FDA and Industry in Dialogue

Centennial Journal

A Time Capsule of Presentations
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The Quality Assurance/Regulatory Affairs
Graduate Program of Temple University's
School of Pharmacy

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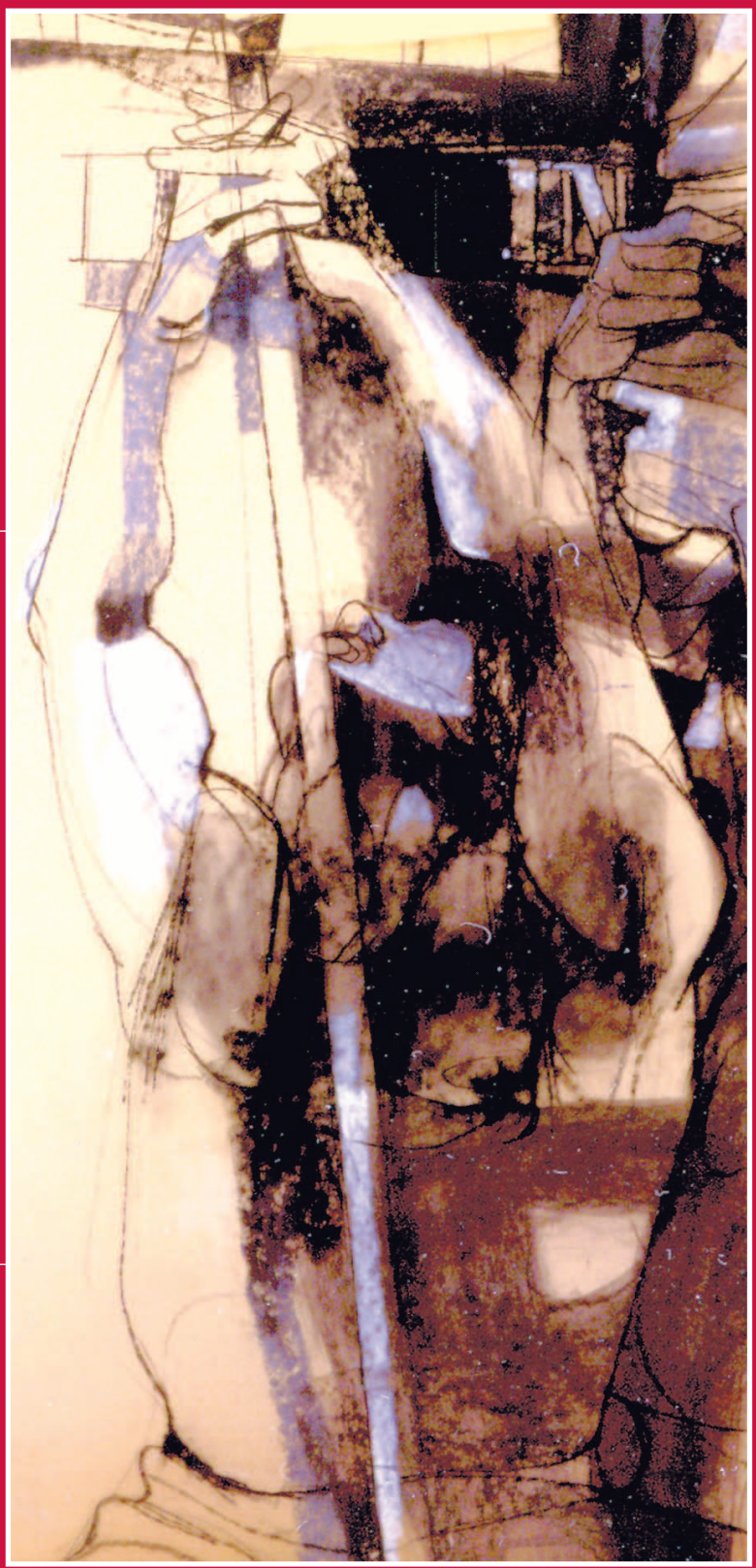
Editor: Wendy Lebing, MALD, MS



School of Pharmacy
TEMPLE UNIVERSITY
Quality Assurance and Regulatory Affairs Graduate Program

ARTWORK:

Front Cover:
Charles LeClair
Standard Bearers, 1964. Presented to Temple University's School of Pharmacy by Fred Gable in memory of his parents. Charcoal, chalk, and collage.

Back Cover:
Laszlo Bagi
Old Morgan Pharmacy, 1991. Alumni Fund Premiums commissioned by Temple University's School of Pharmacy. Silkscreen artist proof.

The School of Pharmacy art collection began in 1968 and developed under the guidance of Assistant Dean Fred Gable. Mr. Gable, a recognized art connoisseur and member of the University General Arts Committee, suggested that the graduating class present a watercolor by Ranulph Bye to the School in memory of Charles Unangst, a student who had passed away during the summer following his first year at Temple. Presently, the School of Pharmacy boasts one of the largest collections of art of the Schools and Colleges within Temple University.

CREDITS:

Editor: Wendy Lebing, MALD, MS
Graphic Design: Carl Wydra

Very special thanks to Richard A. Brashares, PhD, for serving as Assistant Editor for this publication. Special thanks to Jean Finch for transposing and editing many of the speeches and to Patricia Lee and Sylvia McNally for their endless hours of proofreading.

Richard Kaplan (Centocor). The first meeting also included Thomas O'Connor, Associate Dean for the School of Pharmacy, and Wendy Lebing from Temple's Ambler Campus.

Wendy had studied international relations at the Fletcher School of Law and Diplomacy, part of Harvard and Tufts, where she earned a Master of Arts in Law and Diplomacy (MALD). While waiting to take the Foreign Service exam, she pursued a "temporary" job with Temple University Ambler, gaining experience in scheduling, curriculum, and marketing. At the first Steering Committee meeting, she was organizer, hostess, and scribe. Her notes include a quote from Bob Drew, "In ten years, many of the companies sitting at this table won't exist, since the cost of developing drugs will become so huge that only giant mergers will survive." Noted in the margins were the phrases: "GMP. GCP. IND. *Strange language.*"

As President Liacouras of Temple pointed out, the University was strategically located in the heart of the Delaware Valley's pharmaceutical industry. A QA degree was sorely needed by the industry, but its curriculum required a complete overhaul. The Committee voted to save the program and met twice a year in an advisory role to discuss industry trends, suggest curricular changes, and identify prospective faculty from the industry. Over time, a remarkable camaraderie developed. Rather than approaching the meetings as corporate competitors, the participants coalesced as colleagues, generously donating their time, expertise, and cogent ideas. Importantly, Bob Drew at Merck, George Irwin at Wyeth, and Ron Nedich at Lemmon (which eventually became Teva) helped to provide funds through foundation and corporate resources to develop new courses. Without this financial support, the program would have come to a standstill. Richard Kaplan was hired to be the Academic Coordinator.

Along with Associate Dean O'Connor, Wendy Lebing assumed administrative responsibility for the program. Having authored a short history of the Ambler Campus, she was inspired by Jane Bowne Haines, founder of the first U.S. horticultural school for women, which was eventually acquired by Temple University. QA classes were moved to the Ambler Campus on an evening grid, enabling students to enroll part-time. Rather than following the traditional University grid of fifteen consecutive weeks, QA classes met only ten or twelve times but still satisfied contact-hour requirements. The first weekend class emerged when an attorney for Burroughs Wellcome Co., Gail Pilgrim, who created *Food and Drug Law,* was transferred to North Carolina's Research Triangle. Sunday classes soon followed. QA became the first University program to offer an entire weekend curriculum, attracting students from throughout the eastern seaboard. Other student-friendly conveniences were adopted, such as phone and fax registration, saving students unnecessary trips to Temple. Sylvia McNally, who started working for Temple in 1990, and, more recently, Patricia Lee, formed the backbone of these services. Both have handled countless registrations and student problems with serenity, grace, and patience. These simple changes were clearly welcomed by students who were Adult Learners, holding full-time positions in the industry.

Marketing was crucial to the program's success. Theme Open Houses were created, where FDA representatives and Steering Committee members spoke on current industry issues. With the tagline, "*It's About Quality. It's About Time*," the program's brochures and newsletters won national awards. The QA/RA website was created and eventually burgeoned to include seventeen corporate-specific homepages. In 1997, Wendy switched full-time to the School of Pharmacy to implement distance learning for the QA/RA program.

Prelude

A synergy blossomed between the School of Pharmacy and the corporate sector. Rapid response to the Steering Committee's suggestions was key to the program's success. Each semester new electives were created, such as *Quality Audit*, *Good Laboratory Practices*, and *Computer Validation*, gradually forming a true QA curriculum. As RA courses were developed, such as *IND/NDA Submissions* or *CMCs and the Regulatory Dossier,* the Steering Committee strongly urged changing the name of the program to QA/RA.

Suggestions for the program's metamorphosis also came from teachers who were full-time industry professionals. Originally members of the Steering Committee agreed to teach, including Chris Kowtna, who designed the first *Medical Device* course and then *Advanced GMPs, Acceptance Sampling*, and *Statistical Quality Control* and Charles Swartz, who created *International Drug Regulatory Affairs,* which Jurij Petrin later updated to *Global Regulatory Affairs*. Gail Pilgrim, the teacher with the longest tenure in the program, was later joined by attorneys John Cullen, Barry Berger, Paul Savidge, Mitzi Cole, Charlene Gallagher, Brian Bollwage, and Craig Hammes in offering *Food and Drug Law* and *Advanced Topics in Food and Drug Law,* each highlighting their particular area of legal expertise. Jonathon Parker recognized that regulations had evolved to the extent that separate courses on *Labeling* and *Advanced Labeling* were needed. Sandra Cottrell envisioned *Drug Development* and created such a comprehensive course that it became a degree requirement and was taught by Susan Galle, William Hirschhorn, John Zenno, and others. Dan Casaburi, Thomas Schultz, James Krupa, and Rich Bigg designed many science-based courses, such as *Sterilization Processes, Regulatory Sciences, Drug Dosage Forms*, and *Process Validation*. Andrew Clair constructed the highly popular *Industry Interactions with FDA and Health Authorities*, also taught by Dennis Ahern. Marcia Arentz restructured the Medical Device courses, adding one on *Global Submissions* and helped mold an entire certificate in that area. Frank Stevenson, Carmella Gualtieri-Ditmars, Jane Goeke, Gary Wilson, Beverly Zaber, and Peter Smith strengthened the GXP requirements, while Rayanne Berman, Lionel Edwards, Ira Katz, Anita Zuback O'Connor, Patrick Genyn, and Joseph Scavone focused on clinical issues. Courses in *Generic Drugs*, *Pharmaceutical Medicine*, *Pharmacoeconomics*, *Pharmaceutical Marketing*, *Packaging*, and *Computer Validation* were offered by Robert Dettery, Andrew Fletcher, Mirza Rahman, Craig Audet, Michael Lusty, Ken Rothfeld, and Sean Develin. Kevin Malobisky, and Randall Brenner offered *IND/NDA Submissions.* Karen Zimm carved the path for remote learning with her innovative *Post-Approval Changes* course, and Stephen Klincewicz and Adrian Thomas strengthened the curriculum in pharmacovigilence. At best this is a short list of over one hundred dedicated individuals who spent hours of personal time helping Temple shape the curriculum. They were motivated by a personal commitment to give back to industry by educating the next generation. Importantly, the blend of talents, expertise, and experience from so many top corporations established a true fortress of industry knowledge.

The Philadelphia District of FDA and CDER also played a vital role. Debra Pagano and Karyn Campbell (Philadelphia District) created an outstanding course on *Pre-Approval Inspections*; George Pyramides (Philadelphia District) united with Frank Diana (then at Johnson & Johnson) to create the first FDA/industry team-taught course, *Pharmaceutical Laboratory Quality Systems and Operations*. Rick Friedman and Kris Evans from CDER proposed and created *Microbiological Concepts in Pharmaceutical Manufacturing*. Philadelphia District Directors Diana Kolaitis and Tom Gardine kindly encouraged their staff members to speak at numerous QA/RA classes.

The QA/RA administration listened to the corporate and government sectors and also to the needs of the students. Wendy Lebing earned the MS in QA/RA to gain first-hand knowledge of the classes. In 2001, she was promoted to Assistant Dean and implemented additional changes. The GMP requirement was replaced with a GXP requirement. RA students were given the option of taking *IND/NDA Submissions* as an MS requirement rather than just *Quality Audit*. Required courses were limited to four so students could pursue electives which were relevant to their career paths. Graduate certificates were also developed to give students more academic choices. These four-and five-course programs enable students to explore an industry sector without committing to the entire master's degree. They also provide credentials for a cluster of courses in case students' companies relocate them before they complete the MS. Students can pursue a certificate, take several years off to focus on their careers, and then return and finish their degree coursework. The *Drug Development Certificate* provides a foundation of basic QA and RA principles. The *Certificate in Clinical Trial Management* focuses on clinical studies, with *Bioethics* as a keystone course. *Basic Pharmaceutical Development*, consisting of courses with a business focus, appeals to students with business degrees. The School of Pharmacy also launched the first academic offerings and certificate in *Medical Devices*.

Were these "clinical trials" in education smooth and easy? Absolutely not. As word of the program spread, students and companies demanded that Temple provide remote learning. QA/RA was not ready for the plunge but took it anyway. A company in Georgia was the first to request videoconferencing, a technology that seemed deceptively easy but had many hidden pitfalls. Next was an appeal from Norb Dryjanski at Searle Labs (later Pharmacia) in Skokie, Illinois, to deliver the program to his colleagues. Norb had commuted to Temple University on weekends for all twelve courses, becoming the program's first distance graduate. Numerous protocols had to be developed for these remote classes which were broadcast to fifteen sites within three years. Shortly thereafter, Dave Brickett was hired to build videoconference rooms from scratch and oversee remote transmission.

Today QA/RA delivers its program to over twenty-five sites nationwide. While a handful of other RA programs are attempting to establish themselves, Temple's remains the most comprehensive, drawing its faculty and students from most major corporations, including big PhRMA, generic and start-up companies, biologics, medical devices, and clinical, packaging and related firms (including pharmaceutical support, food and chemical companies, and healthcare). Importantly, the administration of the School of Pharmacy remains steadfast in its commitment to *quality* education, fostering the most successful form of learning: the dynamic relationship between teacher and students. True graduate education encourages critical thinking, the ability to determine the validity and cogency of arguments. The burgeoning growth of the program has occurred with a fidelity to the policies and expectations of the Graduate School. Dr. Daniel Canney, Associate Professor of Medicinal Chemistry, has helped maintain these standards by serving as the Director of Graduate Studies, overseeing MS applications.

A milestone occurred in 1999 when FDA Commissioner Jane Henney broadcast a speech to FDA stakeholders via satellite, and Temple was suggested as a site. Nancy Smith (Director), Marcia Trenter (Special Assistant), and Elaine Frost (Special Assistant for Television Production Services) of CDER's OTCOM (Office of Training and Communications) visited Temple's Philadelphia campus and selected it as an appropriate venue. That same year, Tom Kirsch gave a speech at the QA/RA Commencement Celebration, suggesting that FDA and

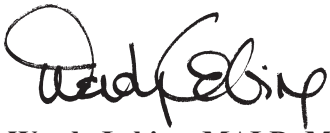
Prelude

industry needed opportunities to hold an open dialogue about needed changes. This speech was the seed kernel of Temple's ground-breaking FDA/Industry conference first held in April 2000 at Temple's Apollo Center with over 300 attendees. Janet Woodcock, Director of CDER, delivered the keynote address and so enthusiastically embraced the theme of dialogue that she joined the audience and posed questions to other CDER and industry speakers, a tradition which Steven Galson graciously continues today. The conference was held again in 2001, 2002, 2003, 2004, and 2006, providing a unique forum for high-level discussions on issues related to drug development. The topics are the result of an iterative process between the Steering Committee and CDER leadership, including Nancy Smith and Marcia Trenter. QA/RA faculty serve as panelists, enhancing the depth and breadth of the frank exchanges. Interestingly, the event soon engendered the *esprit de corps* of Steering Committee meetings, with everyone entering the forum with open minds and listening to colleagues' opinions.

Last year, the School of Pharmacy received a prestigious endowment from the FDA Alumni Association (FDAAA) establishing the first scholarship for QA/RA students. Through the tireless efforts of Robert W. and Kelly Sauer, John C. Villforth, and others, the FDAAA raised the endowment to commemorate the 100th anniversary of the Pure Food and Drugs Act and to encourage academic training in regulatory and quality issues. Currently the QA/RA program awards the MS degree to over one hundred hard-working pharmaceutical industry professionals each year who complete the program on a part-time basis with all of the personal sacrifice that it entails.

This publication includes some of the outstanding presentations given at the FDA/Industry conferences and QA/RA graduation celebrations, based on recordings that were subsequently transposed. While it was not possible to print every speech, those included give a representative snapshot of the thinking on drug development by key FDA and industry thought leaders at the turn of the 21st century. It is fascinating to review speeches from 2000, when electronic submissions were still in their infancy and participants forming the Mutual Recognition Agreements were at odds about what type of paper to use. History is often determined by seemingly irrelevant details which either become insurmountable obstacles or demand true leaders to emerge and provide the inspiration and vision for everyone to cooperate.

We thank every one of our speakers and panelists who took a bold step in participating in our conferences, sometimes presenting renegade ideas, or, other times, asking bureaucracies, whether they be academic, governmental, or corporate, to make essential changes for the greater good. When people come together and give of their hearts and minds, a unique transcendence occurs. This is the history of the QA/RA program and its very special relationship with the pharmaceutical industry and the world's foremost regulatory agency. We are grateful to the special individuals who selflessly give more than is required and thus form an extraordinary program with an unparalleled camaraderie, spirit, and purpose.



Wendy Lebing, MALD, MS
Assistant Dean
Quality Assurance/Regulatory Affairs Graduate Program
Temple University School of Pharmacy

Special Note: This speech given at the May 1999 QA/RA Graduation Celebration inititated the idea of creating an FDA/Industry conference sponsored by Temple University's School of Pharmacy.

The Need for Pre-NDA Interaction

Thomas J. Kirsch, MS
Executive Director*
Regulatory Practices
R.W. Johnson Pharmaceutical Research Institute

I have been privileged to be a part of the Steering Committee of the QA/RA program since 1990. The vision and the drive of the School of Pharmacy for this unique graduate degree are remarkable.

I want to share some of my thoughts regarding the future of the Quality Assurance profession. It is important to realize that the ultimate customer of both the pharmaceutical industry and the Food and Drug Administration (FDA) is essentially the same — the consumer or patient who needs significant new drug therapies. I believe industry and government must work together in delivering this service. While our paths and missions differ, our ultimate destination is the same.

This means we must work together. A "partnership" between industry and the FDA may be too much to expect, especially since the public expects independent protection through FDA. Still, the role of Quality Assurance in the pharmaceutical industry is changing. As we began this decade, we were challenged to do "more with less;" and, as we close the century, we realize we have to do "less with less." QA's function extends beyond compliance and its role has broadened to become a valuable and important management tool. What is its future? Here are some trends I foresee:

1. QA will have an increased role in business decisions such as the review of licensing and acquisition arrangements prior to the establishment of final contracts between partner organizations.

2. QA has actually become a discipline, and the need for effective QA programs will continue to grow.

3. The need for certification of compliance auditors is apparent and can be achieved through professional organizations.

4. QA programs will be used to reduce the cycle time presently needed for approval of regulatory applications, i.e., product development through the launch of new products.

** Vice President, Global Research & Development, Quality Assurance, Johnson & Johnson Pharmaceutical Research & Development, LLC, before retiring.*

range of industry, FDA, and healthcare professionals.

Academia also encompasses assessments of learning in the form of exercises and assignments to determine whether a student has truly mastered a concept or simply memorized a regulation. Most importantly, education judges how much knowledge has been assimilated by providing a series of evaluated assignments and course grades.

