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Regulating biopharmaceuticals under CDER versus CBER: an insider's perspective

William D. Schwieterman

Tekgenics, Inc., 3901 Point Road, Mobile, AL 36619, USA

The FDA has recently transferred jurisdiction for the regulation of certain biopharmaceuticals from the Center for Biologics, Evaluation and Research to the Center for Drugs, Evaluation and Research, where they will be reviewed in the same FDA divisions as are traditional pharmaceutical agents. With this transfer, sponsors of investigational biopharmaceuticals should expect changes in the regulatory requirements the FDA imposes on the clinical development plans, including an increase in the size and number of pivotal studies; more consistent requirements for conducting preclinical tests in two animal species; increased emphasis on organ structure and function as components of primary endpoints; more emphasis on characterizing dose-ranging and pharmacology; more intense scrutinizing of product advertising; and decreased direct communication with the review team.

Recently, the FDA transferred jurisdiction for the review of certain biologic agents intended for therapeutic use from the Center for Biologics, Evaluation and Research (CBER) to the Center for Drugs, Evaluation and Research (CDER) [1]. The agents transferred were proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products, except clotting factors [2]. These included most of the recombinant proteins like monoclonal antibodies, cytokines, growth factors and non-vaccine immunomodulators (referred to as 'biopharmaceuticals' in this article). These biopharmaceuticals are now reviewed in the same divisions as the more traditional pharmaceuticals [2]. Other biologic products, including blood and blood components, cellular and gene therapy products, vaccines, antitoxins, allergenic extracts and venoms, remain in CBER [2]. Approximately 200 staff positions and US$32.9 million from the annual budget of CBER (nearly 20% of the total) were also transferred to CDER [3].

The transfer of biopharmaceuticals to CDER occurred in steps over a period of several years, and was motivated by a desire to streamline review of biopharmaceuticals and integrate their review into a unified regulatory structure [3,4]. Murray Lumpkin, then the principal associate commissioner at FDA, said 'Our thought process was that these particular products [biopharmaceuticals] have become more mature and. . .have integrated themselves into the general medical armamentarium. . .and in a general sense are looked at and used as drugs' [3].

In June 2003, staff in the CBER Office of Therapeutics (OT) were transferred to new CDER management. Most of the CBER review groups in this initial transfer remained intact and operated much as before, although they resided in the newly created Office of Drug Evaluation VI (ODEVI) in CDER [2].

In the autumn of 2005, the FDA again reorganized. ODEVI was disbanded and reviewers were reassigned to more traditional CDER divisions organized by disease area instead of by product classification.

It is also noteworthy that during these reorganizations at the FDA some experienced personnel left the agency, including some in senior management (this author left the FDA before the reorganization), resulting in a loss of valuable expertise for the agency [5].

As experienced drug-developers know, organizational or jurisdictional changes that occur at the FDA, even when on a relatively small scale, can also have a disproportionately large impact on product development. For example, the departure of a key reviewer in a review team or a change in jurisdiction between different divisions within an FDA Center can significantly affect the ease and speed of a product's path to the market.

That biopharmaceuticals are now being reviewed in new divisions, and that many are being reviewed by new supervisors

Corresponding author: Schwieterman, W.D. (wds@tekgenics.org)

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and reviewers, at least some of whom are relatively unfamiliar with biopharmaceuticals, will almost certainly have an impact on how these agents are regulated at FDA.

I was a clinical reviewer and supervisor in CBER from 1992 to 2002, and worked with a large number of reviewers and personnel throughout FDA during my time there. This is my perspective on how best to understand the recent organizational changes at FDA and the impact this will likely have on the clinical development of these agents.

The constancy of change at FDA

Throughout its history and since its earliest days the FDA has consistently grown, reorganized and modified its focus to keep up with changes and advances occurring in medicine. Almost invariably, changes at the FDA are reactions to public health crises or fundamental changes in the healthcare system [6]. For example, the 1902 Biologics Control Act and 1906 Pure Foods and Drug Act – seminal legislation that founded the FDA by mandating the regulatory oversight of biologics and drugs – were in direct response to health disasters occurring in the food processing industry and early days of therapeutic medicine [7–9] (http://www.fda.gov/cder/about/history/histext.htm).

