



BioPharma Industry Roundtable



Quarterly Conference Call / Webcast

December 6, 2007

12- 1 pm EST

Chair:

Karen L. Bergman

Partner

BCC Partners, LLC.

Menlo Park, CA

Welcome

BioPharma Industry Roundtable Quarterly Conference Call

**“The Continually Evolving Healthcare
Regulatory Landscape”**

Today's Speakers

Moderators:

Sally J. Curley

VP of IR, Genzyme Corporation



Daniel Saks

VP of IR, Taro Pharmaceuticals



Guest Speaker:

Linda R. Horton, JD

Partner

Hogan & Hartson LLP



The Food and Drug Administration Act of 2007 (FDAAA)

Its Impact on FDA and the Pharmaceutical and
Biotechnology Industries
NIRI Webcast

Linda R. Horton, Partner

December 6, 2007



HOGAN &
HARTSON

Your speaker

- Counsels clients in the pharmaceuticals, medical devices, animal health, food, and cosmetics industries on regulatory requirements of the EU, as well as the FDA and its counterparts around world
- FDA official, 1968-2002; served as FDA's Director of International Policy; Deputy Chief Counsel for Regulations; Legislative Director
- Recommended in the *European Legal 500* for EU regulatory work in the areas of pharma & biotech and food & drug regulation; selected by FDLI as first recipient of its Leadership & Meritorious Service Award and to author the international chapter in the FDA centennial book
- Focuses on regulatory pathways, EU, FDA and global
- Member of WHO anti-counterfeiting legislative drafting group



Linda R. Horton

Partner

**Hogan & Hartson,
Washington**

T: 1-202-637-5795

Brussels

T: +32 2 505 0931

E: lrhorton@hhlaw.com

FDAAA's Impact on FDA and the Pharmaceutical and Biotechnology Industries

- PDUFA rates and the use of funds by FDA
- Pediatric research requirements
- Citizen petitions
- Provisions of interest in regard to the FDA/SEC relationship

Pub.L. 110-85 signed Sept. 27, 2007



From left to right) HHS Secretary Michael Leavitt, President Bush, FDA Commissioner Andrew von Eschenbach, and Rep. Joe Barton of Texas.

Statement by FDA Commissioner Andrew C. von Eschenbach

- We at FDA are pleased that Congress has passed the FDA Amendments Act of 2007 and thank the Members of Congress and their staff for all their hard work on this important accomplishment.
- We are particularly pleased that Congress has completed the reauthorizations of the Prescription Drug User Fee Act (PDUFA) and the Medical Device User Fee and Modernization Act (MDUFMA)--two programs accounting for nearly one quarter of FDA's annual budget. Over the past years, the PDUFA and MDUFMA programs have resulted in significant public health gains by making safe and effective, yet increasingly complex, medications and medical devices available to patients faster than was previously possible.
- The legislation also includes the reauthorizations of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act--two statutes that have provided invaluable information to the agency about medical products' interaction with pediatric populations.
- These programs are vitally important to the agency and its continued ability to protect and promote the public health. We look forward to working towards implementation of this legislation.

What FDAAA covers

Four of the "Titles" of FDAAA reauthorize existing laws:

- ***Prescription Drug User Fee Act (PDUFA)*** - allows FDA to collect fees from drug companies to help fund reviews of new drugs. The act enables shorter review times and a more predictable review process, while still maintaining high-quality reviews.
- ***Medical Device User Fee and Modernization Act (MDUFMA)*** - allows for user fees, and will allow FDA to make significant improvements in the medical device review program.
- ***Best Pharmaceuticals for Children Act (BPCA)*** - encourages more studies in children and promotes the development of treatments for children.
- ***Pediatric Research Equity Act (PREA)*** – continues FDA's authority to require studies in children concerning certain medical products and under other specific circumstances.

Coverage of FDAAA

Among other things, the law also provides for:

- additional encouragement of specialized pediatric medical device development
- the creation of a foundation (Reagan-Udall) to modernize product development, accelerate innovation, and enhance product safety
- food safety provisions
- advisory committee provisions
- clinical trial registries
- provisions intended to enhance drug safety
- The amendments also authorize a new voluntary program for the collection of user fees to support FDA review of television advertisements directed at consumers.
- An FDA website, <http://www.fda.gov/oc/initiatives/advance/fdaaa.html> has been established to answer questions about the renewed legislation.

PDUFA rates

- Fee Schedule for FY 2008

- -----

Fee Category	Fee Rates for FY 2008

APPLICATIONS.....	
Requiring clinical data.....	
\$1,178,000	
Not requiring clinical data.....	\$589,000
Supplements requiring clinical data...	\$589,000
ESTABLISHMENTS.....	
\$392,700	
PRODUCTS.....	
\$65,030	

Use of funds by FDA

- The total fee revenue amount for FY 2008 is \$459,412,000, based on the fee revenue amount specified in the statute, including additional fee funding for drug safety and adjusted for inflation and changes in workload.