Initially, Temple's QA program was a traditional full-time graduate program. This precluded many pharmaceutical professionals from participating or forced them to take a leave of absence while they pursued a graduate degree. Almost two decades passed before Temple responded to market demand and offered courses on weeknights and weekends year-round. RA electives (such as *Requirements for Product Labeling and Advertising, IND/NDA Submissions,**** and *International Drug Regulatory Systems*) were introduced, necessitating a change in title from the MS in QA to the MS in QA/RA.

Currently Temple's MS in QA/RA consists of 36 credits (or 12 courses). Four are required (*Drug Development*, *Food and Drug Law*, a *Good Practices* course and either *IND/NDA Submissions* or *Quality Audit*). The remaining are electives, permitting students great flexibility in tailoring a curriculum that best suits their career needs. They can major in QA or RA issues; they may also combine both disciplines and add electives from the pharmaceutical sciences to expand their professional portfolio. Even the required courses provide students choices: they may select from *GMPs*, *GCPs,* or *GLPs*+ to fulfill their *Good Practices* requirement; likewise, they may either take *Quality Audit* (preferred by QA professionals) or *IND/NDA Submissions* (usually selected by RA professionals) as their fourth required course.

Temple's program is leaning towards a stronger science base, since there is a crucial need for technical and scientific education in both the regulatory and quality disciplines. "The work of regulatory and quality staff involves the review of technical activities/reports and fielding technical questions from government reviewers," notes Dr. Richard Kaplan, Vice President of Quality Assurance/Environmental Health & Safety at Cephalon, Inc. "Knowing regulatory and good practices is not sufficient. Understanding scientific principles is imperative for staff to perform their responsibilities effectively, allowing them to make reasoned, cogent critiques." Temple eliminated MBA business requirements and electives from the QA/RA program in the late 1990s, since the courses were never truly integrated into the curriculum. In their place electives focusing on pharmaceutical business were added (*Pharmaceutical Marketing* and *Pharmacoeconomics*) as well as electives from the pharmaceutical sciences (*Drug Dosage Forms* and *Pharmaceutical Manufacturing)*.

RA professionals may still enter their field by pursuing the tried and true industry apprenticeship. But today they may also advance more quickly by pursuing a degree from the various RA/QA graduate programs that now exist in the U.S. and worldwide. Graduate education provides students with a comprehensive view of the drug development process, exposing them to the laws, regulations, and guidelines that oversee the industry as well as

*** Investigational New Drug/New Drug Application Submissions.
+ Good Manufacturing Practices, Good Clinical Practices or Good Laboratory Practices.

investing in computers and other up-do-date hardware and software to help streamline our own internal management and aid the industries in our purview in meeting the regulatory requirements.

In addition to these principles, which we could implement unilaterally, we decided to step up FDA's multilateral efforts to bring about international harmonization and cooperation in the regulatory field. This was an important departure from the Agency's traditional self-reliance, but it was a policy born of necessity and irrefutable logic. International harmonization can help us avoid duplication of effort, ease the pressure on our resources, and improve regulatory standards worldwide.

It has become clear that, if anything is constant, it is change. The challenges that change brings are many and varied. All of us, whether we are involved in regulation, industry, or academia, need to reexamine our organizations, policies, priorities, and resources and move without delay to reshape them to meet our best forecasts of things to come. We cannot afford to wait and see. We must take the risk and initiative before the inevitable and accelerating changes steal from us the options that still remain.

Consider some of these facts:

- Population is exploding. It took six million years to reach our world size of 5.3 billion. It will take only fifty years to double that!
- Every five years we double the information and knowledge available to us.
- 80% of technology today was developed since 1900, but it will take only fifteen more years to equal that amount of technological change.
- Food imports to the United States have tripled in the last twenty years.
- 10,000 new products are introduced into the marketplace each year, not to mention the arrival of all those new labels.
- New product packaging is microwaveable — even edible! Products are shelf-stable, vacuum packaged, and recyclable.
- New and emerging pathogens from microbes once thought to be harmless are front-page news.
- Health threats such as tuberculosis are reemerging, and new drugs and devices are in development using biotechnology and microcomputerization undreamed of just a few years ago.

The public wants guarantees of total safety but at no additional cost. Government downsizing and corporate self-certification initiatives are taking place around the world. We are increasingly faced with:

- Conflicting priorities
- New responsibilities
- Reduced or restricted resources
- Changing technologies
- Changes in commerce created by the global economy

Cooperative Efforts Between FDA and Industry: Where Might Efficiencies Be Realized?

David W. Blois, PhD
Vice President, Worldwide Regulatory Affairs*
Merck Research Laboratories

The last century has seen great progress in FDA becoming the premier drug regulatory agency in the world and Temple University becoming a leader in the training of undergraduate and graduate pharmacists. Temple University's Quality Assurance/Regulatory Affairs graduate program has filled a critical need for industry, providing formal education and training in these areas. History shows that within an atmosphere of cooperative and constructive dialogue, the FDA and the pharmaceutical and biotechnical industries can make real progress.

When I began my career in regulatory affairs in the mid-1970s, there was an explicit Agency policy discouraging contact between FDA and regulated industry. Little progress was made in drug development, safety, efficacy, or quality standards due to the absence of constructive dialogue between FDA and industry. Beginning in the 1980s, a number of positive regulatory initiatives emerged from increased interaction between FDA and industry. The first was passage in 1984 of the Orphan Drug Act, which was designed to address a small group of patients for whom adequate drug therapy was unavailable because of lack of patent protection or commercial viability. Through that Act, FDA has promoted research and commercialization of drugs for the treatment of rare diseases, providing the manufacturer with financial incentives and a period of exclusivity in the marketplace. Through this initiative, a significant number of new products are now available for treating patients with rare diseases, and the Act continues to provide incentive for research and development of important drugs.

Also in 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act expediting the availability of generic drugs and restoring the period of patent protection lost (sometimes seventeen to twenty years) for pharmaceutical innovators due to a lengthy FDA approval process. As the extended patent expires, FDA can approve an abbreviated new drug application more easily, allowing for generic competition to enter the marketplace. This balances the needs of industry with those of the generic manufacturers and FDA, an example of cooperation between industry and FDA bringing about positive legislative changes.

One of the best examples of constructive dialogue between FDA, industry, and Congress is the passage in 1992 of the Prescription Drug User Fee Act (PDUFA). This Act resulted from candid discussions among all parties. Prior to the passage of the Act, industry complained about "drug lag" in approval of new chemical entities discovered in the United States but which were approved more quickly overseas. On the other hand, FDA claimed to be working as quickly as possible with limited resources to review new drug applications

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* *Senior Vice President, Worldwide Regulatory Affairs, Merck & Co., Inc., before retiring.*

2000 Conference

For meaningful advances to occur, it is mandatory that industry and FDA engage in dialogue to take advantage of the forthcoming digital era. In our shared mission of providing safe, effective new drugs to patients, we must put aside traditional stereotypes of policeman regulator and commercial sponsor. We must openly discuss and understand our different needs and goals. Nothing to date could have been accomplished without this mutual understanding. We also must investigate innovative approaches to deal with issues important both to industry and FDA. A number of timely issues face us. The success of this dialogue depends on active listening and participation by all involved in each sector.

Clinical Research Quality and Integrity

David Lepay, MD, PhD
Director, Division of Scientific Investigations*
Office of Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

A topic at the forefront for FDA is the quality and integrity of clinical research. Relevant here is the concept and definition of Good Clinical Practice or GCP. GCP was designed from the start as a quality system of shared responsibilities among the key parties involved in clinical research: industry (in the role of sponsors and monitors); the research institutions (with their institutional review boards); clinical investigators, including those at academic sites as well as in private practice; and government regulators.

The history of GCP in the United States goes back to the 1960s. FDA developed certain standards for the conduct of clinical trials and implemented these standards through both regulation and guidance. We also developed compliance and enforcement approaches, integrating between our in-house application review process and a program of onsite inspections. We've been implementing GCP in this way for many years now, with inspections of U.S. clinical investigators dating back to 1962 and inspections of IRBs (Institutional Review Boards) or ethics committees from 1978 (even before FDA regulations were fully in place for IRBs). And the scope of our GCP implementation has expanded internationally as well, with FDA inspection of non-U.S. clinical investigators originating in 1980.

But the concept of partnering in GCP was really a hallmark of the 1990s. Up until this point, FDA largely acted on its own under its individual regulatory authority to develop and implement GCP standards. However, as a consequence of the Prescription Drug User Fee Act (PDUFA), the parties involved in regulated research came together to discuss not only ways to improve timeliness and predictability in regulatory review but also to think about partnering to promote quality and public protection in clinical research — that is, partnering to achieve GCP. As regulators, we at FDA began to appreciate that, to make this system of regulated research work well, there needed to be cooperation rather than confrontation between FDA and industry. This led in 1996 to a *Clinical Data Integrity Symposium* between PhRMA and FDA. And, in 1998, with the assistance and co-sponsorship of the Institute of Medicine, we expanded this dialogue to involve industry, academia, research professionals, and other interested parties through a landmark conference on clinical trial quality and integrity.

From these experiences, I believe we all share common objectives for partnering in the clinical research arena. Among these objectives are:

1) improved protection of human subjects and the assurance of data quality and integrity;

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* *Currently Senior Advisor for Clinical Science, Science/Health Coordination and International Programs, Office of the Commissioner, U.S. Food and Drug Administration.*

2) reduced workloads for all parties, especially where work is not adding value;
3) transparency of systems and information to help build confidence; and,
4) open and ongoing dialogue among all parties with a goal to reduce the time required for approval of safe and effective drug products.

Traditionally, "partnering" with FDA was interpreted solely as partnering between FDA and industry. Now we are seeing other parties involved in clinical trials coming to the forefront, and this is something to be encouraged. Continuing dialogue must include FDA, industry, institutions, clinical investigators and site staff, and the community. Getting the community engaged means interacting with the public at large as well as with the large number of subpopulations affected by clinical trials.

We also have to look globally to the International Conference on Harmonization (ICH) and other international venues for their potential to extend communication between FDA, industry, and our international regulatory counterparts. We must think in a matrix fashion, rather than in a series of linear arrangements.

Clinical trials are receiving a great deal of press attention right now. This seems especially focused at institutions and IRBs, so we should give this some attention today. It is especially important that our partnering efforts be rooted in facts and an understanding of each other's perspectives. FDA performs about 250 - 300 IRB inspections per year from an inventory of about 1,600. Most IRBs are doing a passable job, and in our inspections, we rarely have to take official action. In fact, only about 4 - 5 % of FDA bioresearch monitoring inspections result in any official action by FDA. We view IRBs as allies of FDA for ensuring quality. We are not interested in closing down IRBs but in working to improve their role and quality in clinical trials. In most cases, a violative IRB is notified by FDA and given fifteen days to outline steps to come into compliance. We then follow up to ensure that the IRB carried out its corrective plan. Between January 1999 and March 2000, only fifteen IRB Warning Letters were issued across our bioresearch monitoring program. In only three cases (in fiscal year 1999) did FDA have to impose sanctions requiring restrictions on enrollment of new subjects or prohibition of new studies conducted under the review of those IRBs. It is significant that among all IRBs inspected by FDA, the IRBs that were issued warning letters were, in fact, failing to perform in multiple areas of responsibility.

There were IRBs which failed to prepare and/or follow written procedures. In our most serious cases, they failed to have any written procedures at all. Thirteen of the fifteen IRBs cited in recent Warning Letters failed to adequately document their activities; in the worst cases, this meant no documentation at all of IRB activity. Ten of the fifteen failed to conduct adequate continuing review. Nine of the fifteen were cited for deficiencies in expedited review; seven of the fifteen failed to fulfill the requirements of informed consent (either oversight of informed consent or key elements missing in informed consent).

The point then is that when FDA has taken action, we have acted on serious, uncorrected multi-system problems that compromised the protection of human research subjects.

Beyond our compliance and enforcement role, we have also observed and learned a great deal about research practices and pressures while performing our inspections. We have

seen symptoms of problems which must be addressed. These include heightened workload pressure. IRBs often have difficulty making sense of the increasing number of reports they receive, especially the masses of adverse event reports. In the early days of IRBs (1970s and 1980s in particular), a single clinical investigator might be responsible for conducting a trial. However, a trial today might be conducted around the world by potentially thousands of clinical investigators, which means a dramatic increase in protocol amendments and isolated reports.

IRBs are also often faced with limited resources, limited amounts of useful feedback on multi-site trials, and limited feedback on problem investigators. Receiving information in a timely fashion and knowing what to do with it are serious issues.

The constitution of IRBs can also create challenges as members of the institution and community come in and out of the IRB system in a fluid way. Members with competing commitments often find their IRB commitments are not well recognized by their institution. There is also the concern of adequate background, knowledge, and training (both scientific and ethics training) for participation on an IRB.

IRBs are consistently pointing out that they don't receive summary information that otherwise flows between industry and FDA. This is definitely true for adverse event reporting, which represents an area where we can better dialogue and partner. Confusion exists with incomplete and undenominated data coming to the IRB. The IRB doesn't know how to put that adverse event information into perspective, thus making a reasonable assessment of impact difficult or impossible. Another important area for dialogue is on the subject of data safety monitoring boards (DSMBs). There is a need for more guidance in this area, especially when the use of DSMBs may be most appropriate.

It might be helpful to IRBs to receive annotated reports and amendments highlighted for information pertinent to human subject protection. The IRB could still review, of course, all other components of the report or amendment, but the goal should be to simplify and facilitate their review process. Electronic submissions and other applications of technology could also assist IRBs. We have heard representatives of boards state that receiving informed consent documents on disk would be a tremendous help.

Sharing industry's annual report information to FDA as well as information relating to problem sites or problem clinical investigators would also assist IRBs. In multi-site trials, cooperative agreements between institutions might reduce duplication of workload and save resources. But while we want to minimize duplication, we don't want to lose local oversight and input. So we need to approach cooperative review through dialogue and partnering. There may also be ways to better support IRBs and to partner in the training of IRB members and staff. These are just some of the many ways that we can work together to strengthen the IRB system.

Another area in which FDA and industry need to be more involved is that of informing human subjects. We need to dialogue among ourselves on the process of informed consent and to better articulate what is expected. Subject recruitment practices will become a major focus in upcoming years, because they are already the focus of the

well written and easily understood. It is useless to have a good SOP that no one understands or follows. For GCPs to be effective, staff training is paramount at both the sponsor level (which includes physician monitors) and the clinical investigation level.

Before engaging the services of Contract Research Organizations (CROs), we must assure the processes for the conduct, reporting, and monitoring of clinical trials will be managed from beginning to end. This requires sponsor oversight of CROs, including assurance that their responsibilities are clearly defined in writing. The selection and qualification of Site Management Organizations (SMOs) is also crucial. Sponsors of clinical trials must be involved in the selection and oversight of SMOs involved in supporting the clinical investigational site. The SMO's role in clinical trials should be clearly defined, and sponsors need to review the qualifications of SMO participants.

Any exceptions in subject-entry criteria must also be monitored. The frequency of such exceptions raises questions about the patient population used for that clinical trial and the criteria for admission. Exceptions to subjects for a clinical trial must be approved and thoroughly documented.

Data integrity is also of prime consideration. When it is compromised, everyone suffers. Our first concern should be the trial subjects and patients taking the product. Data presented to agencies and companies must reflect the actual source documents, which are not just patient charts, X-rays, or lab tests, but appointment books, sign-in logs, and study logs. The proof of patient participation in a clinical trial is often found in ancillary documents.

Another important challenge is the monitoring of safety. Methods and processes must be in place. Serious AEs (Adverse Events) recognized at clinical trial centers must be reported promptly to safety and regulatory authorities and to clinical investigators. Safety problems and trends should be reported. Equipment and instruments must be maintained and calibrated, and computer system validation must be fully addressed. Some investigators worry that problems found during their clinical trials will prevent acceptance of their products, but this is not necessarily true. Adequate safety monitoring may help position the product and train physicians who will distribute it.

Fraud and misconduct continue to plague us. Though the number of offenders is still relatively small, every time we discover misconduct in clinical research it is destructive and discouraging. We need systems to detect misconduct and effective procedures to examine, analyze, and report it. We also need procedures after it is reported. Nonconformance with GCPs, protocols, procedures, or SOPs must also be documented in clinical trial reports.

Some misconduct is not deliberate but a result of ignorance. We have discovered many inexperienced investigators and their staff, uneducated consumers, and uneducated subjects in clinical trials. In some cases, healthcare changes in the U.S. have precipitated misconduct. Other causes are increased need for more trials and study subjects, with a greater emphasis on faster cycle times. We have learned that clinical research is not the same as clinical practice. We have found also that scientific misconduct is not indigenous to the U.S. but has been observed elsewhere as well.

Increased inspection by regulatory agencies of investigators and sponsors poses a future challenge for GCPs. Industry has learned that FDA intends to conduct sponsor-monitor inspections for NDAs, which involve new chemical entities. Section 115 of FDAMA asserts that a single clinical trial may suffice, provided there is "confirmatory evidence supporting the single trial." There is little experience with this concept so far, but we must consider the possibilities. We may also find that Phase I and even Phase II studies may require more attention from QA organizations than we typically provide. These studies may be subjected to greater regulatory oversight.

A question arises whether pivotal clinical trials conducted outside the U.S. should be conducted under the U.S. IND. Discussion with the Agency must occur before filing these studies to the IND. Another question is whether selection of clinical investigators will be decided by geographic region and how that selection will occur. We must also ask which patient population will be studied and how those subjects will be selected. What global monitoring approach will be used by the sponsor? How will safety data be collected and reported? How will data be reported across investigational sites throughout the world? How will information get to institutional review boards and agencies? Sponsors often object that these concerns are addressed after the trial has been completed rather than before it begins.

There must be interaction between QA management and FDA before filing an NDA. Before Phase III begins, the sponsoring QA organization and Agency should meet to examine the scope of QA audit plans. They can also identify key procedures, thus ensuring integrity and completeness of clinical research. Partly because industry fails to share these procedures, FDA is not always aware of quality control procedures used in monitoring the trial, collecting and analyzing data, and preparing the final report. As a result, FDA is left to conduct its own inspections with little knowledge of sponsor oversight of the clinical program. When industry agrees to share QC and QA approaches with FDA, we can reduce some of the excess data analysis.

Faster approval of new products addressing medical needs is the ultimate goal for increased Agency-industry interaction. Open discussion will facilitate this review process and subsequent approval. FDA should be invited to visit during the preparation of an NDA to observe directly the QC checks provided for statistical analysis, reanalysis, and peer review. FDA should observe oversight of final report preparation to determine if data were properly analyzed. This open interaction should facilitate ongoing discussion and updates of Quality Assurance, leading to credible decisions by both industry and Agency.

Once again, we must learn to do less with less. Increased trust between Agency and industry provides ongoing interaction at all stages of a clinical trial, conserving limited resources by eliminating duplication of efforts. Negative press has tended to ignore progress made in medical science over the last twenty-five years. Let us celebrate some successes with GCPs over the years. Approximately 300 new therapeutic agents are available around the world today. In the next few decades, as the human genome is defined, this number could increase tenfold. ICH has provided GCP principles that ensure successful clinical studies around the globe. We also can celebrate that, despite distinctly separate roles, FDA and industry are forging a stronger partnership in the interest of serving the public.

exciting, challenging, and vibrant; inevitably, they must be considered when examining regulatory mandates. These regulatory decisions must be science-based and science-led, but they are not made in societal or legal vacuums.

We also find different expectations of various stakeholders, reminding us that FDA, academia, and industry are not the only players in this drama. Many around the world view social and cultural questions as very important when trying to achieve scientific harmonization. We must ask questions such as the following. What do patients expect from manufacturers or regulators? What do practitioners expect? Are these issues the same in Europe or in the U.S. or other parts of the world? What are their expectations of government — to be a protector, a promoter, or a provider of health — or all of these, and, if so, are there inherent conflicts of interest in those roles? How do these roles of government influence the need to harmonize our regulatory decisions? Does the community see the pharmaceutical industry as free-market providers of goods, as charitable organizations, or as something halfway in between? Looking at these questions within the cultural context, we see disharmony in expectations and significant challenges to be addressed within the context of technical and procedural harmonization of drug development, authorization, and post-authorization oversight.