In 1984, when applications for investigational new drugs (INDs) were increasing, the FDA created the new unified review Center for Drugs to meet new regulatory demands. This new Center brought together, for the first time, the review of drugs and biologics at the FDA by joining the Bureau of Drugs and the Bureau of Biologics. However, its existence was short-lived. It was split in 1987 into CDER and CBER to address challenges arising from the AIDS epidemic and an even further increase in the number of new drug applications (http://www.fda.gov/cder/about/history/default.htm).

Changes and growth of CBER 1987 to 2002

From its beginning in 1987, CBER grew and changed to keep up with dramatic advances occurring in biotechnology. In the late 1980s new reviewers, administrators and clerks were hired to help review IND submissions of 'biotech products', which totaled 5 in 1980 (to the Bureau of Biologics) but over 200 in 1990 [10]. New guidance documents and 'Points to Consider' were written by CBER review teams to guide manufacturers grappling with the new, and often difficult, task of adequately manufacturing and characterizing recombinant proteins as safe for human use (http://www.fda.gov/cber/guidelines.htm).

In 1992, five years after its birth, CBER reorganized. The new OT was formed within CBER to facilitate the review of biopharmaceuticals (http://www.fda.gov/bbs/topics/answers/ans00438.html). The OT contained several product-related divisions. Reviewers in these divisions also conducted their own research, both in keeping with CBER's research history and to keep their skills and knowledge sharp and current [11].

In addition, a new Division of Clinical Trial Design and Analysis (DCTDA) in the OT was given sole responsibility for the review of clinical data and protocols. The formation of the DCTDA was a landmark event for CBER. Whereas CDER had long employed staff who were experienced and expert in the review of clinical protocols, CBER before 1992 had assigned laboratory-based reviewers to review the entirety of an IND submission, including clinical protocols. Although many of these reviewers were experts in their field of research, they often had minimal or no clinical training or experience.

Almost all areas of biotech in those days were new and challenging. Reviewers and sponsors alike often struggled to optimize manufacturing processes, characterization techniques, potency assays, viral validation assessments, and so on. In addition, the clinical relevance of data from animal studies, or of data from clinical studies of pharmacokinetic and pharmacodynamic markers, were almost always difficult to ascertain (http://www.grants.nih.gov/grants/funding/sbirconf2004/14pilarofda_cder.ppt). The clinical safety of biopharmaceuticals (including the risks of immunogenicity; autoimmune disease; paradoxical clinical outcomes; long-term immunosuppression; cytokine release syndrome, and so on) were issues with which the agency had relatively little experience in 1992.

There were a few dozen or so charter members of the DCTDA, myself included, who observed firsthand the early days of clinical development in biotechnology. Most of the staff in CBER were keenly aware that they were shepherding a new and promising, but also fledgling and potentially dangerous, field of therapeutic medicine through its earliest stages of development. There were two primary goals at CBER then: to protect the public from the potent, but potentially unsafe, biotech therapies under review and to avoid being overly conservative so as not to stifle innovation. Accomplishing these two goals was often neither easy nor straightforward, and required a flexible, open and constant dialogue between reviewers and sponsors.

By 2002, biotech was part of mainstream medicine

By the turn of the millennium, a wide variety of safe, effective and powerful new therapies for a variety of diseases had been approved for use (Figure 1) [12]. In the years 1997 and 1998 alone, powerful new therapies that offered new treatment options for cancer (Herceptin® and Rituxan®), rheumatoid arthritis (Remicade® and Enbrel®) and renal allograft transplantation (Simulect® and Zenapax®) were approved for marketing [13–15] (http://www.uiowa.edu/~idis/FDA_Approval_Overview.htm). Worldwide sales of biotechnology products, which were absent from the marketplace until 1982, grew rapidly in the 1990s. Biotech revenues in the USA increased from US$8 billion in 1992 to US$29.6 billion in 2001 (http://www.bio.org/speeches/pubs/er/statistics.asp). In same year, it was reported that although marketed biopharmaceuticals represented only 5% of world prescription drug sales, they comprised 6 of the top 50 selling drugs, 13% of new medicines approved by the FDA since the 1990s, and 11% of all drugs in development (http://www.pharmahorizons.com/industry_reporte.pdf).