[PDUFA IV specifies that the fee revenue amount for FY 2008 for all fees is \$417,783,000 (\$392,783,000 specified in 21 U.S.C. 379h(b)(1) plus an additional \$25,000,000 for drug safety specified in 21 U.S.C. 379h(b)(4)).]

- PDUFA IV specifies certain adjustments relating to workload based on historical data.
- FDA is provided additional funding for drug safety programs. This was a change from previous iterations of PDUFA.
- FDA's objective: "Enhancements to the post-market drug safety system will improve the public health by increasing patient protection while continuing to enable access to needed medical products."

PDUFA and drug safety

- To support new safety initiatives authorized by the Amendments Act, PDUFA IV will generate over the five year period total fee revenues of \$392.8 million (with annual adjustments for inflation and other factors), \$29.3 million of which is to be applied each year to hiring new staff to support new post-marketing drug safety activities.
- Congress also authorized assessment of an additional \$225 million over five years to implement the post-market drug safety programs described in the Act and to modernize and enhance the drug safety system.
- Post-marketing safety activities covered by user fees may include:
 - collecting and reviewing safety information on approved drugs,
 - improving data collection systems, reviewing risk management plans, and
 - implementing and enforcing post-approval studies and clinical trials and labeling changes.

September 27 commitments letter

As with each previous PDUFA, FDA sent letters to Congress stating its performance commitments for the year. For example:

I. REVIEW PERFORMANCE GOALS

- **A. NDA/BLA Submissions and Resubmissions**
- 1. Review and act on 90 percent of standard original NDA and BLA submissions within 10 months of receipt.
- 2. Review and act on 90 percent of priority original NDA and BLA submissions within 6 months of receipt.
- 3. Review and act on 90 percent of Class 1 resubmitted original applications within 2 months of receipt.
- 4. Review and act on 90 percent of Class 2 resubmitted original applications within 6 months of receipt.

FDA commitments letter September 27

From FDA letter to Representative Dingell:

ORIGINAL and RESUBMITTED NDAs/BLAs and Efficacy Supplements:

SUBMISSION COHORT	STANDARD	PRIORITY
Original Applications	90% IN 10 MO	90% IN 6 MO
Class 1 Resubmissions	90% IN 2 MO	90% IN 2 MO
Class 2 Resubmissions	90% IN 6 MO	90% IN 6 MO
Original Efficacy Supplements	90% IN 10 MO	90% IN 6 MO
Class 1 Resubmitted Efficacy Supplements	90% IN 2 MO	90% IN 2 MO
Class 2 Resubmitted Efficacy Supplements	90% IN 6 MO	90% IN 6 MO

Meeting management goals

Responses to Meeting Requests

- **1. Procedure:** Within 14 calendar days of the Agency's receipt of a request from industry for a formal Type A meeting, or within 21 calendar days of the Agency's receipt of a request from industry for a formal Type B or Type C meeting (i.e., a scheduled face-to-face, teleconference, or videoconference), CBER and CDER should notify the requester in writing (letter or fax) of the date, time, and place for the meeting, as well as expected Center participants.
- **2. Performance Goal:** FDA will provide this notification within 14 days for 90% of Type A meeting requests and within 21 days for 90% of Type B and Type C meeting requests.

A standard is specified about how a sponsor goes about requesting a meeting

Types A, B, and C meetings

Type A meeting is a meeting which is necessary for an otherwise stalled drug development program to proceed (a “critical path” meeting) or to address an important safety issue.

Type B Meeting is a 1) pre-IND, 2) end of Phase 1 (for Subpart E or Subpart H or similar products) or end of Phase 2/pre-Phase 3, or 3) a pre-NDA/BLA meeting. Each requestor should usually only request 1 each of these Type B meetings for each potential application (NDA/BLA) (or combination of closely related products, i.e., same active ingredient but different dosage forms being developed concurrently).

Type C meeting is any other type of meeting.

The performance Goals and procedures also apply to original applications and supplements for human drugs initially marketed on an over-the-counter (OTC) basis through an NDA or switched from prescription to OTC status through an NDA or supplement.

Meeting management goals, cont.

- **Scheduling Meetings**
 - a) Type A Meetings should occur within 30 calendar days of the Agency receipt of the meeting request.
 - b) Type B Meetings should occur within 60 calendar days of the Agency receipt of the meeting request.
 - c) Type C Meetings should occur within 75 calendar days of the Agency receipt of the meeting request.
- **Performance goal:** 90% of meetings are held within the timeframe.
- **Meeting minutes Performance goal:** 90% of minutes are issued within 30 calendar days of date of meeting.