Even with the same scientific database, we do not uncommonly find different regulatory decisions that reflect different perspectives on the question of whether the product's demonstrated benefits outweigh its known risks for that particular community. In interactions between FDA and our regulatory colleagues in other parts of the world, we do not presume to tell them what is "right" for their country and expect them not to presume to tell us what is "right" for ours. How would we begin to know the myriad of factors that are important in the decisions they have to make and the responsibilities they have to assume in doing their jobs for their citizens? Or they for us? However, there is still much that we have to share that is of significant benefit to us in our decision-making for our own citizens. We want to ensure that we have the same scientific data and are working from the same database to prevent surprises and make the best decisions for our communities.

When considering authorization standards, we see differences in comfort with certain levels of certainty in the knowledge we have about products at various points in their life-cycles. In the U.S. we have provisions that allow us, in certain circumstances, to use an unvalidated surrogate end point as a primary end point for clinical efficacy in deciding whether or not to authorize a product for the general market in our country. In other parts of the world, that level of comfort with using unvalidated surrogate end points may not yet have been reached. Therefore, it is not surprising that we have drugs here that are not yet on the market in other parts of the world, given exactly the same database. This is not a matter of one decision being "right" and the other "wrong" or a matter of different science. Different communities exercise their right to interpret the data in the context of their social environment and community context. It is often a matter of "risk tolerance" within a community, and that is something far beyond our remit or ability to "harmonize."

We must also deal with differences in how the price of a drug fits with the national public health services of some countries, compared with the price set for that drug in this country. Legally, we cannot bring the issue of pricing or economics into the U.S. FDA deci-

sion-making process, whereas, in other parts of the world, this is often a prime factor in regulatory decision-making — again, not "right" or "wrong," but very real factors that are beyond our remit and ability to "harmonize."

Despite the same scientific database, our decisions in the post-authorization phase of a drug's life cycle may also differ. U.S. expectations consider management of risks and potential risks a primary consideration in achieving the greatest good and mitigating possible harm. In different areas of the world, regulatory authorities have different regulatory, legal, and cultural "tools" with which to try to manage the risks of products after they are authorized for sale on the general market. One such tool is whether or not a product will be marketed as "prescription only" or "over the counter." In most countries, but not the U.S., there is a third category of product purchased without a prescription but only from a registered pharmacist in a registered pharmacy. Obviously the level of oversight needed to most effectively manage the risks of a product determine into which marketing category a specific product will fall. Other tools include the labeling (or instructions for use) that must accompany the product when it is marketed — which can include not only the physician-oriented instructions for use but also added measures to help communicate special messages or help assure understanding of special instructions by both physicians and patients. These additional measures include patient package inserts, so-called Medication Guides, and, in some cases, the need for informed consent prior to use of the product, even after authorization for marketing. We are also focused on how the product will be promoted and what kinds of educational activities are planned after approval. Use of black boxes on the labeling are also evaluated as part of the overall risk communication strategy. Detailed risk management plans can also be mandated if deemed necessary to assure safe use of the product. As we learn more about each product during the post-authorization period of its life-cycle, the benefit to risk profile of the product for the intended community may indeed change from positive to negative, in which cases, we can decide whether or not to remove the drug from the U.S. market.

There are different perspectives on risk management and risk communications, and the tools available to regulators in other areas of the world differ. This can result in differences in authorization and other risk management decisions on the same product, with the same database, at the same point in time. When looking at some of these differences in Europe, for example, there is now a requirement for mandatory reauthorizations of the marketing status of each product every five years. For the most part, there is no DTC advertising. The European Union uses mandatory package inserts, called patient leaflets, more extensively than the U.S. does. Distribution of over-the-counter products in the European Union clearly brings the pharmacist into a role as conveyor of medicinal products in a very different way than American pharmacists for a large group of products. Another difference is that many regulators have the authority to suspend a product from marketing while post-authorization safety concerns are being investigated; this is an authority which the U.S. FDA does not have for human drugs. In most countries of Western Europe, user fees are used to pay for post-authorization safety surveillance, while this is not allowed under present U.S. law. It is thus important to understand the many applicable cultural, legal, and societal differences when assessing the feasibility of international harmonization of certain aspects of the regulation of therapeutic drugs.

2000 Conference

One of our primary interactions with counterparts around the world occurs through the International Committee on Harmonization (ICH) engaging with counterparts in industry and regulatory agencies from the European Union, Japan, Canada, and Switzerland. Various guidelines likely to emerge from this common effort are Common Technical Documents (CTDs) and Periodic Safety Reports (PSRs), which are currently being finalized and implemented throughout the ICH regions. The goal of this initiative is that these harmonized core documents can be assembled at one time and submitted to regulatory agencies around the world, understanding one might have to add appendices to address specific local needs.

We also interact with the World Health Organization regarding ethical issues surrounding clinical trials and on topics related to post-authorization safety surveillance. We are a member of the WHO's consortium of safety monitoring centers from around the world that is headquartered at Uppsala, Sweden.

Finally, we interact directly bilaterally with several of our international partners, such as our Canadian colleagues at the Therapeutics Product Program, on many issues of common concern and interest, such as post-authorization safety surveillance and compliance issues. We have a confidentiality arrangement with Canada that allows sharing of certain kinds of confidential data. We are quite involved with our regulatory counterparts here in the Western Hemisphere, especially concerning our responsibilities under the NAFTA agreement. We have had a long-standing interaction with the United Kingdom and Switzerland on many issues, including post-authorization surveillance and GMP, GCP, and GLP inspections. We have held conferences with Canada for two years and with the European Union for one year. Advances in information technology have vastly facilitated these interactions. In coming years, we expect to broaden these areas of cooperation at levels of interaction much more deeply than in the past.

The exchange of colleagues also facilitates our knowledge of international systems. One exciting program with our colleagues at the Japanese regulatory authority is the Mansfield Fellowship program. This fellowship is open to all U.S. federal employees and facilitates a year of intensive Japanese language training at our State Department followed by placement in one's counterpart agency in the Japanese government. Two FDA participants have already benefited from this exchange, providing incredible insight into major changes taking place at our Japanese counterpart agency, which also sends reviewers and other staff to FDA to help them understand our procedures as well.

Our challenge is to use the information we have gained within the context of these different cultures, legal systems, and societies to enhance our own regulatory decision-making processes and our regulatory programs so that we better serve the people of the United States. We see international cooperation and exchange as integral in this new century if we are to meet our mandate to promote and protect the health of Americans.

The European Union seeking the MRA with the U.S. had a process in place called Border Re-Control. Products entering the European Union (any of the fifteen autonomous states) were to be tested at the border before being allowed into the Union. This rule was enforced to various degrees, but at least it was on the books until a MRA with the foreign entity seeking approval could be established.

When the E.U. evaluated the U.S., it only had to consider one autonomous body (the FDA). Conversely, the E.U. has fifteen autonomous inspectorates which FDA must evaluate individually. Each has different laws, regulations, programs, and enforcement techniques. Further complications emerge in dealing with countries (such as Germany) composed of autonomous states. FDA must assess each of these states for equivalence. Of FDA's off-shore inspections performed in 1999, about twenty-five were in Italy and fifteen to twenty in Germany and the United Kingdom.

During the MRA negotiations, it became clear to the U.S. negotiation team that the E.U. did not treat APIs in the same manner as FDA. There was no general practice in inspecting API manufacturers, nor was there a clear authority. The MRA negotiators pointed out the need for a clear authority in the Union among the inspectorates plus some GMP standards for APIs which did not exist. FDA had its own draft API guidance which enumerated expectations for cGMPs. The E.U. petitioned the International Conference on Harmonization to write an API guidance document. The European Commission issued a directive in late 1998 indicating that the E.U. must move towards this authority. The directive must be incorporated into the local legislation. This is something we will examine when carrying out equivalency assessments.

Carrying out over 300 inspections per year, FDA finds its financial resources (although they have increased a little) seriously overburdened. We also have a limited number of investigators and chemists to inspect sites. We must evaluate laws, regulations, and programs, so we have exchanged massive amounts of paper to determine if our operations are equivalent. Once this equivalency is reached on paper, we move on to "observed inspections." Someone in FDA travels to that country to evaluate how a European investigator conducts an inspection, using their laws, regulations, and programs. This phase of the operation is planned for the end of 2000. Two teams have been negotiating and working out the details of the MRA for more than two years. I'm also the FDA representative going to ICH to negotiate the API guidance document with Japan, Europe, and the U.S.

Products covered by the MRA are human and animal drugs, vaccines, therapeutic biologicals, and APIs. Not covered are veterinary biologicals, human blood and plasma, tissue and organs, and medical gases. Radiopharmaceuticals and investigational new drugs are also not covered under this agreement.

At the end of the three-year transition period, the FDA and the European Commission will assess what has been done and jointly determine equivalence. If we find equivalence, we will exchange inspection reports rather than a certificate stating that the firm is satisfactory. It would be difficult for us to assess all fifteen inspectorates for equivalency in only three years. We would need to decide which would be inspected first and if they were the most or least active. What would we do if we found one inspectorate in Europe to

be non-equivalent? We are working through details to ensure checks and balances are in place.

We must also consider surrogate inspections. Could an E.U. inspectorate that has been deemed equivalent inspect one that is not? What happens to products originating in a country whose inspectorate has not been deemed equivalent? If a company in that country meets cGMP standards and the commitments in the applications, that should not affect the company's ability to supply product to the U.S. The U.S. and E.U. would continuously monitor each other's performance for equivalence. If issues of noncompliance arise, safeguards would be in place, and we would converse with our E.U. colleagues. Suspension of equivalence is possible for cause. We have built in certain safeguards, so as these issues arise, we will discuss major implementation activities with our E.U. colleagues. Implementation practices being developed include an alert system, exchanging product quality information, and shared training. Details are being hammered out to share recall and product defect information.

Challenges arise in working out MRA details. One area relates to choosing the language for exchange. Another is freedom of information laws. Historically, the U.S. has been a rather open government in terms of freedom of information. However, in other countries there are confidentiality laws to prevent that kind of sharing. We also must have mutual consultation on cGMP regulatory developments. We must consult with other parties before changing a regulation. We must establish a common inspection report format that meets the needs of all parties concerned so that reporting will be simplified. Public meetings can be held to discuss the MRA, with a docket of these meetings made available.

In establishing an MRA, we must assess all systems, including laws, regulations, and programs. We must examine on-site verification and evaluation of those systems. We must check to see how systems are implemented and maintained. We could decide to assess the different programs by product or process. For example, FDA might find an inspectorate which is equivalent to our handling of oral solid dosage forms and non-injectibles. Mainly, FDA would stress that we expect cGMP compliance for all applications. When routine GMP-type inspections are equivalent, we can move on to pre-approvals.

Final determination is by a joint sectoral committee. Joseph Famulare in the Office of Compliance represents FDA, and the European Commission has appointed Steve Fairchild. After three years, the joint sectoral committee will sit down, each member with one vote, and reach unanimity in their assessment. If not, there is no equivalence. The equivalence could be one-way. Then equivalent authorities would be published in a Federal Register, indicating *exchange reports will normally be endorsed*. This means, quite simply, that once we are equivalent, we would normally accept the findings from that country's assessments.

Implications for industry of a fully-implemented MRA include product quality issues becoming more transparent and concerted actions against adulterated products. Other benefits of an MRA are enhanced market access, decrease of market decontrol, and additional joint ventures.

Implications of an MRA for regulatory authorities include more efficient use of resources, faster action against adulterated products, identification of common barriers, and consultation before making regulatory changes. Implications of this process for consumers include increased levels of protection and, over the long-term, decreased costs because of streamlined inspectional efforts. The public also could expect increased information on imported products.

We have spent over three years in negotiation for an effective MRA, with dialogue beginning in 1994 and the final document having been completed in May 1998. The assessment period, begun December 1998, continues until December 2001. At the end of this period, FDA must consider further issues, such as including inspectorates outside the E.U. At this point, however, with limited resources, we have more than enough to concern us with just the assessment of the E.U.'s fifteen inspectorates.

their obligation to report financial payments and must obtain their commitment to update this information. Disclosure of significant payments must be updated throughout the study and for one year after its completion. At the end of a study, a sponsor submits all financial information to FDA along with the marketing application.

According to definitions in this Rule, "clinical investigator" includes any listed or identified investigator or sub-investigator directly involved in the treatment or evaluation of research subjects, excluding hospital or office staff. The term includes the spouse and children of the clinical investigator. The definition was broadened in the guidance to industry published March 2001 to include the person who signs Form 1572 or who is listed in Item 6 of Form 1572. Some applicants have erroneously included nurses and those who give ancillary care whose financial affairs do not need to be reported.

A "covered clinical study" is any study in which a single investigator makes a significant contribution to the demonstration of safety, or where the applicant or FDA relies on the study to establish a product's effectiveness, or a study that shows equivalence to an effective product. The Rule would not include Phase I tolerance or pharmacokinetic studies. Most clinical pharmacology studies would not be included, unless they determine a product's efficacy. Other exclusions to the Rule are treatment protocols, parallel track protocols, or large safety studies conducted at multiple sites. To comply with requirements of the Rule, applicants should consult with the FDA for details on which clinical studies are "covered."

The Rule defines the party responsible for submitting financial information as the person or group submitting the marketing application to FDA for approval. "Sponsor of a covered clinical study" is defined in Part 54 as the party supporting a particular study at the time it was carried out. Confusion can occur because sponsor is also defined in Part 312.3 as the person who takes responsibility for and initiates the study.

During these initial years of implementation, FDA is willing to work with industry, even when financial information didn't accompany the filing. FDA allows the applicant time to submit information requested for financial disclosure. To ensure reliability of data, the Agency can initiate audits, request further analysis or additional independent studies to confirm results, and refuse to treat the covered clinical study as pivotal.

Procedures to assist in implementation of the Rule include training sessions for reviewers and project managers throughout the Center. The Office of Medical Policy and Office of Drug Evaluation I handle consultation requests from reviewers and project managers and queries from industry.

Comments on the draft guidance document published October 1999 center on four or five difficult issues. We expect to iron them out and have a final guidance available by June 2000. By then a draft of the *Manual of Policies and Procedures*, our SOP document, will also be available.

One area of concern in this draft guidance is the multi-site clinical trials for efficacy, where no single investigator has a significant number of subjects. This particularly concerns studies completed before February 1999, when companies were not aware of the Rule.

Quotes From Our Contributors

"When I began my career in regulatory affairs in the mid-1970s, there was an explicit Agency policy discouraging contact between FDA and regulated industry. Little progress was made in drug development, safety, efficacy, or quality standards due to the absence of constructive dialogue between FDA and industry."

David Blois, PhD
FDA and Industry in Dialogue, 2000

"Partnering requires dialogue. And dialogue can improve our detection of problems and attention to complaints."

"Up-front dialogue can save resources for both industry and FDA. Dialogue on quality initiated at the start of and continued throughout a clinical trial establishes a level of communication and confidence that is critical to moving forward with timely review and ultimate approval of safe and effective drugs."

David Lepay, MD, PhD
FDA and Industry in Dialogue, 2000

"In an ideal healthcare system, drugs would be taken under conditions similar to a clinical trial. But that is not how drugs are used. We like to think that everyone would avoid prescribing interacting drugs, if the label warnings were clear. But we know they will not, so we must not continue thinking that people will follow the labels and everything will be all right."

Janet Woodcock, MD
FDA and Industry in Dialogue, 2001

Evaluation and Research) and CVM (Center for Veterinary Medicine), and from our International Affairs staff and the Office of the Commissioner.

At the end of this transition period, we hope to achieve a final determination of equivalence of each authority by democratic process. Each side has one vote. Importantly that vote is by unanimous consent, so if the U.S. or any member state authority is going to be determined to be equivalent, both sides (the U.S. and E.U.) have to agree.

When determining equivalence of a particular authority in a member state, it's important to distinguish between product and process types. For instance, an authority may be found equivalent for solid oral dosage forms but not for a parenteral dosage form. Lack of equivalence may be due to deficiency in that program or lack of facilities for producing those products. This is why the distinction was put into the Agreement. And lack of equivalence must be documented by the European member state. Similarly, in the European assessment of the U.S., we would be expected to document any lack of equivalence.

The MRA calls for a two-way, rapid alert system. Initiated in February 1999 and incorporated into use in April 2000, joint procedures were created for urgent recalls (Class I and Class II) or products posing life-threatening risks or health hazards. A common SOP now exists to share that recall information between the U.S. and E.U. member states. The Agreement encourages other aspects to be covered in the rapid alert SOP, but it is a long, slow process to come to consensus between all E.U. member states and the U.S.

The Agreement also covers the equivalency process of GMP systems. Article 19 of the Agreement covers routine, product quality issues. We would share results of inspections and databases on quality issues that are not life threatening to public health. While we haven't broached putting together a procedure yet to share that type of information, the U.S. side is encouraging this be done as quickly as we can.

The actual equivalency process of GMP systems started in May 1999. We've committed to be as open and transparent as we could possibly be in this process on the U.S. side. To honor this commitment, the U.S. held a public meeting at the end of the first transition year. This year we held a telephone conference with a number of consumer organizations. Two Joint Sectoral Committee meetings were held (one in the U.S. and one in England) where we discussed the process and plans for putting forward the Agreement. We also prepared an EIR (Establishment Inspection Report) format, which was proposed to the E.U. One of the key provisions of the Agreement is that we agree upon and establish an inspection report format for consistent exchange of information.

We've reviewed and commented on the European community-level GMPs, which had been set forth by the European Commission for adoption into the legislation of every member now. Currently we're looking at the individual member states, such as the laws and regulations of the U.K., to observe how they incorporate the E.C. documentation. Next, we intend to cover Ireland. We're in the midst of an audit ourselves by the E.U. with a number of individual member state inspectors, and, in one case, an administrator in the inspection unit, assessing the U.S. GMP system.

ances to individual industry groups, and they are currently under review. We don't know of any major issues that would prevent us from going forward for what has been produced to date.

What opportunities will be available to us as we move forward with the CTD? First, we would like to accomplish global submissions in the future, and by "global," I mean extending beyond ICH's current three regions. Ideally we could use one application, no matter where we made a submission. Obviously, we have a little bit of a problem here if we talk about intellectual property protection, since some regions do not have it. If you are including all this information in a dossier, it could be problematic to the sponsor.

What about simultaneously reviewing applications? In the past, two regulatory authorities could do simultaneous reviews of one application, but the CTD would make it even easier for this to be accomplished. You can decide whether this is necessarily good or bad. But this is one of the advantages of having a CTD — and probably the most provocative. Will mutual recognition be in the future? One of the stalwarts of ICH is that we would not affect the review process. But if a mutual recognition were accomplished, obviously the CTD would be the commonality of moving forward on that.

Now let's deal a little bit with ethnic factors which we talk about in the acceptability of international foreign data. E-5 was put together to eliminate duplicate clinical trials in the various regions, which were initially thought necessary to expose individual ethnic groups to specific drugs. There are issues associated with actually carrying out a utilization of E-5 in specific areas. For instance, can we extrapolate the clinical results between the three groups that we are saying could be utilized in these trials or utilized in any trials? Since the three ethnic groups we usually talk about are Caucasians, Blacks, and Asians, how similar are the target populations? That's a question that has to be answered. And, when needed, what constitutes a bridging study which is the stalwart of the E-5 document for ethnic factors?

What can we propose to get around these issues? First we need to demonstrate that there is some ethnically sensitive effect that we are going to see with a product or a drug; without that, no one would say we need to do any additional studies, and the products should be accepted in all the regions. Second, we have to demonstrate that this sensitivity is clinically meaningful. If it is not clinically meaningful, maybe we can eliminate the need for any additional work. Next, we have to examine available clinical data for support of potential ethnic concerns. Most of us, in all of our clinical trials, were amassing data on somewhere between 3,000 – 5,000 patients or more. And we can use that clinical database to look at subpopulations to see if we have anything there that we need to worry about.