In many ways, the incorporation of CBER into CDER that began in 2003 simply reflects the new pervasiveness, power and importance of biopharmaceuticals in medical practice, and the need and appropriateness for the FDA to modify its approach to the regulation of this field. Unlike before, many biopharmaceuticals are now approved for therapeutic use, and are 'well characterized', that is, they are produced and able to be characterized by analytic techniques that were relatively standardized [16,17]. In addition, a large number of biopharmaceuticals had been developed for a wide variety of indications, some for the treatment of diseases that were not particularly serious or life-threatening [18,19].

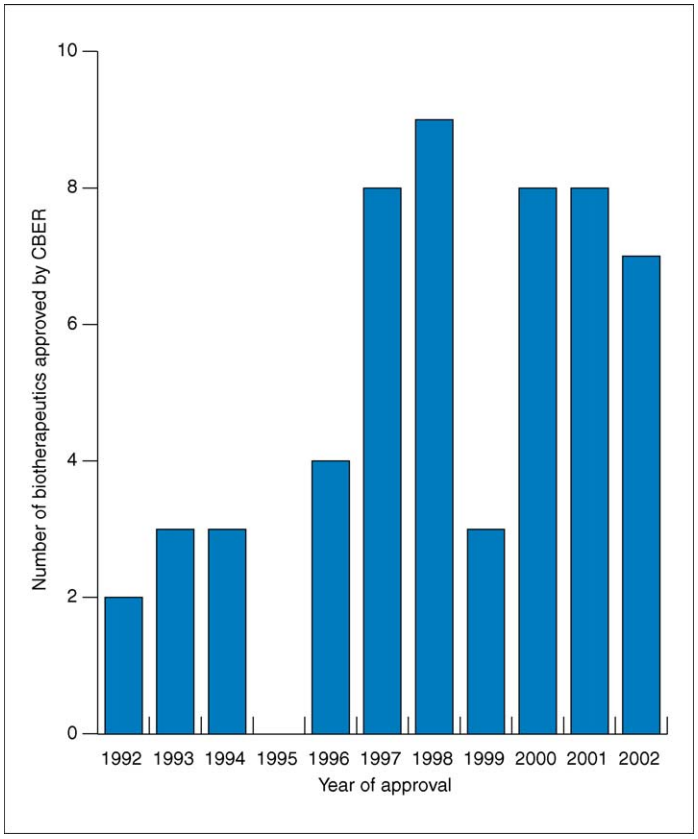

FIGURE 1
Biotherapeutics approved for use by the FDA.

Differences between CDER and CBER

CBER's organizational structure and regulatory approach from the early to mid 1990s emphasized the needs of a new, promising, but unproven, and relatively small sub-industry within a larger medical establishment. More often than not, CBER reviewers reviewed applications for novel agents generated by novel technologies, with mechanisms-of-action that were poorly understood. Most biopharmaceuticals were intended for the treatment of a relatively small population of patients afflicted with serious and/or life-threatening diseases, the majority for the treatment of cancer [12,20]. Often the clinical development challenges were difficult given the potency of the biologic agent, the minimal relevance of toxicological data from animal studies, and the potential for harmful effects in gravely ill patients. The maintenance of open dialogue with sponsors and relatively flexible standards was necessary to allow manufacturing issues and challenges in early clinical development to be optimally addressed.

CDER's organizational structure and regulatory approach, alternatively, had evolved over decades and was geared toward the review of an established and larger industry within modern medicine. The budget for CDER was approximately twice that for CBER. Also, CDER accepted well over twice the number of INDs, had over a dozen large clinical review divisions compared with CBER's single clinical review division, and received ten times the number of product license applications as did CBER at the turn of the millennium [21–23].

In addition, most CDER reviewers were much more accustomed than their colleagues in CBER to reviewing applications for therapeutic agents that were already part of an existing class of agents, and were likely to be widely used in the marketplace, including in patients with non-serious conditions. To regulate these products optimally in this environment, CDER adopted a sophisticated regulatory approach that emphasized more standardized and relatively rigorous requirements for clinical development, including clinical studies that generated large databases for the assessment of safety and efficacy. Table 1 compares the workload between CBER and CDER just before their merger.