Clinical Holds

A. Procedure: The Center should respond to a sponsor's complete response to a clinical hold within 30 days of the Agency's receipt of the submission of such sponsor response.

B. Performance goal: 90% of such responses are provided within 30 calendar days of the Agency's receipt of the sponsor's response.

Major Dispute Resolution

A. Procedure: For procedural or scientific matters involving the review of human drug applications and supplements (as defined in PDUFA) that cannot be resolved at the signatory authority level (including a request for reconsideration by the signatory authority after reviewing any materials that are planned to be forwarded with an appeal to the next level), the response to appeals of decisions will occur within 30 calendar days of the Center's receipt of the written appeal.

B. Performance goal: 90% of such answers are provided within 30 calendar days of the Center's receipt of the written appeal.

C. Conditions: A number of conditions are placed upon the use of this procedure, e.g., sponsors should first try to resolve the procedural or scientific issue at the signatory authority level. If it cannot be resolved at that level, it should be appealed to the next higher organizational level (with a copy to the signatory authority) and then, if necessary, to the next higher organizational level.

Additional commitments Sept. 27

A. Simplification of Action Letters

To simplify regulatory procedures, CBER and CDER intend to amend their regulations and processes to provide for the issuance of either an “approval” (AP) or a “complete response” (CR) action letter at the completion of a review cycle for a marketing application.

B. Timing of Sponsor Notification of Deficiencies in Applications

To help expedite the development of drug and biologic products, CBER and CDER intend to submit deficiencies to sponsors in the form of a “discipline review” (DR) letter when each discipline has finished its initial review of its section of the pending application.

ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

FDA will use user fees to enhance and modernize the current U.S. drug safety system:

- New scientific approaches
- Improvements in the utility of existing tools for the detection, evaluation, prevention, and mitigation of adverse events
- Enhancements and improvements in communication and coordination between post-market and pre-market review staff.
- Support for
 - 1) preparing and implementing a 5-year plan to modernize drug safety, including improving communication and coordination between the post-market and pre-market review staff
 - 2) activities designed to modernize the process of pharmacovigilance
 - 3) developing with sponsors, reviewing, and monitoring implementation of risk management plans and
 - 4) related activities.

5-year plan

1. The FDA will develop and periodically update a 5-year plan describing activities that will lead to enhancing and modernizing FDA's drug safety activities/system. The activities described in the 5-year plan will include:
 - a) Assessment of current and new **methodologies** to maximize the public health benefit associated with collecting adverse event information at various points during the product lifecycle;
 - b) With input from academia, industry, and others from the general public, identifying **epidemiology best practices** and developing guidance(s) describing these practices;
 - c) Expanding CBER/CDER's **database** acquisition and use for the purposes of targeted post-marketing surveillance and epidemiology;
 - d) Developing and validating **risk management and risk communication tools**, including assessing the effectiveness of risk management plan agreements and developing, implementing, and evaluating mechanisms for public communications about the benefits and risks of drugs and biological products;
 - e) Improving **post-market IT systems** (e.g., AERS 2, safety tracking system, and opportunities for linked data management).
 - f) Enhancing and improving **communication and coordination** between the Office of Surveillance and Epidemiology and the Office of New Drugs in CDER and the Office of Biostatistics and Epidemiology and the pre-market product review Offices in CBER, including activities to assess the impact and value of routinely including post-market review staff on pre-market review teams

5-year plan: process

2. The plan will be drafted, published on the FDA website, and updated as follows:

- a) FDA will publish a draft of the plan by March 31, 2008. At that time, FDA will solicit and consider comments from the public on the draft plan. The public comment period will be at least 45 calendar days. FDA will complete revisions to the plan and publish the final version no later than December 31, 2008.
- b) By the end of FY 09, FDA will conduct an annual assessment of progress against the plan to be published on the FDA website. The report will describe progress on issues outlined in the five year plan. In addition, the report will include FDA efforts to facilitate the interactions between OND/OSE related to the process of evaluating and responding to post-marketing drug safety/adverse event reports.
- c) FDA will publish updates to the plan as FDA deems necessary. FDA will publish on the FDA website draft revisions to the plan, solicit comments from the public on those draft revisions, and consider the public comments before completing and publishing updates to the plan.

Review of risk management plans

Review of risk management plans

- FDA may use user fees for the review of risk management plans and related activities (e.g., meeting with sponsors, collaborations between review divisions and the appropriate safety group in CDER or CBER, and reviews of periodic reports on the implementation of any risk management plan).

