on trying to convince potential investors and patients that Merck is a world leader in R&D. There are very few references to the FDA, and when there are, it is typically in reference to press releases announcing FDA approval of Merck’s drug products.
In relation to pharmacogenomics, and how this new technology might shape Merck's R&D strategy, an excerpt from the 2001 Annual Report states:

‘Also exciting is the opportunity to develop genomic analyses for preclinical studies (drug testing before human trials) to evaluate the safety and effectiveness of experimental compounds. Now, preclinical testing takes a long time and a lot of different studies. Merck is aiming to develop genomic methods to predict which molecules will have bad characteristics (such as undesirable side effects) so that those molecules can be removed early in the process and we can focus on improving success for the ones that are taken forward. This technology is also going to allow us to do better and faster clinical trials because we can identify genetic markers that are predictive of an outcome in the clinic. In some cases, SNP markers may also allow differences between individuals (for example, variations in the enzymes that metabolize drugs) to be taken into account in clinical trials to understand why some patients do not respond well to some of our drugs. Lastly, the potential exists for us to develop pharmacogenomic tests that will enable physicians to help choose drug therapies based on a genomic analysis of patients' DNA, and thereby allow physicians to individualize drug therapies for their patients by selecting drugs most suited for their condition’.


3.3.2 SEC Filing: 10-K, 200310-K, 2003

Arguably, the most important SEC filing is the 10-K, which is the company’s annual financial report. This filing contains the most information about a company’s operations, financial performance, and business environment. However, for a large company with a broad range of activities, the impact of specific FDA’s policies around the regulation and definition of biotechnology drugs are not sufficiently important to warrant much attention in the annual report.

One initiative, the PDUFA, was mentioned in Merck’s annual report:

In 1997, the Food and Drug Administration Modernization Act was passed and was the culmination of a comprehensive legislative reform effort designed to streamline regulatory procedures within the FDA and to improve the regulation of drugs, medical devices and food. The legislation was principally designed to ensure the timely availability of safe and effective drugs and biologics by expediting the premarket review process for new products. A key provision of the legislation is the re-authorization of the Prescription Drug User Fee Act of 1992, which permits the continued collection of user fees from prescription drug manufacturers to augment FDA resources earmarked for the review of human drug applications. This helps provide the resources necessary to ensure the prompt approval of safe and effective new drugs.

(http://www.freeedgar.com/search/ViewFilings.asp?CIK=64978&Directory=950130&Year=03&SECIndex=2276&Extension=.tst&PathFlag=0&TextFileSize=489430&SFType=S&DFiled=&DateFiled=3/21/2003&SourcePage=FilingsResults&UseFrame=1&OEMSource=&FormType=10-K&CompanyName=MERCK+%26+CO+INC)

No other references are made to FDA initiatives in the rest of the document. The section on Government & Regulatory affairs in the 2003 10-K is included in Appendix 12.
3.4 Bristol-Myers Squibb

3.4.1 Website
The FDA is referenced in relation to product approvals and submissions, via press releases. There is little data on R&D strategy, except for brief descriptions of specific drug products and BMS’ main therapeutic areas.

3.4.2 SEC Filing: 10-K, 2003
Again, there is very little data on the issues of most concern for this report. The most interesting statement from the 10-K simply emphasizes that regulatory affairs is an important aspect of BMS’ business:

The Company devotes significant time, effort and expense addressing the extensive governmental regulatory requirements applicable to its business. Governmental regulatory actions can result in the recall or seizure of products, suspension or revocation of the authority necessary for the production or sale of a product, and other civil and criminal sanctions.

(Source: http://www.freeedgar.com/search/ViewFilings.asp?CIK=14272&Directory=1047469&Year=03&SECIIndex=10810&Extension=.tst&PathFlag=0&TextFileSize=54515&SFType=&SDFiled=&DateFiled=3/28/2003&SourcePage=FilingsResults&UseFrame=1&OEMSource=&FormType=10-K&companyName=BRISTOL+MYERS+SQUIBB+CO)

3.5 Pfizer

3.5.1 Website
Pfizer’s website provides little information about the FDA or strategic approaches to R&D. Rather, the focus is on products, therapeutic areas of research, and investor relations.