TABLE 1
Comparison of CBER–CDER workload and performance in 2002[a]

Parameter	CDER	CBER
New original license applications	100	9
Efficacy supplements to license applications	158	10
Manufacturing supplements to license applications	1,753	717
Special protocol assessments	245	3
Total investigational new drugs submitted	1018	334
Meeting requests	1075	414
Clinical holds	52	122

[a] Data from Refs [10] and [23].

In addition to quantitative assessments, the workload at the FDA must also be viewed qualitatively to be accurately assessed. For example, it is interesting that despite receiving far fewer INDs to review, CBER placed sponsors on clinical hold twice as often as did CDER [23]. This likely reflects the inherent complexity, uncertainty and potential danger of many biological therapies – many of which are unique and deemed to hold as much peril as promise for patients – and is not likely indicative of an inherent or overzealous CBER conservatism (although CBER reviewers were privately criticized by industry for 'confusion about product development requirements' and 'slow' review times, a charge which CBER denied) (http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=36749). In many ways, the development of biopharmaceuticals can be very different from the situation for more traditional pharmaceutical agents in established therapeutic classes.

Despite their different roles and origins, it is important to note that the differences in regulatory practices between CDER and CBER were never clear or obvious. 'The supposition that there's ever been an absolute bright line between CBER and CDER was never true', Gillian Woollett, vice president of science and regulatory affairs at BIO, a biotechnology industry organization, said in early 2003 [3].

Moreover, from the beginning, CDER has regulated some biopharmaceuticals, including growth hormone and other endocrine peptide therapeutics, as well as insulin (http://www.fda.gov/cder/rdmt/drugclasses.htm). In addition, reviewers of oncology products from CBER and CDER have worked closely with each other for many years. Finally, to a variable extent other review divisions across the two Centers established common 'working groups' that met regularly to facilitate communication, share data and regulatory decisions, and standardize review practices.

The impact of the transfer to the CDER on the development of biologics

With the maturation of biotech and the transfer of jurisdiction for the review of biopharmaceuticals to CDER, the regulation of

BOX 1

Areas of clinical development most likely to be affected following transfer of biopharmaceuticals from CBER to CDER

1. Increase in the number of required preclinical animal studies
2. Increase in the number and rigor of randomized trials required for licensure
3. Increase in the size of the overall safety database required for licensure
4. Increase in emphasis on organ structure and function as primary endpoints
5. Increase in emphasis and a more conservative approach to clinical pharmacology and dose-ranging
6. Decrease in open communication with reviewers, decrease in regulatory flexibility, and fewer individualized approaches to clinical development
7. Greater scrutiny of advertising and marketing practices.

biologics in the future will likely more closely resemble traditional pharmaceutical development than the more individualized CBER approach to product development. Although manufacturing concerns will also be affected, the clinical requirements that CDER is likely to impose are expected to be the most significant. Below are seven areas that will probably change (summarized in Box 1).

1. The number and rigor of randomized trials required for licensure will increase

CDER, largely by virtue of its greater resources and experience, acquired more expertise than CBER in designing clinical trials and reviewing marketing applications [3].

However, it is important to note that regulatory standards set by the FDA are also driven by many factors other than overall experience. For example, in addition to her remarks about the unclear line between CDER and CBER, Woollett also noted that although 'CDER has more expertise in designing clinical trials. . .regulatory mechanisms historically have been created. . .to address particular problems; the first company through [the process] often ends up creating the regulation' [3].

Woollett's observations are valid. The degree of unmet medical need and the stage of development of a therapeutic class are important considerations for the regulation and review of any clinical development plan. Innovative sponsors who address important unmet medical needs in serious or life-threatening conditions are usually given opportunities for accelerated review times and other advantages to speed product approval [24]. Ascribing origins to the differences in regulatory approaches between CDER and CBER (and using these to predict the regulatory future for biologics) is therefore somewhat complicated. Many if not most sponsors of biopharmaceuticals were innovators, developing novel therapies for new indications in areas where the unmet medical needs were high, which affected the regulatory requirements set by CBER, including use of smaller datasets by which to judge safety and efficacy [12].

The development of interferon α-2b is an example of this phenomenon. This biopharmaceutical was the first therapeutic agent approved for the treatment of chronic hepatitis C, approved by CBER in 1991 after the sponsor conducted two relatively small studies totaling fewer than 400 patients [25]. Although therapeutic effects were observed in the individual studies, clinical benefit was only conclusively shown when the data were analyzed in a meta-analysis (http://www.fda.gov/medwatch/safety/2002/intron_a_pi.pdf), a lower regulatory standard infrequently used by the FDA in primary assessments of safety and efficacy.