Review of proprietary names to reduce medication errors

- To enhance patient safety, FDA will utilize user fees to implement various measures to reduce medication errors related to look-alike and sound-alike proprietary names and such factors as unclear label abbreviations, acronyms, dose designations, and error prone label and packaging design. For example:
 - **A. Review Performance Goals – Drug/Biological Product Proprietary Names**
 - 1. Proprietary names submitted during IND phase (as early as end-of-phase 2)
 - a) Review 50% of proprietary name submissions filed during FY 09 within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.
 - b) Review 70% of proprietary name submissions filed during FY 10 within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.
 - c) Review 90% of proprietary name submissions filed during FYs 11 and 12 within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.
 - d) If proprietary name is found to be unacceptable, sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).

First cycle review performance

- **A. Notification of Issues Identified during the Filing Review**
 - 1. Performance Goal: For original NDA/BLA applications and efficacy supplements, FDA will report substantive review issues identified during the initial filing review to the applicant by letter, telephone conference, facsimile, secure e-mail, or other expedient means.
 - 2. The timeline for such communication will be within 14 calendar days after the 60 day filing date. ...FDA will notify the applicant of substantive review issues prior to the goal date for 90% of applications.
- **B. Notification of Planned Review Timelines**
 - 1. Performance Goal: For original NDA/BLA applications and efficacy supplements, FDA will inform the applicant of the planned timeline for review of the application. The information conveyed will include a target date for communication of feedback from the review division to the applicant regarding proposed labeling and postmarketing study commitments (PMCs) the Agency will be requesting.
- **Standard Operating Procedures and Training**
 - FDA will develop harmonized (CDER/CDER) standard operating procedures (SOPs) regarding the notification of planned review timelines.

FDA Guidance Documents

EXPEDITING DRUG DEVELOPMENT

- **A. Guidance Development:** FDA will develop and publish for comment draft guidances on the following topics by the end of the indicated Fiscal Year of PDUFA-IV. FDA will complete the final guidances within one year of the close of the public comment period.
 1. Clinical Hepatotoxicity – FY 2008
 2. Non-inferiority Trials – FY 2008
 3. Adaptive Trial Designs – FY 2008
 4. End of Phase 2(a) Meetings – FY 2008
 5. Multiple Endpoints in Clinical Trials – FY 2009
 6. Enriched Trial Designs – FY 2010
 7. Imaging Standards for Use as an End Point in Clinical Trials – FY 2011

Scientific Collaboration

- FDA will participate in workshops with representatives from the scientific community (including industry, academia and other interested stakeholders) to further the science toward development of guidance documents in the following areas:
 1. Predictive Toxicology
 2. Biomarker Qualification
 3. Missing Data
- FDA will participate in workshops and other public meetings to explore new approaches to a structured model for benefit/risk assessment.

Postmarketing Study Commitments

- FDA will develop harmonized (CBER/CDER) standard operating procedures that articulate the Agency's policy and procedures (e.g., timing, content, rationale and vetting process) for requesting that applicants agree in writing to voluntary postmarketing study commitments.
- The SOPs will be finalized prior to the end of FY 08. In developing these SOPs, the Agency will take into consideration the findings of the contractor study of current Agency procedures to be completed during FY 07.
- FDA will make available a releasable version of the final report within 2 months of receipt from the contractor.
- Training will be provided to all CBER and CDER review staff on the harmonized (CBER/CDER) standard operating procedures. Training will continue for all new review staff and refresher training will be provided to all review staff as necessary through FY 12.

Analysis and implications

Will the adverse event studies and systems funded by PDUFA fees really be much different than the passive reporting systems that exist now, like MedWatch and VAERS?

- With funding from PDUFA fees, the active surveillance systems that this legislation contemplates have the potential to reduce the amount of control that manufacturers have over the analysis of the safety of their products, particularly later in those products' life cycles.
- By using those fees to pay third parties for their health care data, the Government may be able to create large databases from which highly nuanced signals might be derived.
- Moreover, by using PDUFA fees to pay third parties to develop methods to analyze the data, and to perform the analyses, manufacturers will have to prepare to respond to those analyses and perhaps conduct its own analyses to challenge alleged safety signals for their products.

Analysis and implications

- *How can manufacturers prepare to deal with third-party analyses of their products' adverse event profiles?*
- The legislation and performance goals do not appear to provide manufacturers with access to the raw data that third parties will be analyzing – only the analyses.
- Consequently, manufacturers may be limited in the kind of analyses they can do themselves, and as a result may have limited ability to critique third-party's analyses.
- For those reasons, manufacturers should consider playing a proactive role in FDA's guidance-development, to attempt to create fair guidelines and standards that will govern how third parties determine what constitutes a safety signal.
- In particular, manufacturers will benefit from participating, to the extent possible, in FDA's plan to identify epidemiology best practices, and in the joint CDER/CBER guidance document regarding how to carry out scientifically sound observational studies.
- Finally, manufacturers may want to consider participating in, or initiating, rulemaking on how the PDUFA-fee-funded databases are used, with a goal of providing manufacturers with access to the raw data to which third-party contractors will be given access.