Finally, if there is a racial or ethnic sensitivity in the product, we should conduct a bridging study and show that the significant response can be dealt with. The E-5 document deals with the different approaches that exist for bridging studies. We can propose doing a comparative PK study, showing the similar pharmacokinetic profiles that exist in the various groups. If that's not the type of study we need, we can go to limited PD studies, where pharmacodynamic effects are being measured, the end points, dose ranging studies, etc. But we have to make sure we are picking a defined endpoint which we can use in those response or dose ranging trials.

One of the things needed is a standard efficacy and safety study which would be the

Quotes From Our Contributors

"The press and the public don't understand it takes many years to develop products *de novo*. If we need a new vaccine or new treatment, they feel that if we throw a lot of money at it, we'll get it within a year. All of us know that's not true."

Janet Woodcock, MD
FDA and Industry in Dialogue, 2004

"Although since 1991 there has been a 272% increase in FDA-regulated entries crossing our borders, resources to handle imports have been minimal. In late 2000 and early 2001, 170 operational Full-Time Equivalents (FTEs, representing the number of hours a full-time employee works over a fiscal year) were handling about seven million lines of entry."

Benjamin England, JD
FDA and Industry in Dialogue, 2004

"What has been the value of ICH in international markets? It represents the first time that industry has joined together with regulators to develop guidelines. Think of the impact of that statement. Usually guidelines are developed by regulators and handed to industry for comment. At ICH, we are developing these guidelines as partners, sitting down at the table together. We've enhanced communication among the regions having regulators and industry groups from all three regions talking to each other at the same time."

Alexander Giaquinto, PhD
FDA and Industry in Dialogue, 2001

need for this on September 11th. We had to leave our buildings but continue to operate. We all need to improve our preparedness for emergencies.

Achieving these goals requires collaboration across sectors. For FDA it means working with industry and academia and with the healthcare sector and other agencies.

What are the issues around the safety and security of drug products? This is of joint concern to industry and the FDA. Industry doesn't want any threats to the security or safety of its products. Neither does the FDA. No one likes to speak of these issues in public for obvious reasons. For instance, there is a problem with counterfeit bulk drug products. This is more prevalent in countries where knock-off copies are made from a wide variety of substances. Some of them purport to be the Active Pharmaceutical Ingredient (API) and have no relationship to the API. Others are pretty good copies of the API but were not made under Good Manufacturing Practices (GMP) conditions in an approved plant, purporting to be something they aren't. Placing this problem in the context of counter-terrorism is even more concerning, because these counterfeiters are criminals who could develop terrorist links.

Though we have been trying to insure the authenticity of bulk products imported into the United States for some time, now there is a higher concern. Sometimes counterfeit finished products contain excellent knock-off labels. Again this is more common in other countries, but counterfeit drugs could get into the United States through a variety of routes, raising concerns about the safety and the security of the authentic products.

Many Americans now order large quantities of drugs over the Internet. We have made a good effort to control sources of Internet purchases within our borders and to make sure they are from appropriate state-regulated pharmacies and are shipping drugs in response to authentic prescriptions. Unfortunately, our citizens can also order through the mail from other countries, obtaining products without a prescription. What are they getting? People seem to have a lot of trust when they put something ordered from an unknown source from another country into their bodies. This is driven partly by cost and partly by not wanting to go to a doctor and a desire to self-medicate. Now we need to consider this whole activity within the context of terrorist interventions.

We have dealt with drug tampering in the past. It can occur anywhere and has taken place in the United States on a very limited scale in the OTC realm. Tamper-resistant packaging and other interventions were adopted a decade ago to prevent this type of activity. But now we need to think this through again.

Finally we need to consider drug shortages, particularly with medically necessary pharmaceuticals. Americans assume their medicines will be available, but we face shortages all the time. The Center for Drugs is always scrambling to deal with this vulnerability.

How are we approaching this whole set of issues? At all points of entry, our valiant field people have hired many new inspectors. They are primarily for food, but having so many FDA border inspectors should help in other areas — pharmaceuticals, devices, and drugs — as well. The field organization is upgrading its OASIS computer systems for

imports to determine what is questionable. In the long run, we believe that information technology will help us decide which entries are legitimate.

FDA has been considering approaches to the Internet/mail order issue for a long time. Counter-terrorism should accelerate this. Technically, all these entries are illegal, since only manufacturers may import approved drugs into the United States. The Center for Drugs would like to switch from the current, unsatisfactory, paper-based registration listing system to an on-line, Internet-based, real-time registration of listings for domestic and foreign manufacturers. With a complete inventory maintained and updated on-line, we would know all foreign and domestic drug manufacturers and could check their activities more rigorously. Industry would accept this change, since it shares our concerns about product safety and security. The current regulation is overly detailed, spelling out a paper process; it needs to be simplified, starting with a complete inventory.

Concerning imports, the Center for Drugs will designate a senior manager to work on emergency preparedness and response. A counter-terrorism group to work on product availability issues has been funded by Congress within the Center and is headed by Dianne Murphy. When we have hired a senior manager to pull together all the emergency preparedness and response issues, we will reach out to industry on safety and security issues.

Immediate attention is focused on the availability of medical countermeasures. Is FDA a roadblock in getting more products developed? Obviously industry and the FDA have a joint objective: we must get products developed and labeled for counter-terrorism indications.

The press and the public don't understand it takes many years to develop products *de novo*. If we need a new vaccine or new treatment, they feel that if we throw a lot of money at it, we'll get it within a year. All of us know that's not true. Importantly we need to get existing products labeled for these indications, as we did with *Ciprofloxicin* several years ago. Once we have these products, maintaining their availability is equally important. There may not be a big market for them, but they must be held in readiness. Product availability will continue to be a big issue. Finally, deployment — use of these products in a potential terrorist situation — is not as simple as many think, whether it's antibiotics used in response to bioterrorism or chelating agents and radioprotectants for radiation. The Center for Drugs has issued a long guidance on the correct use of *potassium iodide*. Since it has to be administered quickly to be effective, states are stockpiling it. Then there is a whole category for which we have few antidotes or antagonists to toxins of various kinds, such as nerve gases. The military has driven much of the development of these antidotes for battlefield use.

Authorizing new indications for already approved products raises very thorny issues. If there is a true terrorist attack, people will want treatments or preventatives. But *anthrax* demonstrated that there is often ambiguity with those who are potentially exposed versus those who weren't exposed but are worried. If a drug has not been indicated for that use, it creates a whole host of issues and problems. So I think it is extremely important to add the indications to labels for currently approved products. That is what we did for *Ciprofloxicin* and other antibiotics that we labeled specifically for inhalational *anthrax*. Had that not been

done, the level of anxiety would have been much higher. The labeled, approved indication made the public confident that a treatment was available. But we might encounter many pathogens or toxins in a terrorist attack, so it is really important that we work together on new indications.

If drug development is difficult, a slower, harder process that poses even more challenges is the development of novel products. Proving effectiveness poses ethical questions, since you cannot test these compounds on humans. Years ago FDA proposed a regulation that would permit us to approve drugs based on animal challenge or model data to determine efficacy in situations where it is unethical or infeasible to expose humans. This generated much debate and many comments, but now it is obvious why it needs to be done. The Administration is reviewing it, and we hope to have that rule finalized soon. CDER could then issue a draft guidance for comment on the animal studies required for efficacy for a variety of diseases and select agents. After receiving comments and creating guidance, we could do other studies for specific needs. The keystone in getting those indications on the label is having a final regulation. We approved *Ciprofloxicin* based on pharmacokinetic data and a vast amount of other data. But animal challenge studies also helped convince us and our Advisory Committee that that drug would be effective against inhalational *anthrax*. While we hope to issue that regulation very soon, the relevancy of the animal models to clinical situations may not be as clear outside the anti-infective realm. That might be true in some animal infections as well. So we have work to do on development of animal models.

With money from the Supplemental Appropriation on Terrorism, the Center for Drugs is working on issuing contracts to look at off-patent drugs. We will review the data and add new indications to the label.

What about safety? When the drugs for inhalational *anthrax* were approved, it was comforting to everybody to have a robust safety database on dose and duration of use. Many people had been exposed previously, so we were able to predict toxicities. But while a robust safety database is desirable, it may be difficult to get when we have investigational products intended for only one use. So we will have to deal with this issue.

We need to avoid drug shortages. Many stockpiles are being set up, but the issue is ensuring the drugs remain safe and potent when appropriately stored. We work with the Department of Defense, for example, to extend expiration dates on a number of products on a lot-by-lot basis. We already undergo shortages of drugs and are constantly scrambling to ensure an adequate supply even under a non-emergency situation.

Deployment issues will arise when there is a terrorist attack or other emergency. Many different products may be deployed, some of which are approved, while others are not approved for that current indication, that includes Subpart H products which are approved under some conditions but still require the collection of data. Or there might be a need to use an approved product for an unapproved indication. Even an investigational product might be deployed. We are going to have to face this.

Each of these poses a variety of issues. The highest priority for emergency responders is dealing with the crisis. But it is extremely important to collect data. If we do not

learn from emergencies, we are doomed to repeat mistakes. The data we need includes how many people have been exposed? Who took what drugs: infants, children, pregnant women, older people? We need to know as much as possible, but our investigation must not impede our response to an emergency.

We need a collaborative plan for collecting data on adverse reactions. In a military situation, FDA must work together with the armed forces. In a civilian situation, FDA, CDC, and other appropriate agencies must cooperate. How will we collect data? What were the outcomes of using a particular agent in this emergency? Was there any utility in exposing people to an agent whose approval was based on animal data? Were the predictions based on animal data correct? If we had another *anthrax* attack, people would have more confidence not only in using the prescribed drugs but also in the sixty-day recommendation for treatment. Initially people feared they would relapse after sixty days, but it didn't happen. Nor did any treated individual develop *inhalational anthrax*. We do not know how many people were exposed to an effective dose of spores, but we do know that no cases were observed and treated. These are grave deployment issues for our society.

Our facilities must be able to operate in a crisis. We must keep our facilities, production, and databases secure from external hacking or any other disruption. Our personnel must be safe and our facilities must be secure for everyone to continue doing their jobs. When CDER's manager for emergency preparedness is appointed, we will begin our internal planning, but we can't have an effective response unless all the stakeholders are involved. Over the next year we will examine how FDA, industry, and academia will respond in a large-scale crisis. By planning in advance, we will work much more effectively together in an emergency.

Another issue is continuity of operations in an emergency situation throughout the FDA, the federal government, and industry. If a large-scale, regional event shuts down some of our facilities, how do we make sure that we will continue to fulfill our vital role for the public?

In summary, the pharmaceutical sector has much work to do on counter-terrorism. We have to develop more products, we have to work on existing products, and we have to develop response scenarios. Collaboration across all sectors is crucial in planning for events which we hope will never recur.

epidemic in the United Kingdom, took several actions to ensure the safety of those products. A series of letters were issued in 1992, 1993, and 1994 and published in the August 1994 *Federal Register*. These letters were sent to manufacturers of dietary supplements, human drugs, biologics, medical devices, cosmetics, foods, and veterinary medicines. They recommended against the use of materials derived from cattle born, raised, or slaughtered in BSE countries, but milk and milk derivatives are exempt. In mid-1999, CDER, after learning of the first vCJD case in the U.K., issued nearly 3,500 letters informing manufacturers of old drugs (pre-1938), homeopathic and active drug ingredients, and sponsors of New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDA) of the standing FDA policy recommending against the use of materials derived from cattle born, raised, or slaughtered in BSE countries. These letters also requested manufacturers to have adequate documentation, including accurate records of animal material sources to be ready for FDA inspection.

To better coordinate BSE policies within the Agency, an FDA BSE working group and a TSE Advisory Committee were formed to make recommendations on regulatory actions and to ensure any action taken was based on good science. In CDER an on-line tracking system was established for NDA/ANDA application drugs containing active ingredients derived from animal sources. In addition, FDA developed contingency plans to manage domestic BSE cases in the U.S. FDA also held workshops to discuss risk assessment and diagnostic methodologies. It is recognized that more research is needed, especially on diagnostic tools, decontamination, inactivation, and sterilization procedures. Additional funds will be used for the Agency's TSE research. At the international level, a bilateral group (U.S. and Great Britain) and two trilateral groups (U.S., Canada and Europe; U.S., Canada and Mexico) were established to discuss common issues and concerns and determine whether new laws and regulations are needed.

More than 85% of pharmaceuticals contain bovine-derived materials, mainly gelatin and tallow-derived products. This is a huge safety concern. The FDA TSE Advisory Committee has evaluated the safety of gelatin, tallow, and tallow derivatives. In April 1997, FDA held advisory committee meetings on animal sources for gelatin. The Gelatin Manufacturers European (GME) reported a study on the capability of the gelatin manufacturing process to remove/inactivate the TSE agent. The results indicated if animal material is at risk of BSE contamination, the gelatin could also be at risk. Based on these results, the TSE Advisory Committee recommended that no BSE countries should be used as sources of bovine bones for gelatin. The GME was perturbed by this recommendation, claiming that the validation study was poorly done and a second study was ongoing. The Advisory Committee will decide whether gelatin should be exempt from current FDA recommendation of sourcing the bovine materials from BSE-free countries once the final report of the repeated study is submitted.

The Committee's recommendations were not accepted entirely as evidenced by the FDA gelatin guidance issued in September 1997. Because injectable, implantable, and ophthalmic products are of highest risk, the Agency recommends that gelatin used in these products should not be derived from bones originating from BSE countries. The Agency also determined that the BSE risk for gelatin used in products for oral and topical use is relatively low so long as the bovine material itself is BSE-free (i.e., from a BSE-free herd and the head, spine, and spinal cord are removed directly after slaughter).

Importing Pharmaceuticals: Product Security for Drugs and Biologics

Benjamin L. England, JD
Regulatory Counsel to the Associate Commissioner for Regulatory Affairs*
Office of Regulatory Affairs
U.S. Food and Drug Administration

Product security issues have historically focused on counterfeiting in bulk pharmaceuticals and finished products. Cooperation between the Agency and the industry is crucial in these areas, with industry developing increased security for imported products. The Office of Regulatory Affairs (ORA) has brought scientific and legal aspects together to create sound enforcement decisions. Agency work groups have evaluated commercial and informational technologies to create stronger product security.

In June 2002, FDA was invited to the hearing on counterfeit bulk drugs of the Oversight and Investigations Committee (OIC). Two areas of focus concerned FDA's working more closely with industry to solve issues related to counterfeit drugs and FDA's considering the use of chemical tag-ins to help authenticate drug products. FDA was willing to consider these issues, and the Agency reestablished the Counterfeit Drug Working Group. FDA considered chemical tag-ins under the umbrella of the many countermeasure technologies used to avert counterfeiting of drugs.

The events on September 11, 2001, did not create more risks, but perspectives changed. An example is the California case of *Lynn vs. Serrano*, where Serrano was sued for injuries claimed by certain parties using a counterfeit of its product. While the product used was not Serrano's and was not their bottle or label, they sued nevertheless. Prior to September 11th, the jury would have to decide if it was foreseeable to Serrano that someone might counterfeit their product, and thus they must take steps to avert that harm. Prior to a significant terrorist event occurring on U.S. soil, the jury may not even get the question. If it did, the jury probably would have been more inclined to agree that third party criminal acts (like counterfeiting) were not sufficiently foreseeable to a drug manufacturer to hold the manufacturer liable. After September 11th, the jury's perspective on the question may change. Jurors may even go so far as to question why a company would not *assume* their product could be counterfeited and thus cause potential harm. If a terrorist decides to use a consumable product as a vehicle for a chemical or biological agent, the entire industry will take a hit in consumer confidence whether or not legal liability can be proven. Companies currently attempting to avert this kind of disaster will fare better than others in the public affairs arena.

Prior to September 11th, FDA had taken several initiatives regarding counterfeit products. FDA's Ohio-based Forensics Chemistry Center (FCC) has a database that contains labels, certificates of analyses, packing schemes, and batch numbering systems for pharmaceuticals. Most database products are active pharmaceutical ingredients (APIs) for further manufacturing in the U.S. FCC is now uploading some finished dosage products as well into the database. With this database available, FDA field investigators and compliance officers can compare sus-

* *Currently Special Counsel for the Law Firm of Jones, Walker, Waechter, Poitevent, Carrère & Denègre, LLP.*

pect shipments of products with known authentic products.

Another FCC initiative is conducting specialized inspections focusing on the APIs, not just the dosage manufacturer who receives the API to make a drug product. These inspections also cover importers in the business, identifying kinds of products, sources for the products, origins of the products, and kinds of authenticity documentation provided.

The Center for Drug Evaluation and Research (CDER) has a system which tracks applications through the process, called an Establishment Evaluation System (EES). This system registers approved sources of ingredients that have filed a drug master file with the Agency. The master file indicates the finished product manufacturer has referenced a drug and that FDA has conducted inspections to verify that the ingredient manufacturer operates within GMPs (Good Manufacturing Practices). Not privy to the information from EES prior to this point, import investigators and compliance officers at the border level now can track an imported API shipment intended as an over-the-counter drug or an application drug (one for which a new drug application has been filed and approved) against the declared intended use of the shipment. Import inspectors can determine if the source of this import is the same source referenced by the finished dosage form application holder. If not, then the API is actually misbranded. The EES helps identify shipments of APIs coming in which are intended for inappropriate uses. To determine quality of imported APIs, ORA and CDER are performing a two-pronged examination. This joint venture evaluates items declared on the certificate of analysis to see if they pan out through analytical testing, thus identifying authenticity risks.

Stricter controls and intensive evaluations have developed because of the alarming increase in counterfeits in international markets. The World Health Organization (WHO) believes in some countries 50 - 70% of drugs on the market are counterfeit. In countries with increased industrialization and levels of regulatory control, the percentage decreases. WHO estimates that only about 5 - 7% of pharmaceuticals in the United States are counterfeit. Yet, we find no data that supports even this percentage.

Although since 1991 there has been a 272% increase in FDA-regulated entries crossing our borders, resources to handle imports have been minimal. In late 2000 and early 2001, 170 operational Full-Time Equivalents (FTEs, representing the number of hours a full-time employee works over a fiscal year) were handling about seven million lines of entry. For example, in the Miami area, Customs had about 650 operational FTEs, and USDA had 300 - 315. We had only seven during the same time frame. Even after funding increases, that number will only rise to twenty-four people. With Miami processing about 70% of all seafood entering this country, one can imagine the monumental task expected of those twenty-four people, in just one commodity area. In 2002, we expect to evaluate about eight million lines of import entries, which represents one-third of all imported invoice lines of products entering the U.S.

To handle this volume we have focused on mainly administrative FDA actions, such as import shipment detentions, refusals, review of technical product or manufacturer filings or product sample analyses. For instance, we examined drug listings and drug registrations, which unfortunately disregarded quality or manner in which a drug was manufactured. Because of resource constraints, this is where FDA had to focus unless we had inspectional

evidence indicating GMP problems. All information used to evaluate the admissibility of products, however, has been from the import transaction itself. The Customs House broker declares his product with the correct tariff number, manufacturer ID, value, and quantity, all based on invoice data. Because Customs is a revenue agency, their inspectors focus on issues such as duty, tariff, and anti-dumping. They are not evaluating product quality or safety. Therefore, the invoice data proved valuable to Customs but of limited use to FDA.

Nevertheless, these procedures functioned for many years until the 1980s, when the U.S. began the shift from being a producing to a consuming nation. Formerly, the majority of FDA-regulated imports were ingredients for further processing into finished products. Even when we performed a sampling and analysis of imported ingredients, we relied heavily on the Agency's domestic inspection process to verify the quality and safety of the finished product and the means by which the imported ingredients were received, quarantined, tracked through the batch numbering system, and moved through the GMP process. This has changed dramatically. The vast majority of what now enters the U.S. is the finished product. Therefore, the answers to questions relating to quality and manufacturing have moved offshore and largely out of FDA's reach. FDA's emphasis on manufacturing and product quality and safety has not changed. In order to evaluate quality, we must consider in what environment a product is made, how it is packed, and what process is used. The problem is that the importer does not necessarily have this information on the invoice. The life-cycle of drugs has changed over the years with the rapid growth of international and global drug manufacturing.