After the approval of interferon α-2b and by the mid 1990s, sponsors of interferon-based therapies were required by CBER staff to greatly increase the size and rigor of their development plans. Studies from these sponsors included many times the number of patients as before enrolled in multiple large randomized clinical studies (see package inserts for Roferon® and Pegasys®). These new standards were comparable to those used by CDER for similar agents for this condition (see package insert for Rebetron®).

In another example of this evolution in regulatory requirements, in 1998 CBER approved etanercept for the treatment of rheumatoid arthritis (RA) (http://www.fda.gov/cder/biologics/review/etanimm110298r2.pdf) and in 1999 infliximab for RA (http://www.fda.gov/cder/biologics/review/inflcen111099r4.pdf) with relatively small datasets. Both were novel biopharmaceuticals in a new class of therapeutics that inhibited tumor-necrosis factor (TNF). Each was studied in a single pivotal study with an overall database of about one thousand patients or fewer. In this instance, the databases for these agents were smaller than required at the time by CDER for the development of leflunomide, an anti-inflammatory agent used for the same indication (see package insert for Arava®).

However, by late 2002, when the third anti-TNF agent, adalimumab, was approved by CBER (http://www.fda.gov/cder/biologics/review/adalabb123102r1p1.pdf), the sponsor was asked by CBER reviewers to study more than twice the number of patients that had been required for the sponsors of etanercept and infliximab.

It is important to note that in other therapeutic areas, where regulatory pathways were more defined and agents from both Centers were developed in parallel, CDER and CBER regulatory standards did not differ at all. CDER's regulatory requirements for bivalirudin, a direct inhibitor of thrombin for the treatment of post-infarction angina with angioplasty, were nearly identical to those used by CBER for abciximab, a biopharmaceutical that inhibits glycoprotein IIb/IIIa used to treat the same Indication (see package inserts for Angiomax® and ReoPro®).

Close cooperation between the oncology groups at CBER and CDER, including joint authorship of a guidance document outlining clinical requirements for the development of oncology agents, ensured comparable regulatory standards between these two review groups (http://www.fda.gov/cber/gdlns/canclin.htm).

In summary, there was never a clear demarcation in overall regulatory clinical requirements between CBER and CDER. However, it was not uncommon for CBER to initially require relatively small datasets for approval for products meeting unmet clinical needs for serious or life-threatening conditions, and then later to increase sharply those requirements for subsequent products developed in the same therapeutic class.

CDER reviewers during this time sometimes required that sponsors conduct somewhat more rigorous clinical development plans

than did CBER reviewers for similar products to demonstrate their safety and efficacy.

Consistent with its history, experience and greater resources, CDER is likely to generally require a more rigorous, and more standardized, approach to the development of biopharmaceuticals. Although the more individualized, flexible, and occasionally less-rigorous standards imposed by CBER reviewers in emerging medical fields are likely to be adopted by CDER in some cases, it is equally likely that sponsors in many of these situations will be made to do more than would have been required by CBER. Greater scrutiny will likely be paid to all aspects of late-stage clinical development, including secondary endpoints, safety studies and potential pharmacologic interactions.

Finally, it is possible that CDER review teams might be more likely to grant more Fast Track applications and priority reviews than did CBER, given the existence there of greater resources and somewhat different standards and context for these designations. The FDA recently issued a guidance document to clarify certain terms and codify standards in this area (http://www.fda.gov/cder/guidance/5244fnl.pdf).

2. More patient data will be required for the overall safety database and license application

Data will be required for many of the same reasons listed above for the likelihood of increased efficacy requirements under CDER review, and as biologics become even more mainstream (and as the FDA increasingly focuses on the safety of the nation's drug supply) CDER is likely to require sponsors of biopharmaceuticals to submit larger safety databases in marketing applications than were generally expected in CBER.

3. More emphasis on measures of organ structure and function as primary endpoints

CBER reviewers tended to focus on clinical outcomes as primary endpoints in studies, whereas CDER reviewers often focus on histologic or functional outcome measures for the same indications.