Analysis and implications

- *If a small company sponsors an orphan drug product, but contracts with a large company to perform its marketing, will the PDUFA fee exemption still apply?*
- The statutory language creates some ambiguity with regard to drugs owned by or licensed to one company and marketed by another.
- In this situation, it appears that both companies must have revenues below the \$50,000,000 threshold in order to qualify for the additional user fee exemptions.
- Thus, smaller companies need to exercise caution when deciding whether to contract for marketing of an orphan drug with a larger company.
- In fact, it is possible that contracting solely for marketing with any other company forfeits these user fee exemptions altogether, since in that circumstance, the marketer is neither the owner nor the licensee of the orphan drug, and the statute can be fairly read to require one or the other.
- It is not clear whether Congress truly intended this result or what rationale there might be for withholding the exemption from small companies that rely on larger companies to market orphan drugs, but unfortunately, the legislative history on this matter is sparse. FDA guidance is in order.

Pediatric research requirements

The Pediatric Research Equity Act of 2007 (PREA) reauthorizes, for the next five years, FDA's authority to require "pediatric assessments," or data assessing the safety and effectiveness of certain drugs and biological products in pediatric populations.

Congress:

- strengthened and clarified the fundamental provisions and, consistent with the overall theme of the FDA Amendments Act (Act),
- imposed new requirements for monitoring drug safety issues and
- provided greater transparency in the agency's decision-making process.

PREA provisions

- The PREA enables FDA to continue mandating that each new drug application (NDA), biological license application (BLA), or supplemental application submitted on or after September 27, 2007 for a new ingredient, indication, dosing regimen, dosage form, or route of administration, contain a pediatric assessment.
- FDA also maintains authority to require pediatric studies for already approved products if certain conditions are met, namely that the sponsor declined to comply with FDA's written request for pediatric studies under the Pharmaceuticals for Children Act of 2007 (BPCA) and FDA has determined that pediatric patients would benefit from pediatric studies or additional pediatric labeling. These assessment requirements, however, do not apply to any indication for which orphan designation has been granted.
- Sponsors may still request a waiver or, for new applications, a deferral of some or all assessments, but documentation now is required to support any request for a waiver on grounds that formulating a drug for pediatric populations is not possible.
- The new law also clarifies FDA's authority to require labeling changes and formalizes dispute resolution procedures to address disagreements over such changes.

Key changes

- Notably, Congress expanded PREA to enhance drug safety surveillance, increase transparency, and promote consistent decision-making.
- For instance, all adverse event reports following pediatric labeling changes will be referred to and reviewed by an advisory committee.
- The Act also establishes a new internal committee tasked with reviewing all submitted assessments and requests for deferrals and waivers for consultation to review divisions, and conducting a retrospective review by September 27, 2008 of a sampling of assessments and approved deferrals and waivers.

Key changes

- The Act also requires FDA to track and make publicly available certain data, including the number and type of completed pediatric studies, number of requested and granted deferrals and waivers, labeling changes under the PREA, and certain of FDA's review documents.
- Further, the Institute of Medicine (IOM) and the Government Accountability Office (GAO) must evaluate and report to Congress on pediatric research under the PREA.
- **Enforcement**
- The PREA clarifies that a drug may be misbranded not only if the sponsor fails to submit pediatric assessments within certain timeframes, but also if it does not comply with pediatric labeling changes requested by FDA at the conclusion of the dispute resolution process.

Key Dates

- Sept. 27, 2007 PREA went into effect
- Oct. 27, 2007 By this date, the internal committee begins reviewing assessments, deferrals, and waivers and consult with review divisions
- Sept. 27, 2008 By this date, the internal committee must conduct retrospective analysis of representative sample of assessments deferrals and waivers
- Jan. 1, 2011 GAO report to Congress is due
- Oct. 1, 2012* PREA sunsets

PREA Dispute Resolution

- Further, the dispute resolution procedures specify timeframes if FDA and the sponsor are unable to reach agreement on pediatric labeling changes.
- Within 180 days after submission of the application, FDA will request the sponsor to make the changes it considers to be appropriate.
- If the sponsor does not agree to make these changes within 30 days of the request, the matter will be referred to the Pediatric Advisory Committee.
- Within 90 days of referral, the Advisory Committee will review the matter and make recommendations to FDA.
- Within 30 days of receiving the recommendation, FDA may submit another request to the sponsor for labeling changes.