Investigating the current import life-cycle (for drugs or any other FDA-regulated product), we see the first step taken when the customs broker declares the product to the U.S. Customs Service. Customs then refers that information to FDA. From that time, we begin to determine whether the goods should be refused or released. If we refuse a product, the importer must export or destroy it. The information we receive for our review comes from the importer or broker (hired by an importer). These two parties in the supply chain may have very little if any direct knowledge or information on that product's quality.

Those in Customs, the Department of Transportation, the Coast Guard, and other agencies regulating international trade see the wisdom of an expanded life-cycle for imports. We must also begin the life-cycle of imported drugs with inspection of raw materials entering the foreign facility, traveling through the border process, and ending with the consumer. Quality should be evaluated throughout, beginning with the first raw materials obtained by the manufacturer, to the shipper, to the carrier, to the broker hired by the importer, moving to the Customs evaluation, and to the FDA workers evaluating the product to be released to the market or refused. The released imported product continues to the distributor and ultimately is retailed to the consumer. This encompasses a complete cycle for an imported product to be consumed in the United States. The expanded life-cycle of an import shipment provides information on quality and safety to the FDA all along the route. That information should be gleaned to help us understand the manufacturing of that product, because the expanded life-cycle includes the foreign manufacturer. By conducting a foreign inspection, FDA can understand the quality of the product from the beginning. But there are other ways to determine the manufacturing quality at the foreign site — even without a foreign inspection.

For instance, another way to determine quality of a product is to notice if it has ever

been recalled from the market. FDA can then determine if an inspection is needed to understand the recall and to determine the quality of API material rejects. An even more common way to glean information about API manufacturing quality lies in the quality control process occurring at the end-user finished dosage manufacturer. Imagine, for instance, a domestic end-user receiving an API, analyzing it, and, based on the Certificate of Analysis, finds the API is to be sub-potent. The end-user rejects the product and returns it to the foreign manufacturer. During an inspection at the end-user, FDA may learn of this rejection of API material, which may alert the Agency to the quality of process used by this API manufacturer. Similarly, product recalls, consumer complaints, and reports of adverse events can all lead FDA to information about an imported article, whether it be a drug, a biologic, a device, or a food. Throughout the life-cycle of the drug, there is available information not yet being used to assess the quality of foreign manufacturing.

This brings up the question of requiring in the new drug application extra information for obtaining an approval of an end product. In Food and Drug Law (under Section 801 of the Act), the FDA does not have to prove a preponderance of evidence in order to refuse admission to imported goods. All that is needed is the appearance of a violation. FDA can refuse entry if it *appears*, by analysis, or the examination of samples, or otherwise, that the product is in violation of the law. FDA already exercises this authority through its import alert system. Currently, if FDA evaluates a domestic API manufacturer and rejects the quality of their products, there may very well be the appearance of a GMP problem at the foreign manufacturer. The way to build quality into an FDA-regulated product is by having a manufacturing process that conforms to good manufacturing practices. When an article is found to be out of spec, or substandard, or adulterated, such as finding holes in latex patient examination gloves, by way of example, FDA can then require the manufacturer conduct an internal investigation into the cause of that problem. This is true whether the manufacturer is in the U.S. or a foreign country. If the Agency has the authority to refuse admission to products that appear to violate the Act (*e.g.,* products manufactured in facilities that fail to comply with FDA GMPs), the Agency could require the foreign manufacturer to demonstrate what internal investigative and corrective action steps it took to remedy the apparent problem. This can occur without an FDA investigator traveling to the foreign site to conduct an inspection. The statute already gives the FDA the leverage to require foreign manufacturers to produce data and evidence that demonstrate the facility is in compliance with its regulations. This is using the expanded import life-cycle to inform better decisions at the border when FDA-regulated articles are crossing the border.

Product security is not unlike product safety — and yet it does require one to think about risk from a different perspective. Evaluating product security includes verifying authenticity and identifying inventory control, anti-tampering technologies, upstream and downstream evaluation, distribution control, and in-house security. Product security must be considered all along the supply chain line, whether a product is received or distributed or both. Each organization must consider risks to the product while in the distribution channel, before it enters that channel and from the sources providing the product. Industry must use registered, licensed suppliers and samples of authentic labeling to compare with product coming through the supply chain. Anti-counterfeiting measures must be considered. If a product is received from Hong Kong, for example, how does industry evaluate what is being offered? Companies must require anti-tampering information for verification upon receipt.

sons back into the decisions that we are making. Much is vested in the memories of individuals, and risk management needs to be more analytical and more comprehensive. We could be doing more interacting with certain stakeholders, such as payer organizations, some of the professional organizations, and some pharmacy and nursing groups. These are the people who are really making the decisions about how drugs are used in this country. More interaction with these groups could make a big difference in some of our activities.

The assessment of risks and benefits really has to apply to all the different parts of CDER's operations. Of course, it already goes into our new drug approval process and the post-marketing work. We'd like to see it applied to all of our activities.

What are some of the things currently going on in risk management at CDER? The tool kit discussions that we've been having with PhRMA for more than a year involve talking about various items like our Subpart H approvals, our Med Guides, other kinds of restricted distribution schemes, and questioning and discussing how effective these are. It's clear we can't keep piling these on one after the other, because eventually the regulatory system and the people that have to follow the restrictions will not be able to keep them straight anymore, and the whole thing will collapse. So we've been discussing this with PhRMA for some time. Last year, it became very apparent that there are many other groups who are very interested in suggesting improvements to CDER. So we've scheduled a meeting, a Part 15 hearing on our regulations, for May 22, 2002. Everyone is invited. We're expecting to hear from all parts of the healthcare community and industry about what the Agency could do to better manage risk.

Concerning initiatives, we have a number of very good activities that evaluate the effectiveness of our current risk management strategies, particularly using the advisory committee. A new Risk Management Advisory Committee that began as a subcommittee will be elevated to a full advisory committee status in the coming months. Its first substantive meeting is scheduled for next week with our Digestive Diseases Advisory Committee to consider the drug *Lotranex*. It's exciting that the members of this group aren't necessarily experts on specific medical product areas, but are experts on risk itself and on how to communicate and manage risk.

We've been very involved, since its creation through a public-private partnership, with the Centers for Education and Research on Therapeutics (CERTs), a nationwide effort that is funded by AHRQ (Agency for Healthcare Research and Quality). These centers, located at academic institutions around the country, have undertaken dozens of highly relevant research projects. CDER will be reviewing them in terms of risk management, including improving adverse event reporting, looking at cost-benefit issues and risk analysis, improving epidemiological and biostatistical issues, and evaluating ongoing programs.

Communication will also be improved. The new Physician Labeling Rule[1] will be a

[1] The final Physician Labeling Rule was issued in January 2006, with an effectiveness date of June 30, 2006.

Quotes From Our Contributors

"My view is that regulations must be informed by the greatest scientific understanding possible. Particularly science can tell what is feasible to do. Science can help you perform risk analyses that sharpen your understanding of the trade-offs."

Janet Woodcock, MD
FDA and Industry in Dialogue, 2003

"Drug development is akin to someone hiring 10,000 young artists and hoping one paints the *Mona Lisa*."

Timothy R. Franson, MD
FDA and Industry in Dialogue, 2003

"For a system to work, a company must have accountable people who understand what needs to be delivered and how to improve the system continually."

C. Greg Guyer, PhD, MBA
FDA and Industry in Dialogue, 2003

Scientific Base for Regulation

Janet Woodcock, MD
Director*
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

I was asked to address the difficult and rather broad subject of the scientific basis for drug regulation. Dr. Burlington and I have decided to do a point/counterpoint discussion. But first I'd like to reflect on the often misunderstood issue of science and regulation, and also I'd like to examine how science plays into regulation in what is essentially a legal process. As you know, drug regulation in this country is based on laws created by Congress. Hopefully, scientific knowledge and policy inform the framework's creation and implementation which are particularly embodied in regulations and subsequent guidances, offering an additional opportunity for scientific knowledge to affect the results.

When Congress establishes a legal framework, it is by no means a simple and clean process. Some congressmen say that lawmaking is like sausage making — the less you know, the more comfortable you feel. Lawmaking involves compromise among competing societal interests. For example, in drug regulation there is tension between the desire for access to medicines and the need to be certain that they are safe and effective. To some extent, these interests compete and have to be balanced.

There is a desire that regulatory oversight should make society and consumers confident that everything has been done right — with a special oversight to safety. But there is also a desire for efficiency in the process. Obviously the first amendment and freedom of speech are important issues in our country, but they have to be counterbalanced against the harm that can be done by making misleading claims about a drug. How do you balance those two interests? In the investigational stage, it is obviously desirable to get important medicines into the clinic to study them and help people. But we have to protect human subjects and volunteers in trials, which is another competing interest. To the extent you put a large edifice over subject safety, you are slowing the approval process. These things are trade-offs.

Once a law is passed and Congress has established some framework for these trade-offs, regulations are needed for specificity. They provide versions of a law which can be readily implemented. They go through a much more public process: there is public notice, comment, and input, creating a balance among competing interests. The public often misunderstands what happens. Regulations are influenced by policy directions that the administration has decided to take which can affect the implementation of the law. If the most important thing in implementing a law is to place the fewest burdens on industry, that would be a policy direction. Conversely another direction might be to give priority to the ultimate protection of consumers. Or you might pursue a policy in which international harmonization is one of the highest priorities. On the other hand, you might say we don't really care what other countries are doing, and we're going to implement or develop our regulations in unilateral isolation. That could be a legitimate policy, depending on what the societal goals are.

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* *Currently Deputy Commissioner and Chief Medical Officer, U.S. Food and Drug Administration.*

CDER organization, or any other suborganization made these agreements was beside the point. FDA has made these agreements, and we will continue to honor them.

We agreed mutually to adopt the best practices of each organization, recognizing that each had strengths that could be included in the larger unit. Most of you are familiar with the products that moved to CBER. The therapeutic vaccines, mostly tumor vaccines, is one class that didn't move. A substantial number of products were moved: about fifty-two approved products, about 1500 BLAs, and about 250 INDs per year. So this is a substantial workload that will be added to CDER.

One of the first things we decided after consulting extensively with our CBER colleagues is how they will fit into CDER's organization. We adopted a transitional structure with the Office of Therapeutics Research and Review (OTRR) mainly moving intact to continue reviewing the same products indefinitely. We added a sixth Office of Drug Evaluation. The Office of New Drugs will have two clinical review divisions from CBER. The CBER clinicians will be organized into two clinical review divisions, including their clinicians and clinical pharmacology toxicology groups. And we'll also have a division that will do project management, which was how OTRR was organized. There is going to be a new Office of Biotechnology Products in the Office of Pharmaceutical Sciences which has a generic drug review program and a new drug chemistry review. So the CBER people moving into CDER will not experience very much change, especially in the Office of Therapeutics. By October 1, which is the beginning of the government fiscal year, we hope to start operating formally in the new structure.

Two models help us manage scientific activities and review processes. CBER, originating from NIH, uses a lab-based reviewer model except for most clinical reviews. In recent years, driven by workload pressures, the Office of Therapeutics at CBER has transitioned to allow office-based scientists to associate with laboratory scientists in performing reviews. This lab-based approach benefits CBER as the staff becomes expert in specific areas, especially important with novel products. They also develop expertise in general laboratory techniques, such as high-end analytical techniques for complex biological products. The lab-based approach also allows CBER to recruit, retain, and develop high-quality research personnel for review of biological products. Increased workloads caused CBER scientists to prioritize research programs based on mission relevance, quality of research, and output of papers. Following a site visit, reviewers apportion resources within CBER laboratories and OTRR according to these parameters. This best practice approach facilitates scientific management of the research program in a regulatory setting.

In contrast, the CMC review at CDER is an office-based review, which is more efficient and less costly than the lab-based review. However, we experience some scientific management challenges, including matching our scientific expertise in chemistry against science problems raised by these products. Staff in both CBER and CDER exchange views regarding product quality to use the best practices of each group as we build a stronger product review program within CDER.

With CDER currently located in NIH labs, physical space constraints are a major challenge. CBER staff do not want to leave the NIH campus, a wonderful setting for biomedical

nologies. FDA is analyzing the root causes for multiple-review cycles and delays in approval. The need for multiple-review cycles markedly prolongs approval, if approval even occurs. Safe products should require only one cycle of review. Increased communication between FDA and industry would help this process.

The second initiative is the institution of Quality System and Review Process. A third is expanding the use of guidances in drug development. The Center for Drugs plans to concentrate on pharmacogenomics and several other disease-specific topics. Introducing a quality system and new science into the review process makes a difference for industry and FDA. We review submitted data against developed scientific standards. At CDER, we file a minimum of 22,000 scientific reviews every year. Assuring a consistent level of scientific quality and application of standards is extremely challenging in this mass production environment.

What is a quality system, and how does this relate to it? ISO 9000 — or actually the drug GMPs — stipulates quality system elements. But how can that be applied to what we do at CDER within the review process? The FDA Science Board has strongly recommended that we use such quality systems in our reviews. This initiative begins in the CMC review area at CDER as we implement a system-wide review process focusing on customers' needs. For example, in a chemistry program, the clinicians are customers, because they rely on our recommendations about product quality. The field investigators also are customers, because they need the product information to conduct rational inspections. The generics program is our customer, because it compares its data against what we accept. Industry is a customer receiving our information and responding to it. Understanding those impacted by the information helps us configure it more clearly. The quality systems approach focuses on peer review and exchange of scientific knowledge among reviewers. We are developing a transparent, predictable process with clear standards for industry. Quality systems help FDA rapidly identify problems and institute preventive actions, creating consistent, high-quality products every time.

Pharmacogenomics in drug discovery development and in preclinical and clinical studies is another example of innovation. Pharmacogenomics is the science which examines human genetic contribution to individual variability in drug response. People respond differently to drugs; pharmacogenomics helps us understand and predict the differences. It analyzes genome differences in an individual's DNA, giving insight into functional cell biology and responses to drugs at the molecular level. Scientists can now redefine the genetic variables contributing to drug effectiveness. Clinicians may lump together many diseases with multiple causes, such as asthma or irritable bowel. However, diseases do not respond uniformly to drug intervention. For example, the cholesterol transport process differs among individuals. Differences in the functioning of this transport protein may predict a patient's ability to respond well to a drug such as a *statin*. With new guidances, we will clarify use of this technology.

Individual metabolism also affects the response to drugs. Hyper-metabolizers utilize certain drugs so quickly that they have little effect. Tests performed on these people show no detectable blood level. On the other hand, some people cannot metabolize a drug, so it remains in their bodies for a long time. Some of the *thiopurine* drugs used in chemotherapy can cause horrendous toxicities as a result. Some people lack a converting enzyme to activate

a drug; they may not obtain pain relief from a drug such as *codeine*, simply because they lack the activating enzyme.

Cardiac repolarization can be genetically prolonged. If such patients take a drug that prolongs the QT repolarization, they could die. Because underlying normal body states differ, some people have a hypersensitive response to drugs. With knowledge of pharmacogenomics, scientists can genetically determine possible drug toxicity. For example, patients with differences in beta adrenergic receptors might not respond effectively to a beta adrenergic agonist used to treat their asthma. Pharmacogenomic knowledge allows scientists to screen out those with variations, so drugs are not administered to those who cannot respond to them.

Pharmacogenomics can advance us from the current empirical process of drug development, towards a mechanism-based process driven by knowledge-based hypotheses. We could see lower costs, faster drug development, more effective and less toxic drugs available for a smaller population. However, implications of most data are not yet known. Industry has concerns about how regulators might over-interpret safety risks and possibly impede development. Industry fears excessive limitation of a product if subpopulations are determined. To address these concerns, FDA is developing guidances outlining use of scientific data and policies on the regulatory impact of pharmacogenetics. We are also creating guidances for diagnostic tests and therapeutic intervention. FDA knows that the underlying diagnosis must be identified to target people for better efficacy and less toxicity.

The challenge for regulators is to incorporate new science into our policies, balancing diverse needs of stakeholders without impeding innovation. While developing new technologies, we must alleviate concerns about them. We must continue to examine whether or not the right societal balance and tradeoffs have been achieved. The current trend at CDER is now on science and innovation.

In addition, the Agency undertakes exacting statistical reviews. Industry develops the data set and sends it to FDA, including the SAS data files. FDA then replicates our statistical reviews, often going places that we may not have.

FDA doesn't settle for merely looking at the submissions. They go back and sample the primary data. They send out scientific investigators to ask whether there is a real basis for a conclusion. They even have peer review of conclusions within the Agency to a certain extent. Certainly, they have a model of supervisory management review of the conclusions that the company has brought to the primary reviewer and then have to be agreed upon by management before the market authorization is obtained. As Janet alluded to, they have laboratory research to back this up followed by Advisory Committees that allow more public discussion of the data. So there are lots of scientific tools available to FDA.

What is missing from FDA's approach is the context of science that exists in the academic and private sectors. Outside of government, we have to bring ideas and the scientific process to bear in the context of getting funding. We must be successful in the competition of our scientific ideas and our findings. We have to achieve the opportunity to present our ideas in public and get recognition of our ideas and validation of our ideas. We have to compete for publications. We don't just automatically get published because of who we are. We must send them to refereed journals.

None of those controls are routinely applicable to the way FDA goes about doing its work, leaving us with a system that produces unintended results. I will give you some anecdotal examples, rather than a systematic survey to demonstrate that there are problems, and that FDA is too often driven by technological imperatives.

Consider good manufacturing practices. Are we really following a technological imperative? Or are we applying good manufacturing practices in a way that accommodates the body of scientific knowledge in a logical fashion that allows companies to apply that knowledge to the given process with which they are dealing? An example of this is the requirement to validate sanitization procedures. Even if you were going to use undiluted hyperchloric bleach straight from the bottle to sanitize a stainless steel surface, you are required to have a validation protocol to challenge it with a variety of microorganisms and produce data in your own facility on your own stainless steel surface that bleach, in fact, kills the bugs. Now, is that really worthwhile, or is that an example of having taken the ability to use a scientific method and driving it down to the point that it's eliminating a risk that doesn't exist?

With CMCs there is an increasing emphasis on defining and characterizing trace impurities at below the one-in-a-thousand level without particular regard for or evidence of whether these trace impurities may be toxic and defining them if they are over the one-in-a-thousand level, independent of their impact on the product. Again, this smacks of technological imperative. FDA's scientists know we can drive characterization down this far, so they

say, you've got to do it, whether or not it's a good idea or adds value to the customer.

When we look in the realm of defining safety of pharmaceutical products, we get into an area where given the growing societal concern for patient safety, FDA has moved ever further into saying that you need to define risks at a very small level. We are now actually engaged in discussions on vaccines where we may be looking at clinical trials in the 200,000 and up range in order to define the frequency of rare adverse events or to show that a rare adverse event does not occur more commonly among those vaccinated than it occurs among the unvaccinated population. This is getting to the point that it has a huge impact on our ability to make decisions about products that we will bring forward.

In animal toxicology we've all faced over the last decades a proliferation of *in vitro* tests and *in vivo* toxicological models without validation of the predictive value for anything known to happen in humans. Again there's a proliferation of requirements, all based on FDA's model of science.

Concerning the anti-infective area, as Janet indicated, we don't have innovation, and we're not bringing forth new antibiotics this country needs in an age threatened by bioterrorism. And what has happened to the guidance framework FDA asked us to use to develop these antibiotics? We have subdivided diseases to the point that we now no longer have infections: we now have hundreds of different types of infections with thousands of organisms in every different body location. So independent trials must be conducted as well as analyzed by the gender, age, and ethnicity factors that might affect the effectiveness of any new antibiotic. Driven by the desire for science, we are making the job too big to do in the ordinary case. This creates a situation where, of course, you can only surmount these hurdles with the extraordinary molecule that offers a blockbuster potential, often defeating the opportunity of developing a new, useful drug.