The reasons for this are not entirely clear. It is not unlikely that given the potency and/or toxicity associated with many biologic therapies, and the often relatively poorly understood mechanisms-of-action of many biopharmaceuticals, reviewers in CBER were often reluctant to accept anything less than full and direct evidence of benefit to patients, as measured by clinical phenomena, and were skeptical of the use of non-clinical data as primary outcomes.

The differing regulatory approaches to the study of investigational therapies for the treatment of asthma is an example of this. Reviewers in CBER recommended counting and comparing the rate of patient asthmatic attacks as a primary outcome measure for pivotal studies in this field, whereas those in CDER emphasized capturing results from pulmonary function tests (e.g. FEV_1) to assess product efficacy (see package inserts for Xolair® and Advair®). Similarly, results from liver biopsies were secondary endpoints in most CBER-regulated studies of biopharmaceuticals for the treatment of chronic hepatitis C, whereas CDER reviewers incorporated these outcome measurements as part of the primary endpoint in their trials (see package inserts for Pegasys® and Rebetron®).

4. The number of animal studies required preclinically will increase

The utility of animal studies in the development of biopharmaceuticals is often marginal, given the absence of commonality between animals and humans between molecular targets or pathophysiologic mechanisms used or affected by biopharmaceuticals. For example, animal models for the treatment of sepsis almost universally failed to predict the utility of investigational agents in human trials, a field where many biopharmaceuticals were studied [26]. In another recent example of this, serious adverse events in patients treated with TeGenero's biopharmaceutical TGN1412 were unpredicted by data from preclinical studies [27,28].

In CBER there was often considerable discussion among the toxicologists, clinicians and pharmacologists regarding the appropriate animal species and number of animal studies to be conducted. In some cases, it was determined that sponsors need not study their biologic agent in two separate species, given the unlikelihood of generating meaningful data, but rather conduct a single definitive study in one relevant species (http://www.fda.gov/cber/gdlns/ptc_tga.txt). A guidance document that reviews requirements for animal studies for biopharmaceuticals produced by the International Conference on Harmonization reflects this standard [29].

CDER reviewers have usually required of minimum of two animal toxicology studies be conducted for pharmaceutical agents, and are likely to ask for two studies for biopharmaceuticals of considerable duration – even if the animal data are likely to have minimal biologic relevance to humans. Studies are also likely to be requested to be done earlier in development than before, including teratology and carcinogenicity studies in some cases. The usual six-month testing limit seen with many biopharmaceuticals could disappear, and sponsors could be routinely required to study agents longer-term (e.g. nine to twelve months).

5. Decreased open communication with reviewers, decreased flexibility and fewer individualized approaches to clinical development

As a consequence of their different histories and regulatory scope, CBER and CDER had different approaches to the regulation of their respective fields. CDER is a more experienced, formal and hierarchical clinical review organization than CBER was, where a more informal, protocol-specific and egalitarian (e.g. entry level reviewers had considerable influence at CBER) review style existed. CDER's regulatory requirements are felt by some to be less confusing and more consistent and predictable than were CBER's (http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=36749). Conversely, others acknowledged the advantages of having a more open and direct dialogue with review teams in CBER (http://www.morganlewisresources.com/pubs/31bc4e6a-f48b-4a3a-9b53750c52fa7644_publication.ppt).

It is important to note that the amount of communication between sponsors and all FDA staff dropped significantly after the enactment of Prescription Drug User Fee Act (PDUFA) 2 in 1997, legislation that some cite as having changed the priorities and work environment in all of the FDA [30].

Of all the likely changes resulting from the CDER review of biologics, the loss of more direct access to clinical reviewers might be the one felt most immediately by sponsors of biopharmaceuticals.

6. There will be more emphasis on, and a more conservative approach to, clinical pharmacology and dose-ranging

There are many more clinical pharmacologists who reside in CDER than there were in CBER. An entire Division exists in CDER to review and address data and issues in pharmacology, whereas only a few individuals in CBER are trained in this field. Probably for this reason, and because for some biological therapies it is difficult to predict clinical effects from pharmacology data alone, there tended to be less emphasis on clinical pharmacology parameters in CBER than in CDER.