Reauthorization of Best Pharmaceuticals for Children Act

- Enacted as part of Congress's first reauthorization of the PDUFA program, in the 1997 Food and Drug Administration Modernization Act ("FDAMA"), the agency's pediatric exclusivity program provides sponsors with six months of additional marketing exclusivity and patent protection for their drugs, in return for conducting clinical studies in pediatric populations.
- After its initial passage, the program was amended and reauthorized in the Best Pharmaceuticals for Children Act in 2002.
- With Title V of FDAAA, known as the Best Pharmaceuticals for Children Act of 2007, Congress has again amended and reauthorized the program, which now expires on October 1, 2012.
- The amendments took effect immediately upon enactment, and did not require the promulgation of regulations or guidance documents.

Requirements for exclusivity

- To receive the six months of exclusivity, a sponsor must conduct and report the results of one or more clinical studies that are responsive to a “written request” from FDA.
- Upon receiving a written request, a sponsor must conduct the requested studies and, within the timeframe set by the agency, submit reports of the studies to FDA in the form of a supplemental new drug application.
- No approval of the data is required, and the studies need not be successful.
- The sponsor simply has to conduct the requested studies in manner that “fairly responds” to the written request and submit the information to FDA.

Effect of exclusivity

- On FDA's acceptance, pediatric exclusivity extends by six months all marketing exclusivities and patents on the sponsor's entire line of products that contain the studied active moiety (e.g., five-year new chemical entity exclusivity becomes five and one-half years).
- Pediatric exclusivity cannot truly extend a patent, but instead prevents FDA from approving a generic drug application for a period of six months from the expiration of the "extended" patent.

FDAAA changes in exclusivity law

- FDAAA makes numerous changes to the pediatric exclusivity program, which apply to all written requests issued on or after the date of enactment.
- Several provisions of the law also apply to *all* written requests pending on the day before enactment (but for which no exclusivity determinations have been made).
- Among the changes that apply only new written requests, FDA will now have 180 days from the date of submission of pediatric studies to determine whether to award a sponsor pediatric exclusivity; twice the time provided under prior law.
- Also, if this determination is made later than nine months prior to the expiration of any particular marketing exclusivity or patent, that six-month extension will not be awarded.

FDA can order labeling changes

- The new law provides FDA with the authority to “order” the labeling of a drug to include information about the results of a pediatric study conducted pursuant to a written request.
- This is the case regardless whether the study showed that the drug is safe and effective in any pediatric population, or whether the study was inconclusive.
- To facilitate this, the law also states that written requests will include requirements that sponsors submit proposed labeling changes to FDA along with the results of their studies.
- And sponsors will be required to disseminate to healthcare providers information about any labeling changes that result from their pediatric studies.
- In the event that a sponsor and FDA cannot agree to a labeling change, the agency has been provided with greater authority to refer to the matter to the Pediatric Advisory Committee and ultimately to declare the drug misbranded.

No change in standards

- While the law did not change the standards under which FDA will issue written requests or review submitted studies, it did change what studies the agency may seek and who may review them.
- The law adds preclinical studies to the definition of what FDA may seek in a written request, and states that an internal review committee, regarding the reauthorization of the Pediatric Research Equity Act) will review all written requests prior to issuance.
- This committee also may review submitted studies and make recommendations to FDA whether to award exclusivity.

Off-patent drugs

- The law makes several changes to the way in which the government attempts to ensure that pediatric studies are conducted on off-patent drugs (where pediatric exclusivity is of no value) and on drugs for which sponsors have declined written requests.
- In the case of a drug that has an unexpired patent, FDA may now seek to determine whether the Foundation for the National Institutes of Health has the resources to fund a study. If not, FDA may make a determination whether the study may be required under the Pediatric Research Equity Act.
- Where there are no unexpired patents, FDA shall refer the drug for inclusion on a list of drugs for which pediatric studies are needed.

More transparency

- Finally, the law increases the amount of information that FDA will compile on the performance of the pediatric exclusivity program and publish on its website. Most notably, FDA is required to publish the fact that it has awarded pediatric exclusivity to a sponsor within 30 days of making its determination, and to include in this announcement a copy of the written request itself. Until now, written requests have generally not been available publicly.
- The agency recently published the first of these written requests.
- *See Pediatric Exclusivity Determinations Made under Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the FDA Amendments Act of 2007 (FDAAA), available at http://www.fda.gov/cder/pediatric/bpca_determination.htm.*

Implications

- Of all the changes made to the pediatric exclusivity program, the most significant aspect of the new law made be one change that was *not* made.
- The final version of bill omitted a controversial provision that would have shortened the six-month pediatric exclusivity award to three months, for any drug that had annual gross sales of \$1 billion in any calendar year prior to the time the sponsor agreed to a written request.
- The proponents of that provision, including Rep. Henry Waxman (D-CA) and Sen. Edward Kennedy (D-MA), argued that the smaller incentive was appropriate for so-called “blockbuster” drugs.