In advertising and promotion, the adequate and well-controlled study model has been embraced to such an extent that now we cannot differentiate molecules in a class unless two independent clinical trials say this difference is real and will have an impact on patient care. It's an abandonment of many models of how we learn about drug products.

Overall, FDA is further hampered by their inability to change the framework in which they work. Janet started out by saying that this is basically a legal process. It's a legal process that applies science to make decisions about drugs in a context of competing values. And that's absolutely correct. But because it's a legal process, embodied in law and embodied in regulation, both of which are extraordinarily hard to change, FDA cannot accommodate its framework to changing science as science moves on. This is unlike other fields, where, of course, if one framework doesn't work, we change and go to a different framework, such as in biotechnology, cosmology, and a number of other areas.

So what are the effects of all this? We have higher costs in the development of products, which doesn't just mean that the drug products cost more. It means that we make

decisions not to develop drug products where the market potential is not there to offset those high entry costs. We have an excess amount of time, both in pre-development and in development that increases the costs of developing products and decreases the net present value of drug products — they're going to take a long time to get to market — and as a consequence that further limits our ability to bring new molecules to the market. We have many lost leads that would undoubtedly be valuable to humans, but because of artifactual, unvalidated toxicological findings, we abandon them. We're chasing artifactual end points all too often. That is to say, in a number of areas, we chase end points because they are easy to measure rather than because they are valuable to the human who might be taking the product. As an example, in oncology where we focus on survival — that probably is important to the patient, it certainly would be to me — but we also focus on time to progression, we focus on complete responses, as opposed to looking and saying, "Is this drug going to have a favorable impact on the quality of life of that individual?"

All this together creates situations in which we have fewer drugs in each pharmaceutical class coming to market. If you think back to the past two decades when we had *antacids*, *beta-blockers*, and *ACE inhibitors*, we were bringing ten to twenty products in these classes to market. If you look at what's happening now, you realize you might get to four or five products in a class before the industry loses interest, but we're not seeing a dozen or more different products in one class coming to market anymore. Is that important? Having a multiplicity of products offers value in terms of increasing the choices that physicians and patients have. It offers value in terms of providing products that may fit better for one patient than for another. And it offers value in an economic sense. When you go back and look at drug pricing, and you look at the number of entrants in a pharmaceutical class, it doesn't take long before you come into a realization that there is very little price competition among the first three or four in a class. It isn't until you get to five, six, or seven in a pharmaceutical class before price competition really starts to kick in and offer the benefit of lowering costs of products with similar benefits and safety to the public at large.

If we are concerned that FDA is making its decisions outside of the scientific context within which the rest of us work, and if that produces adverse consequences for the industry, then we have to ask ourselves, what controls do exist? Because FDA does operate in a context of controls. They certainly have management, policy, and supervisory review. They have Congressional oversight, and they have the Inspector General's audit of their processes and procedures. They have the Office of Management and Budget, which looks at FDA's regulations, including an economic analysis of them. They take some of the guidances to advisory committees for public discussion. And they have internal processes on clinical holds, on carcinogenicity assessment, where they are obtaining peer review. Is that enough? I don't think so. I think FDA needs to go a lot further in embracing surrogates for the kind of competition we live with, which has created vigorous science in the private sector. I think advisory committees ought to be looking at every guidance, not just a few of them. And I think that they ought to look at those guidances in public discussions, and they ought to be asking industry and the people who pay for pharmaceutical products as well as the patients

Philadelphia and New Jersey District Offices: Quality Systems Approach to Systems Inspections

Susan Laska, MS
Supervisory Consumer Safety Officer*
Philadelphia District
U.S. Food and Drug Administration

FDA's mission is to conduct comprehensive regulatory coverage of all aspects of production and distribution of drugs and drug products to assure compliance with the Federal Food, Drug, and Cosmetic Act. However, we don't have adequate resources to audit every aspect of Current Good Manufacturing Practices (GMPs) in all facilities during every inspection visit. We have a statutory requirement to inspect firms every two years. But even conducting inspections every forty-four to forty-eight months, with some firms being inspected several times a year, placed a great strain on resources. In addition, local compliance branches and CDER's Office of Compliance noted that 483s were sometimes thirty pages long, further increasing review time.

The FDA Field Offices are now in our second year of the revised compliance program for drug GMP inspections. First piloted in six districts, the program was implemented nationwide on February 2, 2002. The inspection program was revised, because the old program was out of date: many contacts were no longer with the Agency; labs were incorrect due to the laboratory consolidation, and references were no longer accurate.

The new program creates a more efficient way to use resources, providing a systems approach to inspections, shifting focus from a few profile classes to an overall evaluation of the firm. Updating the profile classes allows GMP acceptability determinations to be made without having to revisit the firm. The writers of the program were CDER's Office of Compliance, field investigators, field compliance officers, and national experts from the Field Investigation Division. Not significantly different, the program uses a more refined systems approach. Team inspections, collection of samples, and written inspection reports will still occur. However, inspections will be more oriented towards systems rather than profile classes, which is how the companies view operations. In the reports, we identify what systems are to be covered.

The significant difference for field investigators is that all profile classes need not be inspected. Prior to the systems implementation, at least one product in a profile class (meaning a particular dosage form and associated manufacturing process) was inspected. With the new program, one biennial inspection will determine acceptability or non-acceptability for all profile classes. Following GMP subsections, the six systems in a firm are quality, facilities and equipment, materials, production, packaging and labeling system, and laboratory control. The systems selected for inspection would be at the discretion of the lead investigator and represent all applicable profile classes. In the past, FDA could have deemed the firm acceptable for gelatin capsules but not for immediate-release tablets. With the new inspection procedures, if the

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* *Currently Investigator/Drug Specialist, Philadelphia District, U.S. Food and Drug Administration.*

tem. An abbreviated inspection covers at least two systems with at least one being the quality system. Compliance inspections also evaluate any corrective actions following a regulatory inspection. These inspections begin with the full inspection option. "For cause" inspections investigate a specific problem brought to the Agency's attention through field alerts, industry complaints, or recalls.

A full inspection would be required for the following:

- if it is the initial inspection;
- if the firm has a history of fluctuating compliance;
- if significant changes have occurred, such as the new potential for cross contamination; or,
- if there are new technologies, equipment, or facilities.

Follow-up after a warning letter involves a full inspection, although it may revert to an abbreviated option with District concurrence. The abbreviated inspection occurs if there has been no significant recall for product defects or alert incidents. This is an efficient, updated evaluation of current operations. Systems inspected would be rotated to build comprehensive information on the firm's total manufacturing activities.

During an inspection, the 483 should be organized by systems and in order of importance within each system. Observations should be related to a policy regulation. Investigators must report on the Form 483 only significant observations relating to an observed or potential problem with the facility, equipment, processes, controls, products, employee practices, or records. Redundant observations should be avoided. These observations on the 483 do not represent final Agency determination regarding the firm's compliance.

The control of all systems ensures that the firm produces drugs that are safe, have identity and strength, and meet the quality and purity required. Deficiencies found in one system may indicate deficiencies in others. If errors are found, the investigator may delve into other systems to prevent significant deficiencies occurring in the firm.

This new program provides more efficient use of resources. Biennial updating of all profile classes will allow for GMP acceptability. The program eliminates multiple visits to the firm to cover all profile classes. Pre- and post-approval inspections may still focus on specific issues related to any application. This approach ensures up-to-date profile class information and avoids delays in approval decisions.

The Field Drug Committee evaluated the program before its nationwide implementation. Field investigators believed that it was more focused, efficient, and better able to provide guidance. Inspection reports were more organized and efficient. Over 80% of the compliance officers said the program improved the review, organization, and efficiency. Thus, the program has been well received by the field force.

Flawed trends or deficiencies within a system could constitute failure of the system and result in a warning letter. Warning letters would be issued for violations of regulatory significance where failure to take corrections adequately and promptly could result in enforcement action. A warning letter would render all profiles unacceptable. If significant deficiencies

occur in a system, the type of action recommended would be based on the seriousness and/or frequency of the problem. This could result in a warning letter or other regulatory action by the District. In the quality system, the following constitute deficiencies. A pattern of failure:

- to review approved procedures;
- to document procedures;
- to execute operations as required;
- to review documentation;
- to conduct investigations and resolve discrepancy;
- to assess other systems; or,
- to ensure compliance with GMPs and standard operating procedures.

For the facility and equipment systems, critical deficiencies are a pattern of failure:

- to validate cleaning procedures for non-dedicated equipment;
- to document investigations of discrepancies;
- to change control for equipment; or,
- to qualify equipment (including computers).

Deficiencies can be found in contamination of bulk, objectionable organisms, toxic chemicals, or other drug chemicals. A potential for contamination from airborne organisms or through unclean equipment also constitutes a deficiency.

Some material system deficiencies are release of materials for use or distribution that do not conform to established specifications, failure to conduct specific identity tests for components, failure to document investigation of discrepancies, failure to establish or follow change control, or a lack of validation of order or computer systems.

Some production system critical deficiencies include a pattern of failure:

- to establish and follow change control systems;
- to document investigation discrepancies;
- to establish in-process controls, tests, and specifications.

Other deficiencies include finding incomplete or missing batch production records or finding a lack of process or lack of computer validation.

Deficiencies in the packaging and labeling system include a pattern of failure to establish and follow change control for packaging and labeling operations, failure to document investigational discrepancies, finding a pattern of incomplete or missing records, or a lack of control in packaging or labeling operations that creates a potential for mislabeling.

Some laboratory system critical deficiencies are a lack of validation of computerized systems and automated data collection systems, a pattern of inadequate sampling practices, not following approved analytical procedures, failure to retain raw data, failure to follow stability programs, or a lack of validated analytical methods.

Additional information is available on the CDER and ORA websites.

In quality management, there are six interconnected core systems. The three primary systems at each site are production, packaging and labeling, and the laboratory system. The production system ensures that processes are in compliance with regulatory filings and operating procedures and that batch records are consistent with the process described in the company's regulatory filing. The packaging and labeling system ensures that the right label is put on the right product and goes to the right market, a challenge in servicing over 130 countries with sixty languages. Finally the laboratory control system ensures that methods are consistent with the filing, that we meet our commitments, and that we create a stable product.

These systems are part of a materials system controlling the flow from production to packaging to laboratory. A facility must control materials from the time they enter to the time they leave. The materials system also controls the inventory, flow, and accountability of finished products. The facility and its equipment must support the production, packaging, laboratory, and materials systems. All fall within the quality system, ensuring that overall production functions smoothly in compliance with FDA regulations and company expectations. The quality system is the infrastructure under which the entire process is continuously evaluated.

With quality assurance systems, FDA can improve the focus and organization of an inspection. Past inspections were often disorganized and disconnected. However, GMP evaluations based on systems has helped FDA determine whether the organization was in control. This systems-based approach maximizes industry and Agency resources, providing a common language for both parties.

Quality systems organize inspection observations, allowing a faster, clearer industry response. Over the years, FDA noticed similar themes in inspection comments and with the QMS initiative grouped similar observations together. We learned through GMP evaluations whether the *system* was in control, not just whether a piece of the process was malfunctioning. This approach shows how the error happened, helping to prevent future errors.

As we analyze the system, map the processes, and hold people accountable, each area must be carefully evaluated, and each person must be involved in developing the system's design and expectations. Sometimes failure lies not in design but in execution. For a system to work, a company must have accountable people who understand what needs to be delivered and how to improve the system continually. Pharmaceutical company leaders must also examine problems systematically so that their approach carries over into the entire manufacturing organization. Leaders involved in the system's design and process should ensure proper execution.

Quality systems also require adequate measurement tools for evaluation. The performance of each aspect of a system must be routinely measured for effectiveness.

Training of personnel is critical at all levels. Merck has found quality systems to be enlightening in training people to understand their roles in the entire process. The quality system approach is a tremendous training tool.

Over the past several years, compliance failures have resulted from one of three con-

The high cost of manufacturing pharmaceuticals and vaccines requires pharmaceutical companies to operate efficiently. It benefits everyone to create systems compliant with GMPs that are efficient and cost effective. When we evaluate the performance of individual systems over time, we can identify the sites with the best system practices. When we speak the same quality system language and streamline and standardize procedures, we create efficiency in our own company around the world and eliminate duplication. If a problem is corrected at one site, we can apply that knowledge to all sites. This saves time at FDA inspections as well, because once a problem is corrected at one plant, the Agency knows it will be corrected at all the sites. Each inspection observation can impact the whole system.

Implementation of new regulations becomes easier with quality systems. With each new regulation, a company can observe its impact at each site. Understanding procedures at all sites, the company can propose alternatives to FDA regulations that may be more efficient and cost-effective while maintaining equal effectiveness. Using a QMS approach allows a company to collect data not just for compliance. It implements a system that continuously creates high-quality products, giving a company a variety of ways to achieve the same objective desired by the FDA regulations.

Quality systems give us a framework for continuous improvement. We can use them as a training tool to initiate conformity among various sites, leading to continuous learning rather than reinventing the wheel at each plant. When we focus on core strategies, a systems approach allows us to concentrate on similarities and ways to learn from each other, rather than working in isolation as we did in the past. With quality systems, we routinely and rigorously audit each site, much as FDA does. We ensure our staff is working consistently with design, execution, and delivery of the system. This prepares the company for FDA and international inspections.

Quality systems have helped us apply the precepts so important in academia — the need to reevaluate and constantly improve as we learn. We've learned a great deal about quality systems in the last five years and understand that they make sense not only from a compliance standpoint but are also good business. We've integrated quality systems to be more prepared for Agency inspections. FDA and other major regulatory agencies also have taken a major stride forward in adopting quality systems, creating efficiency in inspections. Those involved in the drug development process can all benefit from the quality systems initiative.

PDUFA III

John Jenkins, MD
Director
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

The history of the modern drug paradigm and PDUFA (Prescription Drug User Fee Act) really dates back to 1962, when the amendments to the Food, Drug, and Cosmetic Act to add the requirement for demonstration of effectiveness were passed by Congress. In the 1970s, what some referred to as the "drug lag" began to emerge, since drugs were approved in Europe and other countries years before being approved in the United States. In the 1980s there was an emphasis on early access to drugs for patients, stimulated by the HIV epidemic and other life-threatening diseases, such as cancer. And, in 1992, PDUFA was Congress's attempt to address the chronic under-funding of FDA's new drug review program.

Why is PDUFA important? Prior to 1992, timeliness of drug review was a big concern. The PDUFA program allowed user fees to be added to FDA's base appropriations, resulting in more review staff, elimination of the backlog of application reviews, and improved review times. In exchange for these additional resources, FDA agreed to meet specific performance goals, initially focused on application review and later focused on drug development. With PDUFA, according to the Tufts Center, "We've had a revolution in regulation of pharmaceutical products. We now have a more predictable, streamlined process, and we've seen reduced review and approval times."

PDUFA is a five-year program, which sunsets after five years unless it is reauthorized by Congress. PDUFA I covered fiscal years 1993 through 1997 and focused on review times for marketing applications. PDUFA was reauthorized in 1997 as part of FDAMA. PDUFA II went beyond PDUFA I in further reducing review times and also shortening drug development times. Reauthorized in 2002 as part of the Bioterrorism Preparedness and Response Act, PDUFA III covers the next five years.

PDUFA I was very simple: in exchange for fees from industry, FDA agreed to meet certain performance goals for review of applications and other administrative and procedural goals. It eliminated the backlog of applications that existed prior to PDUFA and aligned reviews according to standard and priority. In PDUFA II, new performance goals branched out into the drug development process. PDUFA performance goals relate to the review and processing of applications, not their approval. In considering the various phases of drug development, PDUFA I focused on the end of the process by establishing goals for the review of marketing applications; PDUFA II added goals during Phase 1, Phase 2, and Phase 3 of the drug development process.

During this revolution in drug review and drug regulation, FDA has performed remarkably well over the past decade, often exceeding PDUFA goals. When PDUFA was

passed in 1992, no one that expected FDA would perform as well as we did over the past decade. In essence it was truly a revolution in how we review and regulate new drugs in this country. We met or exceeded essentially all of the performance goals during PDUFA, with some very minor exceptions. I think that others would agree that PDUFA has been good for public health.

More than 700 new drug and biological products have been approved during PDUFA, including 200 priority reviews for products considered significant therapeutic advances. Most of these drugs were approved routinely within six months, revolutionary compared to before 1992. This early approval of priority drugs for HIV, cancer, and other serious diseases has saved countless lives. The perceived "drug lag" with other countries in the 1970s has been reversed. Now we see "drug lags" in European approvals, because 80% of new drugs introduced anywhere in the world are either approved first in the United States or within one year of being approved somewhere else they are approved here. That's a dramatic turnaround.

But we have also faced challenges with PDUFA over the last several years. The Agency workload under PDUFA II was far greater than predicted during the negotiations for the PDUFA II program. Despite a decreased number of NME applications over the past couple of years, the overall review workload has increased substantially because of more new INDs. The number of efficacy supplements has risen exponentially. PDUFA II management goals include over 1200 formal meetings with industry a year, requiring hundreds of hours of FDA staff time preparing for, attending, and finalizing minutes for each of these meetings. During PDUFA II many other initiatives were added under FDAMA without an increase in resources, such as in the area of pediatric exclusivity, which has created a mountain of work without additional resources for the new drug review staff in CDER. When PDUFA was reauthorized in 1997, projections were made about the number of applications that would come in and their fee revenues. However, the amount collected over the last several years of the program was much lower than estimated. During the last several years of PDUFA II, we were in a deficit spending mode, just to keep the program running. We were able to borrow some funds from revenues accumulated in earlier PDUFA years. However, twenty to forty million dollars a year over collected revenues have been spent just to keep the program running. This can't continue forever.

With workload and resource pressures, it became more difficult under PDUFA II to meet performance goals. In the early PDUFA II years, we met or exceeded most goals, but in the last few years, performance has slipped. Workload pressures have led to "just in time" completion of reviews, creating a mass production mode for reviews reminiscent of air traffic control — where lots of planes are coming in as quickly as others are taking off. We had less time to work with sponsors to remedy problems during the review process, resulting in multiple-review cycles, which is inefficient for the American public, for FDA, and for industry. There was less time available for staff to do professional development and training, which does not bode well for long-term survival of the organization, either from the perspective of its intellectual capacity or retention. We also experienced inadequate time for our staff to develop clear guidances for industry.

PDUFA has had a major impact on approval times. There are two ways to look at

approval times. The most common way is the calendar year approach; however, these only exist as an exit cohort, since these are the applications that are approved in a given calendar year and really have no relationship to one another. They could have been submitted five or ten years — or even six months — ago with different regulatory histories. But it is the most up-to-the-minute performance measure available.

With implementation of PDUFA, the standard NME review approval time was nearly twenty-three months. Even priority applications took about fifteen months. During the latter part of PDUFA I and early in PDUFA II, approval times fell. However, starting in 1998-1999, for the standard NMEs, we saw a gradual rise in the median approval time. Approval times have fallen over the last few years for NMEs, with an increase in 2002, which may have been an aberrant year. However, many in industry see this as FDA's slowing down and becoming more conservative.

Many factors influence this change. One relates to the timing of submissions, which can be poorly organized, incomplete, or submitted prematurely. PDUFA states that a complete application will receive a complete review within a given period of time. Many companies still submit applications on a corporate cycle, rather than when it is complete and ready. Some applications are submitted with scientific deficiencies. Factors regarding FDA workload and staffing impact approval times. Reviewers with multiple competing priorities may be delayed in beginning a review. There may not be time to work with the sponsor to resolve issues before we must create a letter to meet the goal date and initiate a new cycle.

We've actually seen a paradoxical effect on our calendar year approval time in that we've been seeing a decrease in the number of NME submissions. People think, "less applications, less work," therefore reviews should be done faster. The opposite is true. While we may be seeing fewer NME submissions, our overall work continues to increase. Although we've experienced a decrease in the number of NME submissions, we are not able to complete the work more quickly. This trend is an artifact of the calendar-year exit cohort. If fewer new applications arrive with a potentially short approval time, then more of the applications approved in a given year are older ones, submitted from one to five years ago. This skews the numbers, forcing the median upward. After a peak year in 1995, we see a fairly linear decrease in the number of NMEs submitted to the Agency each calendar year. The slump in product development is reflected in fewer products approved by FDA.