A direct comparison of the type, amount and format of presentation of pharmacokinetic data in the package inserts for interferon (IFN) α-2b plus ribavirin and pegylated IFN α-2a, is informative in this regard (see package inserts for Rebetron® and Pegasys®). Both are interferon-based products approved contemporaneously by CDER (Rebetron®) and CBER (Pegasys®) for the treatment of chronic hepatitis C.

Although both package inserts contain much relevant useful pharmacology data, data for the interferon component of Rebetron is presented somewhat greater in scope and detail than are similar data in the Pegasys package insert, emblematic of CDER's greater focus on clinical pharmacology than CBER's.

Expect CDER reviewers to emphasize more acutely than did CBER reviewers the collection of pharmacology data, including establishment of a minimally effective dose, during product development.

7. There will be greater scrutiny of advertising and marketing practices

Because of greater resources within CDER, reviewers there are likely to impose more consistently stringent standards on the advertising of marketed biopharmaceuticals than was done in CBER. CDER has an entire division of ~25 individuals within the Division of Drug Advertising, Marketing and Communications (DDMAC) dedicated to the review of advertising. A total of 5 (4 full-time) individuals from CBER were responsible a similar function in CBER's Advertising and Promotion Labeling Branch at the time of the transition from CBER to CDER (http://www.fda.gov/cder/ddmac/presentations/fdli_ddmac%20update%20slides%20091103_ta/fdli%20ddmac%20update%20slides%20091103.ppt; see CDER DDMAC organization).

Conclusion

In recent years, biopharmaceuticals have become a significant and growing part of mainstream medicine. What was once an emerging field that needed to be developed and nurtured is now a mature industry for which tighter and more standardized requirements for development are appropriate.

In many instances reviewers in CDER will likely require many of the same data requirements for the development of biopharmaceuticals as they do for pharmaceutical agents. Sponsors of biopharmaceuticals, at least in some areas, should anticipate the need to study larger numbers of patients in pivotal studies, generate larger safety databases in license applications, place increased emphasis on pharmacology and collect more rigorous data from multiple studies than was required before by CBER. There are likely to be increased requirements for more preclinical studies for biopharmaceuticals, and for these studies to be extended for longer durations.

In other areas there is likely to be little change in regulatory standards for biopharmaceuticals. For example, in oncology, where there are two separate review divisions under the new structure, one for biopharmaceuticals and the other for pharmaceuticals, and where there has been a history of close cooperation between these review divisions, there are likely to be few significant changes observed. In cardiology and other fields where regulatory standards are reasonably well-defined and where biologic and pharmaceutical agents have been developed in parallel, the same is likely to be true.

In the long run, the transfer of review of biopharmaceuticals from CBER to CDER is likely to be beneficial to their future development. The higher quality data generated from larger and more rigorous clinical studies are likely to manifest in better information on many issues related to safety, efficacy and overall benefit–risk for biopharmaceuticals.

However, the potential costs of this approach are not inconsiderable – particularly in the near-term for some sponsors developing biopharmaceuticals in novel or emerging fields. The more flexible and individualized approach of CBER reviewers that is not currently emphasized in many areas of CDER will probably hamper the early development of some agents by increasing development costs and delays through the imposition of unnecessary requirements during early clinical development. Although these effects will be muted in some CDER divisions that will benefit from the experience and expertise of reviewers transferred from CBER, it will nevertheless take time for some CDER review teams to understand the nuances of biologic development and adjust their regulatory approach.

The development of biopharmaceuticals flourished during CBER's reign and is likely to continue to do so under CDER. Biopharmaceuticals are now commonly recognized as prominent and effective therapies in many areas of mainstream medicine. The transfer of the regulatory oversight of biopharmaceuticals to CDER is appropriate given their therapeutic importance and the need to integrate their review under the same structure as more traditional pharmaceutical agents. Numerous programs, including the FDA's 'Critical Path Initiative' are being implanted to streamline and expedite development of all investigational agents, including biopharmaceuticals.

Finally, adapting to change has always been a central strength of the FDA. This, along with the reasons listed above, is likely to help make reorganizing the approach to the regulation of biopharmaceuticals ultimately successful for the FDA, sponsors, patients and the public alike.