Other changes not included

- Another change that was not made to the law concerns the availability of second periods of pediatric exclusivity.
- The new law leaves intact a provision that allows sponsors to seek second written requests from FDA, to conduct additional pediatric studies, and to receive second periods of pediatric exclusivity.
- The agency interprets this provision very narrowly (limiting the second six-month exclusivity to extend only the three-year exclusivity earned as a result of a pediatric labeling change), and advocated as early as 2001 that the provision be repealed entirely.

Significance of timing changes

- The most significant of the changes that were made are the timing provisions:
- Going forward, FDA will have six months to make pediatric exclusivity determinations, rather than three.
- And if such a determination is made less than nine months before the expiration of an exclusivity or patent, that extension will not be awarded.
- The combined effect of these provisions is that sponsors must now plan to submit pediatric studies significantly earlier in their drugs' lifecycles.
- Sponsors should submit studies a full 15 months prior to the expiration of the most valuable patent or exclusivity, to ensure that it may be extended.

Significance of timing changes

- This longer timeline also resulted in the repeal of a provision that provided for interim, 90-day delays of the approval of generic drug applications.
- Under the prior version of the law, pediatric studies could be submitted on the eve of patent or exclusivity expiry, so long as they were submitted within the timeframe set forth in the written request.
- If any generic drug applications were eligible for approval before FDA made its determination whether to award the pediatric exclusivity, the agency was authorized to delay approval of the applications until it had made its decision.
- Under the new law, because exclusivity may not be granted later than nine months before the patent or exclusivity expiry, this provision is no longer necessary.

Content of labeling

- A final provision likely to have a significant impact on sponsors concerns FDA's newfound authority to order labeling to include the results of pediatric studies, regardless whether those studies demonstrate the safety or efficacy of drugs in pediatric populations.
- In the past, it has not been uncommon for sponsors to conduct studies that ultimately were not incorporated in their products' labeling. Now, sponsors should expect all studies to be described somehow in labeling.

Effective date

- With regard to implementation, most of the changes to pediatric exclusivity are prospective, and apply only to written requests issued on or after the date of enactment of the law.
- Several provisions do apply, however, to sponsors currently conducting studies pursuant to written requests.
- Among the most significant is the provision that gives FDA the authority to order labeling to include information regarding pediatric studies, and the provision that requires FDA to publish exclusivity awards and written requests within 30 days of its determinations.

Citizen petitions

- **The FDAAA contains a number of provisions to restrict the ability of citizen petitions to slow down the approval of generic drugs.**
- **This provision limits the filing of petitions to delay the approval of a pending ANDA or 505(b)(2) application.**
- **Under the new law, FDA may not delay the approval of such an application unless it is necessary to protect the public health.**
- **The Secretary may deny any petition at any time upon determining that the petition was submitted with the primary purpose of delaying the approval of an ANDA or 505(b)(2) application and does not on its face raise valid scientific or regulatory issues.**
- **The Secretary may issue guidance to describe the factors to be used to determine whether a petitions was submitted with the primary purpose of delaying an application's approval.**
- **FDA must take final agency action not later than 180 days after the petition is submitted, and the Secretary shall not extend that period for any reason.**
- **Final agency action within 180 days means a final decision by the Commissioner, or expiration of the 180-day period before any such final decision.**

Citizen petitions

- **Courts shall dismiss without prejudice any civil action with respect to any issues raised in the petition if the action is filed before the Secretary has taken final agency action on the petition.**
- **The 30-month period in which a generic company has to obtain tentative approval under 21 U.S.C. 355(j)(5)(D)(i)(IV) would be extended by the amount of time from the filing of the petition to final agency action.**
- **The petition must contain a certification that the petition includes all information and views upon which the petition relies, that the petition includes data and information that is unfavorable, and that the petitioner has taken reasonable steps to ensure that any unfavorable data or information had been disclosed to the petitioner.**
- **Furthermore, the petitioner must certify as to the date of receiving the information upon which the petition is based and the name of the persons or organizations paying to file the petition.**
- **Supplements or comments on a petition require a certification that the petitioner did not intentionally delay submission of the supplement or comment, as well as the date of receipt of information upon which the petition relies and the name of the persons or organizations paying to file the petition.**

Citizen petitions

- The provision does not apply to petitions related solely to the timing of approval of an application pursuant to 21 USC 355(j)(5)(B)(iv) (regarding the 180-day exclusivity period) or to petitions made by the sponsor of an application that pertain only to the sponsor's own application. The Secretary must submit an annual report to Congress on delays in approvals due to "blocking" petitions. Furthermore, by September 26, 2008, the Secretary must also submit a report to Congress on ways to encourage the early submission of petitions under this new provision.