3.5.2 SEC Filing: 10-K, 2003
Pfizer only makes general reference to the impact that FDA regulations could have on its business interests:

‘In recent years in the U.S., various legislative proposals have been offered at the federal and state levels that would bring about major changes in the affected health care systems. Some states have passed such legislation, and further federal and state proposals are possible. Such proposals and legislation include, and future proposals could include, price controls or patient access constraints on medicines and increases in required rebates or discounts. Similar issues exist in many foreign countries where we do business. We cannot predict the outcome of such initiatives, but we will work to maintain patient access to our products and to oppose price constraints.’

(Source: http://www.freeedgar.com/search/ViewFilings.asp?CIK=78003&Directory=950123&Year=03&SECIIndex=3360&Extension=.tst&PathFlag=0&TextFileSize=574169&SFType=&SDFiled=&DateFiled=3/27/2003&SourcePage=FilingsResults&UseFrame=1&OEMSource=&FormType=10-K&companyName=PFIZER+INC)
3.6 Issue-related responses

The literature review did not give a great deal of insight into industry perspectives. However, a few articles have included interview transcripts with members of industry, although the degree to which these people are broadly representative of industry is difficult to know.

3.6.1 CBER/CDER Re-organization

The industry appears to be ‘sitting on the fence’ on this issue, waiting to see how smooth the transition is. A statement by the PhRMA revealed concerns about the possibility of personnel leaving the CBER, rather than accepting the CDER as their new employer:

‘It certainly would be a shame for all sides if we were dealing with all new staff.’ (Dove 2003)

Otherwise, as evident from the lack of information on their websites, and as reported by Dove (2003):

‘Neither PhRMA nor BIO has taken an official stance on the restructuring, and companies are understandably reluctant to comment on the agency that regulates their products.’ (Ibid.)

3.6.2 Pharmacogenomics Guidance

The FDA acknowledges that the industry is apprehensive about its guidance on pharmacogenomic data. Janet Woodcock, director of the CDER, recognized this during an FDA workshop on pharmacogenomics:

‘Much fear exists, but the reality is that most of the pharmacogenomic data currently available is not suitable for regulatory decision making.’ (Savage 2003)

Despite being ambivalent about reporting pharmacogenomic data, it appears that the guidelines have been generally well received:

‘The appearance of guidelines in this emerging field is sincerely welcomed by all practitioners’, stated Bill Pennie, director of molecular and investigative research toxicology and drug safety evaluation at Pfizer (Savage 2003)

3.6.3 PDUFA

As mentioned in 2.5.2, consumer advocates and academics have suggested that the PDUFA has led to unsafe drugs reaching the market. With regards to industry, the PDUFA has been shown to drastically reduce drug evaluation times, from an average of 2.5 years in 1993 to 1.4 years today (Dove 2003). The industry is widely supportive of this fast-track system, even though recently drug approval times have started to increase slightly. This is supported by one quote from Gillian Woollett, VP for Science & Regulatory Affairs at BIO:

‘It [PDUFA implementation] was a huge mindshift for everybody in how you were going to fund an agency, and I think it was hugely important.’ (Dove 2003)

3.7 – Conclusions & Avenues for Further Research

Through mass media communications like press releases and websites, the large pharmaceutical companies appear not to widely disseminate their views on specific FDA initiatives. Many reasons may account for this. Firstly, the PhRMA is a body that represents and lobbies on behalf of all pharmaceutical companies. The advantage of
this is that no individual firm is exposed – statements on FDA policy could either create enemies at the FDA or alert rival firms to their R&D strategies. Another possible explanation is that many of the initiatives dealt with in this report are considered relatively minor for large companies – investors and the public, for example, are more likely to be concerned with macroeconomic policies (such as Medicare), financial performance, and information about drugs (marketed and in research).

This is not to suggest that pharmaceutical companies do not pay careful attention to the FDA and its policies – relevant employees in regulatory affairs, marketing, and R&D, for example, would be expected to pay close attention to FDA policies that could significantly affect them. This is exemplified by the fact that over 500 representatives, many from industry, attended the FDA workshop on its draft pharmacogenomics guidance. We may also assume that, because pharmaceutical representatives are in constant contact with the FDA, the industry has a degree of influence over FDA regulatory policies.

The fact that the PhRMA has a great deal of lobbying power in Washington, it would be useful to assess the extent to which the pharmaceutical industry, via PhRMA pressure and industry interaction with the FDA, helps shape and inform FDA policy and guidelines. One might expect that mutual shaping of regulatory policy is a significant issue.
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