Another way to analyze approval time data is based on a fiscal year cohort of receipt, examining a group of applications submitted at the same time frame, subject to the same goals and rules, with the same Agency resources and workload pressures. We think this is a better way to look at the data. Unfortunately, it can take up to two years for this cohort to mature enough to see what the trends are. Looking at the fiscal year data, in 1994 it took approximately eighteen months for half of the priority applications that were submitted in the 1994 fiscal year to be approved. Over time, PDUFA had a dramatic effect of bringing down these approval time numbers. But starting in 1997-1998, we've seen a progression upward with standard and priority NMEs. The increase in approval times occurred simultaneously as we were implementing the new PDUFA II goals in an environment where we didn't have adequate resources.

As the Agency approached PDUFA III, we had two main goals:

1) To get the program back on a sound financial footing, covering program costs and ensuring that our performance obligations were met with adequate resources and to relieve the stresses caused by PDUFA II; and,
2) To enhance risk management by allowing user fees for the first time to be applied to post-approval safety activities.

PDUFA III was reauthorized by Congress and signed by the President last summer. It began last October, which was the start of our 2003 fiscal year. We believe PDUFA III created a significant increase in resources coming to FDA, balancing staff with workloads for the first time. And, for the first time, it allows user fees to be used for post-approval safety activities for drugs approved during PDUFA III. We hope to increase our staffing across the Agency for all programs involved in PDUFA III by about 400 people. In summary, PDUFA III expands further on the PDUFA II goals of application review but focuses on new initiatives to further speed drug development. Fundamentally the performance goals for reviewing applications stay the same for the next five years as they were last fiscal year, with some minor exceptions.

One enhancement to PDUFA is a pilot program for a Continuous Marketing Application (CMA). These initiatives are directed at trying to improve the first-cycle review performance, a major concern of industry regarding multiple-cycle reviews. There are also risk management initiatives focused at improving our ability to monitor drug safety after approval. Another provision allows us to bring in expert consultants for biotechnology Phase 3 protocols. Other initiatives focus on performance management and IT or electronic submissions.

The concept for the CMA originated from industry. Currently the industry develops the drug and application, but the Agency does not begin review until the application is complete and fully submitted. Industry has requested earlier FDA involvement in the review/development process. Having done this for years in certain cases, we agreed to expand current activities under the pilot programs. However, it is important to evaluate these pilot programs in terms of cost, impact on drug development, and effect on drug review.

The first program is limited to fast track drugs and biologics that have a significant public health benefit. The program is designed so that FDA and the sponsor would reach an agreement about pre-submission of reviewable units of the NDA or BLA in advance of the complete application. For these reviewable units FDA would complete its review within six months. FDA would provide feedback to the sponsor on those units in a discipline review letter. A guidance is being created to implement this program, targeted to start on October 1, 2003, the beginning of fiscal year 2004.

The second pilot program expands proactive interactions with companies during the IND phase. Again, it's limited to fast track drugs and biologics, since they have a potential significant public health benefit. The program could start as early as the end of Phase 1. To limit the workload on our divisions while expanding experience across all of our review

divisions, this program is limited to no more than one product per review division. The fundamental concept is that there will be an agreement developed between FDA and the sponsor about the types of interactions, submissions, and feedback during the drug development program, maximizing FDA input. Guidance for the program is currently under development and targeted to start in fiscal year 2004.

Both pilot programs include an independent consultant review and analysis to assess value, cost, and impact on the drug development and review processes. The consultant will be reviewing both FDA and sponsor activities, so it will be a two-sided rather than one-sided evaluation. The consultant's preliminary report is expected by the end of fiscal year 2006, since the hope was the results would influence discussions about PDUFA IV. This represents the first systematic assessment of the cost and impact of FDA actions to speed drug development review. The Agency has always believed that rolling reviews and being proactive during the IND phase made sense. This represents our chance to evaluate benefits and costs systematically.

Both FDA and industry share the goal of reducing multiple-cycle reviews prior to a drug's approval. In PDUFA III, there is a focus on reducing the number of multiple-cycle reviews prior to approval. If a drug eventually is shown to be safe and effective, but it takes multiple-review cycles to be approved, it is an inefficient use of both industry and Agency resources. Our goal is to eliminate those multiple-cycle reviews whenever possible. One component of this program is the filing review issues letter, which is essentially an early warning or heads-up to the company during our filing review. The purpose is to bring substantive issues to light, not to prevent the filing of the application.

A guidance is being developed on good review management principles, with a training program to implement the Good Review Management Principles (GRMP) guidance once it's finalized. The GRMP guidance focuses on the review process rather than scientific issues and outlines FDA expectations for the sponsor and our review staff for efficient management of first-cycle reviews. We plan a two-way evaluation by an independent expert consultant of first-cycle reviews, which will evaluate both FDA and industry practices. Based on the results of this independent analysis, we can better determine the root causes of multiple-cycle reviews.

Since this new program under PDUFA IIII has been implemented and applied to all original NDA and BLA applications and efficacy supplements after October 1, 2002, I can give you some early performance data. The program states that within fourteen days of the sixty-day filing date, FDA will notify the sponsor of substantive deficiencies identified during our preliminary review. We phased in performance goals to meet this fourteen-day time line. For the first six months of the FY-03, October through March, approximately sixty-two NDAs of all types were submitted. Within those sixty-two, we've sent eighteen "issues" letters to sponsors. By this I mean that we identified filing review issues, and they were communicated to the sponsor in a letter. The letters contained anywhere from one to eighteen issues. Twenty no-issues letters have been issued, which does not signify automatic approval of the drug but that we have not identified any problems based on our preliminary findings. Letters have been issued 64% of the time within the goal date. Since the goal for FY-03 is 50%, we are exceeding our user fee goal on this program.

PDUFA III: What do FDA and Industry See as the Next Step?

Timothy R. Franson, MD
Vice President*
U.S. Regulatory Affairs and Regulatory Policy
Eli Lilly and Company

The cover story of this morning's *USA Today* reads, *"Focus Turns to Rebuilding: Combat Subsides. Slow Start Worries Transition Chief."* This Iraq headline could relate just as well to PDUFA. *Focus turns to rebuilding* because Dr. Jenkins just informed us that PDUFA II's workload exceeded the resources, so this is a time of rebuilding with sound financial footing. *Combat subsides*? Actually there were parties opposed to PDUFA III, but it wasn't PhRMA or FDA. In fact, there was a good consensus. Many in industry feel that PDUFA III brings positive developments for patients, especially in benefit-risk management. Finally, S*low Start Worries Transition Chief* could be attributed to Dr. Jenkins or Dr. Woodcock, or maybe my boss, because there are elements of a slow start. It is distressing that PDUFA funds couldn't be spent for about six months after PDUFA was activated because of a continuing resolution in Congress. We're very concerned there is multi-factorial pipeline sludge which must be addressed, presenting opportunities as well as challenges.

In discussing PDUFA III, I'd like to focus on the "P" in terms of the statistical perspective. What is the "significance" of what's been done, in terms of "significance" for patients, the FDA, and the healthcare practice community, especially physicians and pharmacists, and what are the next steps? I could stop my talk here and say *collaborative implementation*, because that's where we are now. The agreements are made — but the test will be how well we effectively execute on the promise inherent in these agreements. Without further ado in that regard, I am going to talk about the "significance" elements (each beginning with the letter P), in terms of what are the elements in preserving productivity, proactive safety enhancements, predictability, process improvements, pediatrics, partnering and planning, and then a P value summary. Now that we've completely exhausted that letter of the alphabet, we will try to focus on what those outcomes will be for patients, practitioners, pipelines, and Park Lawn (with apologies to those who live in Woodmont or other FDA offices).

Many in industry have looked primarily at the process in terms of one or two years surrounding negotiations. However, in the perspective of a decade, we see the incredible progress that PDUFA I and II have brought and believe PDUFA III should bring in the future. We must preserve productivity, proactive safety enhancements, predictability, process improvements, pediatrics, partnering, and planning, focusing on positive outcomes for all.

An excellent illustration is my personal experience with review times. The review time for *Prozac* (*fluoxetine)*, now a multi-source product, was four years in the late 1980s, pre-PDUFA. The review time for many AIDS compounds was four weeks — a huge difference to patients in terms of access — and there is no indication in the data that an increased risk has been foisted upon the public as a result of PDUFA. In fact, drug withdrawal rates are the same or have lessened pre- versus post-PDUFA. Also, the compounds introduced in 2003 show greater complexity than those in 1993.

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* *Currently Vice President, Global Regulatory Affairs, Eli Lilly and Company.*

For example, currently we're seeing many new compounds for oncology (as opposed to many new acute care antibiotics ten years ago), showing the system is working — and working well.

There is a lot to build on, because PDUFA is one of the first examples of drug regulation which has not been made responsive to a patient-related crisis. All of us are familiar with the history of legislation for drug safety and efficacy. PDUFA is an opportunity borne out of seeing the need and the obligation to provide more benefit for patients in a timely fashion, without escalating risk. In essence, it goes back to the term "regulate" which is defined in Webster's Dictionary as either "to control or direct according to rules or law," which would be a process focus or "to adjust for accurate or proper functioning," which is more of an outcome orientation. I believe we ought to think of regulation in terms of the same ways our body controls *homeostasis*. That is, there is up and down regulation when there are disparities in a variety of feedback cycles. And PDUFA has provided that kind of feedback cycle with new process improvements.

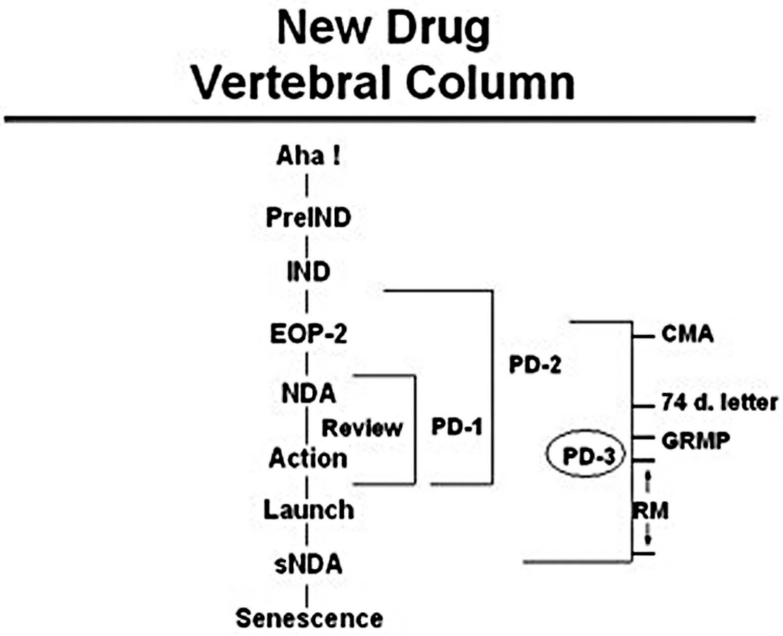
The user fee concept is unique. It is not a tax. A tax means you pay money and *caveat emptor*. A user fee means there is fundamentally a service provided for an assessment. As Dr. Jenkins has already emphasized that service is a high-quality, timely review with integrity. It does not guarantee an approval (in fact it can result in rejection of an NDA), so there is no inherent conflict of interest.

Drug development is a very complex and highly risky business. If you weren't already personally investing in it, you'd probably prefer to invest instead in a nice, safe mutual fund. Drug development is akin to someone hiring 10,000 young artists and hoping one paints the *Mona Lisa*. PDUFA III has the potential to minimize risks and expenses while expediting development.

While we like to think that every new molecular entity affords a cure, I submit that incremental improvements have every bit as much value to patients who are individually affected by those advances. I'd also like to indicate that I don't believe in the concept of "Me Toos." I actually believe in "Me Too Lates." I have direct experience in the *H2* category all of which are now OTCs. The first *H2* in early development was *Nizatidine* developed by Lilly, which ultimately finished third in getting to approval. People asked "why do you want to get into a market that involves only minor dollars to compete with antacids?" Obviously the *H2* market brought a tremendous incremental benefit to patients, which was not foreseen by many and were very successful products.

PDUFA also targets the need to restore staff, to build on current improvements, and to reverse the slow processing of standard applications. The improvements in innovation will span the entire spectrum. PDUFA I focused on the primary NDA review period. The expanded focus of PDUFA II and FDAMA brought a different scope to improvements in the pre-NDA innovation process, leading into PDUFA III. All of these changes ultimately impact those practicing institutional pharmacy, in-service study drug coordinators, investigators (physicians or pharmacists) in new drug studies, and those in Phase IV studies through experience with new compounds.

I also want to present these development considerations in a different dimension. You've seen the sequential development steps along the horizontal axis before, but I'd like to present them as a vertical/vertebral column, because there is value in thinking of things in physiologic equivalents:



As you look at things, the first three-letter acronym is very important. Somebody has to have an "Aha!" in a lab before you can get an NDA later. The kinds of improvements in innovation that the new FDA commissioner and others are talking about probably will span the entire spectrum of these vertebral bodies. PDUFA I focused on that primary review period. As you heard, the expanded focus on PDUFA II and FDAMA brought a little bit different scope to improvements in the pre-NDA innovation process, and then Dr. Jenkins has nicely outlined some of the key points as they relate to new provisions in PDUFA III. All of these changes again affect those in pre-approval – through Phase IV studies.

As Dr. Jenkins indicated, first-cycle filing letters are one improvement that allows industry to receive earlier advice about whether issues exist regarding a drug's approvability. Lilly's early experience with one compound has been exceptionally good. In the first review cycle, these letters come out at seventy-four days post-NDA submission. Industry must view this as an opportunity, not to see whether there is a probable approval, but to get an idea where gaps or questions exist. In essence, first-cycle review helps industry prepare to address issues promptly and improves communication with FDA. When you submit the NDA, the question is, "Does it have wings?" With the seventy-four day letter the question is, "Do the wings flap?"

This morning we heard an excellent discussion on risk management, so I want only to highlight a few additions. Those who are attuned to PDUFA and drug regulations are well acclimated to these matters. But we must be explicit in our terminologies, so others don't misunderstand what we are talking about. For instance, does risk-management mean needle stick injuries, process validation in manufacturing, or managing stock portfolios? Benefit-risk management and, specifically, pharmaceutical benefit-risk management means optimizing that relative ratio of safety and efficacy data for patients which includes better understanding the kind of data that must be collected, assessed, and then communicated well into a product's life span. Anticipatory surveillance requires having good baseline knowledge of background event epidemiology and populations to be studied for balanced comparisons over time. This is an area where academic pharmacy and academic medicine can truly assist in providing a backdrop or landscape across therapeutic classes.

It's difficult to throw multiple compounds into the same benefit-risk buckets when you don't have some sort of yardstick or stratification on that benefit side. When there is no "currency exchange rate equivalent" that allows one to compare benefit and risk across selected drugs, we may end up struggling to stratify things. Others have spoken of looking at life-saving agents very differently in benefit-risk equations than one would look at life-altering (quality of life) agents, such as those that impact one's core activities of daily living versus life-style agents. This doesn't demean that latter category; it just confers a different comparative perspective on benefit-risk.

Industry and FDA are deeply interested in everyone's inputs relating to benefit-risk communication, including risk communication from a sponsor or the FDA to practitioners and then to practitioners and patients. Often we as a healthcare enterprise don't do this well or consistently. When labeling changes come out from various companies, as a practitioner I can't routinely read them (like many colleagues) given both their volume and inconsistency in quality. We've discussed the idea of improving utilization by sending those changes in a letter from a state licensing board, which would probably impel you to open it. While it doesn't solve the program, it's an example of better communication attempts.

Patients, in turn, represent a huge communications challenge, since risk management involves so much information and focus. Balanced benefit-risk advisories are key. As practitioners, our challenge is how do we enlighten patients instead of frightening them? Consider presenting an informed consent document to a Phase I patient. One option is to present it in the vein of "here's an opportunity to enhance the insight into a disease entity where no other current intervention exists, and you have a chance to really be a part of science's history." Another would be, "Well, you know, this is pretty dangerous. Nobody really knows what could happen with this thing when we shoot it into you. Your arm could fall off." Same basic situation, but two very different approaches. How informed consents are presented to patients in these kind of situations affect whether or not they are receptive to medications. There's a sheer challenge that all of us must deal with in terms of risk communications but also a very important and real opportunity.

Returning to the risk management programs that Dr. Seligman has talked about, it's fair to say that we need to find some way to improve the kinds of interventions that are necessary to better convey benefit-risk to patients. It's important to view this as a dynamic process and part of our collective responsibility as medical and pharmacy practice communities. We're still learning things about "ancient" drugs like *Vancomycin* for new indications, new uses, and so forth, even though the drug has been on the market for over forty years.

Predictability is a huge factor when we talk about how one plans communications so that the access of patients to a new compound is in sync with known safety and efficacy data. If there is predictability, you can also better plan manufacturing, labeling, and all sorts of other components to improve efficiency. Without predictability, one risks being disjointed and thereby ultimately disadvantaging patients in terms of access. There have been some recent technical fixes that I think help FDA and industry better manage the paperwork in these processes to aid efficiency.

So what about process improvements? You've heard about CMA (Continuous Marketing Applications), IT, and so forth. It's important that each of us, across industry, share and learn from our best practices. That was the intent with PDUFA III: that industry needed to share in that self-diagnostic and learning process as much as FDA. That implies that we learn from each other, not only in best practices but worst practices. Dr. Seligman's example of the seventy-four day filing let-

FDA Today

Nancy Smith, PhD
Director
Office of Training and Communications (OTCOM)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

It's good to be here, and I bring you greetings from the Center for Drug Evaluation and Research. I plan to talk about some of the changes going on at the Agency and CDER in a number of areas; then I'm going to discuss application trends, including how we can improve drug review and work together to improve drug development. Finally, I'll speak about the Agency's role in addressing activities, especially in terms of what appears to be the depleting pipeline.

There have been a number of personnel changes at the FDA the last few months. Dr. McClellan left to head the Medicaid Program. Dr. Lester Crawford became the new Acting Commissioner, and we have three new Acting Associate Commissioners. Dr. Janet Woodcock, the Director of CDER, is the Acting Associate Commissioner for Operations, Dr. Amit Sachdev is the Associate Commissioner for Policy, and Dr. Mac Lumpkin is the Associate Commissioner for Special Programs.

CDER and other Agency centers are in transition. At CDER, Dr. Steven Galson, Deputy Center Director, has been Acting Center Director since October and will continue. Dr. Mark Goldberger, Director of Office of Drug Evaluation IV, has been the Acting Deputy Center Director but wants to return to the Drug Review Program. Dr. Douglas Throckmorton, Director of the Division of Cardio-Renal Drug Products, will step in as Acting Deputy Center Director in early May. These position changes allow a number of people to move through the departments, bringing new ideas and gaining insights across the Center, while expanding their experience outside their usual realm of drug products.

Despite these personnel changes, the impact on overall Agency processes will be minimal. Dr. McClellan set forward a program of initiatives, including a strategic plan that is available on the FDA website. The Agency is very committed to improving innovation and drug development. We are committed to making drug review a more efficient and, hopefully, more rapid process. We also have a strong commitment to early communications with sponsors. These three things will be stressed across the Agency, not just within CDER.

Changes from the legislative front affect what we're doing, such as the new Medicare Legislation recently passed by Congress and the publicity about importation. While the Medicare Legislation does not directly apply to FDA, we have an important role in the major provisions. One program emphasis is the availability of generic drugs, so we have a number of major efforts going on in this area. Electronic prescribing is extremely important and is tied to several of our current initiatives, including the Physician's Labeling Rule, the Electronic Drug Registration and Listing, and Electronic Label Information, a project that Randy Levin will speak on later today.

We're trying this out to see if it will help sponsors to submit part of the application and get a response, perhaps before or during the time they're submitting the rest of the application.