Impact on FDA

- Prior to passage of this law, FDA had 180 days to respond to a citizen petition either by approving it, denying it, or providing a tentative response indicating why the agency had been unable to reach a decision on the petition.
- This last option effectively allowed the FDA to consider a citizen petition at length before reaching a decision as to the approval or denial of the petition.
- Likewise, for a petition for stay of agency action, the regulations simply provided that the Commissioner must “promptly review” a petition for stay of action, but the regulations did not provide for a specified time frame in which the Commissioner had to respond to the petition.

Impact on FDA

- The new law, however, provides for “final agency action” within 180 days from the date a petition is submitted.
- FDA is considered to have taken final agency action on a petition if this 180-day period expires without a final decision.
- We interpret this new provision to mean that final agency action within 180 days, or the expiration of this period, serves as the exhaustion of administrative remedies, after which one can file a civil action in a court for judicial review.
- We believe that this new provision thus serves as a spur for the agency to respond quickly to petitions, rather than allow a petition to languish.

Provisions of interest in regard to the FDA/SEC relationship

For discussion:

What will be the impact of the provisions on the FDA/SEC relationship?

How will company spokesmen be affected by the new law?

THANK YOU!

Questions?

For more information on
Hogan & Hartson, please visit us at

www.hhlaw.com

Baltimore
Beijing
Berlin
Boulder
Brussels
Caracas
Colorado Springs
Denver
Geneva
Hong Kong
London
Los Angeles
Miami
Moscow
Munich
New York
Northern Virginia
Paris
Shanghai
Tokyo
Warsaw
Washington, DC

Linda R. Horton

Linda Horton counsels clients in the pharmaceutical, medical device, animal health, food, and cosmetic industries on requirements of the EU regulatory authorities, the U.S. Food and Drug Administration (FDA), and similar agencies in other countries. Clients turn to her for assistance not only in meeting requirements, but also in designing strategies for developing and marketing products in Europe, the United States, and internationally. She is recognized as a leading lawyer in international regulation, harmonization, and trade law issues involving food, pharmaceuticals, and medical devices.

She joined Hogan & Hartson in 2002 after a long career in the FDA's legislative, legal, and international policy offices. During her last eight years at the agency, she was Director of International Policy, leading activities on harmonization, agreements, trade, imports, exports, EU relations, and legislative models for national regulatory systems. From 1979 until 1993, she was Deputy Chief Counsel for Regulations and Hearings, playing a leadership role in pharmaceutical regulatory reform, medical device approval, food labeling, tobacco control, and other significant FDA initiatives. She was in charge of administrative litigation on withdrawals of approvals of human and veterinary drugs due to safety or efficacy concerns, as well as proceedings to address clinical investigator misconduct. Earlier, Linda served FDA as its first management intern, a legislative analyst, Director of the Legislative Branch, trial attorney, Associate Chief Counsel for Medical Devices, and Advisor to the Commissioner. She helped U.S. Congress to write, and the FDA to implement, the landmark medical device laws and 1996 export reform law, among others.

Today Linda counsels clients on EU legislation, such as the clinical trials directive, the Community Code on medicinal products, the regulation on the European Medicines Agency (EMA), the medical devices directive, the various laws on animal feeds and veterinary medicinal products, and member state laws that implement EU legislation. Linda has taught international food, drug, and medical device law as an adjunct professor at Georgetown University Law Center and FDA administrative law at The George Washington University Law School.

Looking Forward to 2008



Register now for the Annual Dinner Event during the JPMorgan 26th Annual Healthcare Conference in San Francisco on Wednesday, January 9, 2008

- Shareholder Activism is our topic. Bring your questions!
- Featuring Mason Morfit of Value Act as our guest speaker
- 6 pm cocktails & 7 pm dinner, E&O Trading Company (walking distance from the meeting)

To register, go to:

<https://www.niri.org/calendar/eventdetail.cfm?EventID=2030&ChapterID=99>

Looking Forward to 2008

- Watch for:
 - Q1 Virtual Webcast;
 - NIRI Annual Conference in June;
 - And more...
- Join the on-line discussion group at Yahoo.com
- Send us your ideas for future virtual calls and events

If you have any questions or
comments, please contact:

Katherine Philipp

Director, Professional Development
National Investor Relations Institute

703-506-3580

kphilipp@niri.org