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References

1 Federal Register, Vol. 68, No. 123, 26 June 2003. Notices
2 Federal Register, Vol. 70, No. 56, 24 March 2005. Notices
3 Christensen, D.E. (2003) FDA reorganization, intended to streamline review process for biologics. *J. Natl. Cancer Inst.* 95, 576–577

4 McClellan, M. (2003) Expanding FDA's Mission, *U.S. Medicine* January
5 Pollack, A. (2002) Biotech and FDA: blame game, *New York Times*, 16 December
6 Hilts, P.J. (2003) *Protecting America's health: The FDA, business, and one hundred years of regulation*. Alfred A. Knopf
7 Junod Suzanne, (2002) 100 Years of Biologics Regulation, *Update* 6 (November-December)
8 Young, J.H. (1981) The Long Struggle For The 1906 Law, *FDA Consumer*, June
9 Anderson, O.E., Jr (1958) *The Health of a Nation: Harvey W. Wiley and the Fight for Pure Food*. University of Chicago Press
10 FDA (2002) Management discussion and analysis; biologics program, *FY 2002 Annual Financial Report* (http://www.fda.gov/oc/oms/ofm/accounting/cfo/2002/CBER.htm)
11 FDA (2002) FDA's Center for Biologics commemorates 100 years of biologics regulation, *FDA News*, September 23 press release (http://www.fda.gov/bbs/topics/NEWS/2002/NEW00840.html)
12 Reichert, J.M. (2004) Biopharmaceutical approvals in the US increase. *Regulatory Affairs Journal Ltd*, July, 1–6
13 Milenic, D.E. (2002) Monoclonal antibody-based therapy strategies: providing options for the cancer patient. *Curr. Pharm. Des*. 8, 1749–1764
14 Jones, R.E. and Moreland, L.W. (1999) Tumor necrosis factor inhibitors for rheumatoid arthritis. *Bull. Rheum. Dis*. 48, 1–4
15 Olyaei, A.J. *et al*. (2001) Use of basiliximab and daclizumab in kidney transplantation. *Prog. Transplant*. 11, 33–37
16 Schiff, L.J. (2004) Biotechnology products derived from mammalian cell lines: Impact of manufacturing changes, *Regulatory Affairs Focus*. October, 29–31
17 Henry, C. (1996) FDA, Reform, and the well-characterized biologic. *Anal. Chem*. 68, 674A–677A
18 Weinberg, J.M. *et al*. (2002) Biologic therapy for psoriasis—the first wave: infliximab, etanercept, efalizumab and alefacept. *J. Drugs Dermatol*. 1, 303–310
19 Cather, J.C. *et al*. (2002) Update on botulinum toxin for facial aesthetics. *Dermatol. Clin*. 20, 749–761
20 Nagle, P.C. *et al*. (2003) Defining and characterizing the late-stage biopharmaceutical pipeline. *Am. J. Manag. Care* 9, S124–S135
21 FDA (2005) Prescription drug user fee act (PDUFA): Adding resources and improving performance in FDA review of new drug applications. *White Paper* (http://www.fda.gov/oc/pdufa/PDUFAWhitePaper.pdf)
22 Dept. Of HHS, FDA, Office of Public Affairs (2002) *Countering Bioterrorism*. Publication No FS 01-4
23 FDA (2002) FY 2002 Performance report to Congress for PDUFA of 1992, FDA, HHS (http://www.fda.gov/oc/pdufa/report2002/pdf/report.pdf)
24 Rados Carol, (2006). The FDA Speeds Medical Treatments for Serious Disease. *FDA Consumer Magazine*, 40, March-April
25 Fisher, L. (1991) Interferon set to treat hepatitis. *New York Times*, 26 February
26 Esmon, C.T. (2004) Why do animal models (sometimes) fail to mimic human sepsis? *Crit. Care Med*. 32 (Suppl. 5), S219–S222
27 Hansen, S. and Leslie, R.G. (2006) TGN1412: scrutinizing preclinical trials of antibody-based medicines. *Nature* 441, 282
28 Wood, A. and Darbyshire, J. (2006) Injury to research volunteers—the clinical-research nightmare. *N. Engl. J. Med*. 354, 1869–1871
29 Preclinical safety evaluation of biotechnology-derived pharmaceuticals. International Conference on Harmonization (ICH) guidance document S6
30 Okie, S. (2006) What ails the FDA? *N. Engl. J. Med*. 352, 1063–1066