Continuous Marketing Application Pilot II promotes better feedback between industry and the Agency. Better communication throughout the process can lead to more efficient and effective drug development. This Pilot is limited to no more than one product per review division and involves CBER and CDER. The guidance was issued last fall. Several INDs have already been accepted to see if this additional interaction will shorten drug development time and improve the product.

One of the initiatives under this is the End of Phase II-A Meeting Program, where the goal is to obtain better information from Phase III clinical trials. The Agency and industry meet early in Phase II to develop a better design for Phase II B and Phase III. While the Agency issues many guidances, they are exactly that: our best advice on how to proceed. We welcome input from industry with suggestions they think can improve the process. If industry finds a different or better way to carry out the process, we are open to it, but we encourage industry to approach us early in the process and work with us. We want to avoid complaints or problems about the process at the time of the application submission. These meetings are voluntary for sponsors, and there already have been several end of Phase II-A meetings.

These pilot programs will all be evaluated by an independent consultant, which will be the first systematic assessment of costs and the impact of FDA's actions. We're looking forward to seeing the results, whether we get the results we hope for or not.

We're also developing Good Review Management principles, which include talking about our process to determine how we can more efficiently manage application review. The main focuses include working with industry to get more complete applications, trying to improve our review planning and execution, and again improving communication. The key to everything is communication. The goal of Good Review Management Practices is to improve the first-cycle review. It's important to note this is not to increase the rate of approvals. The goal is to improve the number of applications that get a final decision after the first cycle. This will eliminate unnecessary and inefficient review cycles, giving applicants more timely notification if there are deficiencies. We hope this will lead to more consistency in our process.

One of the things that has been implemented already is "Issues Notification Letters," known internally as our 74-Day Letters, because they're supposed to be issued within two weeks after the filing meeting, which has to be held within sixty days (sixty days plus two weeks equals seventy-four days). The idea is that we would communicate the substantive deficiencies we already identified early in an application and give the sponsor time to respond to those, if possible, while we're completing the review. This began the first year of PDUFA III, which was fiscal year '03, and our goal was to do this 50% of the time. We actually did over 80%, so we're off to a good start. Not only are we doing it fairly regularly, but we're trying to improve the letters that we send to make them more useful to industry.

An independent consultant will review this pilot program, looking prospectively and

retrospectively at the NMEs and BLAs under PDUFA III and soliciting opinions from sponsors and the Agency. There is a formal report due to the Commissioner of FDA by the end of PDUFA III, about three and half years from now. The contract needs to be let very soon. We have also been working to improve guidance to sponsors in several disease areas and in terms of pharmacogenomic data.

In summary, FDA has undertaken a multiyear and multidimensional project to improve the efficiency and effectiveness of drug development and review. The initiatives are built on PDUFA success and are consistent with our public health mission. The success of these efforts will require FDA and industry commitment and adequate resources, a touchy subject. Thank you for having me here today.

Risk Management

Janice Bush, MD
Vice President*
Liaison, Quality Management, and Business Support in the Benefit Risk Management Department
Johnson & Johnson Pharmaceutical Research & Development, LLC

Risk management means different things to different people, but there are many shared goals and understandings between industry and FDA. The specific PhRMA perspective includes how to focus on quality in risk management plans, how to design programs, how to choose risk management tools, how to measure improvement, and what these plans imply for the future. In my mind, risk management must be comprehensive and proactive, including the identification, assessment, communication, and minimization of risks in any product. Today I will primarily focus on the minimization aspect.

The shared goal of both industry and FDA is to provide patients with safe medicines with a positive benefit-risk balance. It's important to have a continuous process, where the product's benefits as well as risks are learned and interventions are implemented to minimize those risks. These interventions must be evaluated in the light of new knowledge and revised as needed. The key point is that risk management must occur throughout the life-cycle. Both FDA and industry agree that sponsors should evaluate risk to determine how to minimize it for every product, with some drugs needing more extensive risk management plans than others. Generally good labeling and post-marketing surveillance are really going to be adequate to do this for most drugs, but the tools used for the more extensive plans should be related to the specific risk management plan (RMP) objectives.

In risk management, we also must not ignore input from the stakeholders. The ultimate goal of evaluation is to ensure that all of the efforts and costs put into a risk management plan lead to a positive risk-benefit balance.

The PhRMA perspective is that any attempt to identify all risk in a product (the rare, the uncommon, and the minor events from select populations) prior to approval (or even during the approval process) will result in significant delays in drug development. This can have an overall adverse impact on public health. Any assessment and decision about a RMP really has to be based on the benefits as well as the risks of a particular drug.

Industry also believes that quantitative benefit-risk measures must be instilled in the decision process, so there can be consistent standards across divisions. I agree with Paul (Seligman) that currently there are no validated methods, making it difficult to prepare a benefit-risk analysis. Measures across companies are not the same. In spring 2004 a small group of experts (half from European regulatory agencies and half from industry) met at the London School of Economics. A new decision analysis tool was introduced to help evaluate the risk-benefit of a hypothetical drug. Many were surprised at how useful the tool was.

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* *Currently Vice President, Quality, Education & Business Support, Benefit Risk Management, Johnson & Johnson Pharmaceutical Research & Development, LLC.*

However, such a tool is very difficult to use and would require training for those who use it. It does mean though that there are viable models available as tools to measure benefit-risk. Such a tool could be invaluable for industry, FDA, and many health facilities. It could lead to risk management plans primarily based on scientific evidence.

Finally, from the PhRMA perspective, every drug does *not* require an extensive risk management plan: however, those with serious and avoidable risks that could impact the public health do. Guidances that increase collaboration between regulators and industry from the early stages in a drug's development are critical. However, it is equally critical that the system not become overburdened with too many resource-intensive tools in RMPs.

Looking at what has been used and has worked in other industries, we see an emphasis on metrics and continuous evaluation of risk management programs. As the pharmaceutical industry has not made this a priority, it is time to focus on clear measures and continuous evaluation in order to increase the quality of the risk management plans that we have. Sponsors and industry accept the responsibility to address safety issues. Since the pharmaceutical industry has an above-average hazard rate, we need to do more to mitigate risk. Although saying a drug is safe doesn't mean the absence of risk, we must do better in evaluating the level of risk by choosing the right tools for evaluation.

Labeling and communication efforts have had issues in the past. We have relied upon post-marketing surveillance for most drugs, but we know that there have been issues. When we need to communicate risk beyond the drug's label, we must have tools at hand. We know that access and distribution restrictions not only reduce the risk but also reduce the benefit. And when they do reduce risk, it's mostly by way of delaying or restricting exposure (and access).

What tools exist between labeling and restricting access? *A Framework for Pharmaceutical Risk Management*, published in 2004, shows programs available in other industries. The book helps us learn what is already known in risk management. It stresses the need for evidence-based risk assessment and regular interventions, by beginning with a plan which includes the concept of continuous quality improvement. We also need to design and validate interventions with end users in mind. We have to incorporate behavior change techniques in any plan that we put together, and we must measure again and again.

Why does risk assessment need to be evidence-based? Evidence is key to several different areas. First, there must be actual risks driving the need for risk management planning. It can't be, "well, maybe, perhaps, what if?" There must be actual evidence of the need for risk management planning. And that planning must include a process to determine where potential failures lie. This will help determine the choice of specific tools. We must evaluate the system for potential barriers. Again, when you assess the risk management plan, you need to use evidence. If there is no clear reason for using a specific tool, evidence received will be arbitrary. Many companies just pick a program without knowing if it really works, just because they've used it before and are comfortable with it.

Using evidence-based risk assessment can show where existing processes have failed, how often this has occurred, and how important it is to the overall drug process. A

can't just measure once, and you can't just measure one thing: you must measure broadly and deeply. How quickly are people adopting the new process? How is the process change moving along? Do the surrogates and outcomes actually work? Most important, you must measure frequently. It's important to include trend analysis, so a company does not wait years to realize that their tools are ineffective.

Measurements must also be meaningful. This is a challenge if a company starts a risk management plan after a drug has been on the market. Decisions can be made then to reduce a little here, add a little there, in order to make the drug safer to use. But measurements for a new drug must be more creative; for example, they might examine the clinical trial data for that particular drug, looking at such things as liver function tests. In the clinical trial, one can examine the rate of the liver function tests that physicians ordered. If the drug required twelve tests per year, and in the clinical trials only ten were performed, then more than ten should not be expected once the drug is on the market. Ranges from other drugs which need liver function tests can be examined, so that information can be extrapolated to current trials.

Evaluating the range of responses to a tool can be helpful. For example, in the case of the liver function tests, some specialists may obtain ten out of the twelve blood tests per year that are required. However, patients of family practitioners in a managed care organization may only receive three liver function tests per year. In that case, interventions can be more focused on the family practitioners as the ones who need to improve their rate of testing. If a company knows where to direct their efforts, they will have a more successful program.

When a company designs a program, hopefully, the researchers can just tweak the design if an error is found; however, a total redesign may be needed. Only after a program is in use will it be possible to determine which aspects work and which don't. With continuous quality improvement and adequate measures, a redesign can occur more easily. The pharmaceutical industry and healthcare providers must continuously evaluate the process to understand risks of certain drugs. When there are no measurements to determine how effective a program is, and the Advisory Committee points out that the program is not working adequately, a company is stuck repeating the same mistakes over and over.

Evaluating the program of risk management, we begin with detection, move to assessment, go on to intervention and finally to measurement. The new aspects needed are really in the assessment phase. It's not just assessing what the risk is for your drug. It's assessing the possible areas of risk for a drug and where failures might occur. With this evidence, you can design and carefully choose your interventions.

Validation is another important area to briefly mention. As a company moves from assessment to measurement, what has been assessed directs the researchers to understand what works and what doesn't. The new cycle can be continuously improved based on new knowledge.

This intensive risk management activity is only for the minority of drugs. With any risk management plan, it is important to pay attention to making sure the plan is evidence-

based. Targeted intervention works more efficiently than the old shotgun approach. Industry must try more than one thing, educate to change behavior, and not just try to control people. We must measure trends rather than just the end point, monitor continuously instead of every so often, and really understand what the risk management plan is illustrating.

In summary, the goal of industry is to work with FDA to ensure that safe medicines reach the public. Both must ensure that evaluations and decisions concerning individual drugs are made on a scientific basis. Industry must focus more on ways to design good risk management plans, to choose the right tools, to build in accurate measurements from the start, and to evaluate continuously to ensure quality results.

Agency adoption of the Steering Committee's newly developed framework. We are now establishing organizational structures to coordinate these efforts within the Agency, creating the embryo of a quality systems organization. Our hope is to develop a plan for broad, internal implementation of quality systems within FDA.

In 2003, FDA administrative functions that were decentralized years ago were consolidated under a shared services organization in the Office of the Commissioner. As they become better organized, they can plan quality system implementation within that organization.

As we put forth a conceptual model for a quality system of a science-based regulatory agency, some at FDA felt that quality systems don't apply to us but serve only for the manufacturing process. They said, "We make policy; we don't make sausages!" But, for the public good, our processes must be efficient, consistent, and uniform. Once we receive a legal mandate, we need a process to develop policy in conjunction with good guidance practices, as we have been doing over the past decade.

Our Agency activities now have much better transparency. We make procedures for our Advisory Committees available to the public. We explain how we elicit input and how we deal with the GMPs and other standards. Understand that policy development is a process with both input and output: it is important to manage the quality of the process. We also need a rigorous, consistent science management process, insuring that science informs our policy development. As policy-making involves values and judgments, science should feed into policy but not create it. Quality systems are always important in the execution of the program but evaluating them with science management and policy development are equally important. We will focus attention on proper program execution, evaluating such things as consistency of action. Just as manufacturing plants have various subsystems, each with a quality system, FDA has various processes using uniform quality systems within the regulatory framework. This is our goal at FDA.

As program benefits derive from successful subsystem implementations, we must help FDA staff to understand how quality systems can create a smoothly running Agency. True payoffs occur as we perform customer analyses and understand the kind of work product and process brought by successful quality systems. In the past, FDA has suffered from lack of focus on the internal customers for each unit and their needs. Certain processes fell through the cracks due to chasms between various units. Quality systems ensure that all processes are preserved and that the work momentum carries over to the next unit.

This carryover throughout the Agency is extremely important in our regulatory work. Many within the Center for Drugs complain that timeliness is our only concern. It is not. If an organization is only focused on measuring one thing, the signal it sends to employees is that only one thing is important. We can change this skewed perspective by developing additional and meaningful metrics regarding our processes and products. Using quality systems, we gain better cross-organizational flow and achieve clearly unified goals.

Change management must be addressed as we put quality systems into place across all units of the Agency. This may be difficult, since federal agencies may change direction

as they convey the message to the whole organization. Priorities shift as administrations shift, and FDA must have systems in place to evaluate the ongoing work. Unit managers can better understand performance in their sub-areas when quality systems are in place. As the system comes under better control, the goal of an effective organization emerges: bringing the best possible products to our customers efficiently. As a result, industry and other stakeholders also experience better consistency and transparency of standards. These changes indicate positive trends within the Agency.

FDA lacks resources for the wholesale implementation of our quality regulation program. However, with cross-system efforts, funding for initial implementation is feasible in some areas. The GMP Steering Committee carefully selects sub-areas in which to implement a quality system, such as the Process Analytical Technology Program (PAT). We are establishing the Pharmaceutical Inspectorate within FDA over the next several years. Another cross-center initiative is the Team Biologics effort. Positive results from these improvements can provide impetus for broader implementation across FDA.

The Medical Technology Innovation Initiative is committed to using quality system approaches in reviewing new drugs. We expect substantial changes when the New Drug Review Program moves to the FDA's White Oak campus, bringing together the program for the first time in more than a decade. Since FDA lacks resources for a complete quality system in the New Drug Review process, wholesale implementation cannot occur immediately. But specific projects are being developed as part of the PDUFA-specified performance enhancement. Since some PDUFA monies were set aside for FDA to assess and improve performance of the review process, we can begin to implement the quality system, as performance enhancement is really the same as having good quality management. We have begun to ensure accountability in areas such as process mapping and identifying standards/best practices within the review process. Our Quality Assurance Unit conducts audits of work outputs and produces baseline reports recommending changes. FDA staff members are proposing projects for the summer of 2004 in all discipline areas, not the New Drug Program alone. Though our resources are limited, we are seeing a good deal of positive innovation from this quality management program.

In approaching external quality systems, the FDA focuses on the expectations that the regulator has for industry versus those for ourselves. Evaluation of GMP regulations is advancing with input from quality science. Through various forums as well as from ICH, we've heard a wide range of suggestions regarding the direction FDA should take. Some say we should scrap the regulations or use HACCP (Hazard Analysis and Critical Control Point) or ISO (International Organization for Standardization). Others feel we should have device-like regulations or harmonize with the Europeans. We must recognize that, in the current federal environment, changing regulations is not easy, fast, or even sometimes achievable. It can take eight years or more to change regulations. However, the current GMP regulations are broad and flexible. Within this context, we can look at current disparities and desirable directions.

Another important issue is international harmonization. It is difficult to justify competing regulatory requirements or differing interpretations of the same requirement for a single manufacturing facility. If the goal for all is a safe and effective product, why would dif-

from clinical investigators from all over. And I have personally received literally thousands of e-mails from individual Americans who have sent me their views about safety. Overridingly, American society (not industry) does not believe it credible that industry support for safety work at FDA has an arbitrary cut-off under PDUFA in the peri-approval period and does not include post-approval. As we know, product safety is a concern of industry and FDA throughout the life-cycle of a product, and to have an arbitrary cut-off, saying industry only supports safety evaluation by FDA up to point X, is just not credible to the public.

When we meet with the public, people also often express the opinion that the PDUFA program is skewed towards approval. There is a widespread misconception that user fees go towards getting drugs approved, not towards getting drugs reviewed. Many people believe there is some sort of *quid pro quo* between FDA and industry. As we negotiate PDUFA IV with industry, we need to ensure that, in the end, members of Congress, the medical profession, academic medicine, the payers, and all the public watching so carefully understand that PDUFA is solving some of the safety issues people are so worried about — that PDUFA is *not* part of the problem. That perception is out there. We must be able to ensure that the renegotiation process and final deal are part of the solution.

Hot Topic—Generic Drugs

All of you recognize that payers, Congress, and members of the healthcare profession see FDA's generic drug review program as an important part of controlling healthcare costs in the United States. Although more and more generic drug applications are being approved, the workload for Gary Buehler, Director of the Office of Generic Drugs — who is here today — and his staff and other parts of CDER involved in generic drug review is really outpacing available resources. Because this has happened over the same period of time when PDUFA funding has been increasing, some people on the outside see this as a conspiracy. They see all the resources going into new drugs while funding of the generic program has not kept pace with the increased workload. This is a problem for FDA and Congress that must be addressed. It affects the credibility of all FDA-industry interactions. It is critical that we find a solution to the generic drug review process soon.

Drug Safety—Broad Overview

Dr. Seligman has been the lead in our postmarketing safety efforts for the past few years, and he will address this later today, so I'm going to give only a broad overview. I've been very involved with drug safety. The FDA has been at the forefront of new efforts to address drug safety for the last couple of years. In 2004 FDA asked the Institute of Medicine (IOM) to do an assessment of our drug safety program. The assessment has been a big resource commitment, but we hope the results will come out this summer.[1]

Let me very briefly summarize some of the other actions we have taken during the last two years:

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[1] The IOM results were issued Fall 2006. On January 30, 2007, the Agency issued a report on the IOM recommendations, describing FDA's commitment to those recommendations and to continuing to strengthen its drug safety program.

progress in this area and discuss the challenges we still face.[4] We hope to seek additional stakeholder input on what problems you are having with the policies we have already put in place and how can we work more effectively with you as challenges evolve.

Critical Path Initiative

As we all know, there is an urgent need to modernize the medical product development sciences, which is what the Critical Path Initiative is all about. We have just published our opportunities list, containing many of the suggestions we received from FDA staff and from industry, academia, patient groups, and others. There are almost eighty specific projects listed, organized into six key topic areas:[5]

- Better Evaluation Tools
- Streamlining Clinical Trials
- Harnessing Bioinformatics
- Moving Manufacturing into the 21st Century
- Developing Products to Address Urgent Public Health Needs
- Specific At-Risk Populations — Pediatrics

New tools will help us overcome some of the development challenges we face, such as why are drugs still failing? And why do we get to the end of the evaluation and development cycle and find we're unable to approve a product?

These challenges often have to do with the evaluation tools we are still using and our inability to predict safety and effectiveness early in the development process. Because of these uncertainties, clinical trials are becoming more and more expensive, gobbling up a larger part of development dollars. Improving our development sciences will help streamline clinical trials as will planning and executing smarter trials, such as active controlled trials and those using enrichment designs.

The bioinformatics world is changing our review process from paper to electronic format. We are now receiving information electronically, managing it electronically, and communicating with the public electronically.[6] This is part of a larger federal standards-setting and automation initiative that will significantly improve our ability to communicate health information across systems efficiently and effectively.

We also have urgent research needs in counter-terrorism and to help us treat potentially emerging infectious diseases. We need better ways to identify pathogens and design

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[4] The *Pharmaceutical Quality Initiatives* workshop is February 28 - March 2, 2007, Bethesda North Marriott Hotel and Conference Center, Bethesda, Maryland, co-sponsored by FDA, AAPS, and ISPE.

[5] In December 2006, FDA posted a list of Critical Path activities that are underway with FDA participation. FDA was a key catalyst in organizing (or is directly involved with) more than thirty specific activities.

[6] At a December 2006, Part 15 hearing, FDA solicited public input on plans to amend its regulations to eventually require all submissions to be made electronically.

FDA and Industry Today: Update from Industry on Current Trends and Concerns

D. Bruce Burlington, MD
Executive Vice President
Business Practices and Compliance
Wyeth

I hope my presentation complements Steve Galson's, but since I've been involved with the PDUFA negotiations with PhRMA, I'll be covering some aspects from a different perspective. I will focus on:

- Public perceptions and how the reputation of the innovator pharmaceutical industry has changed from being one of the most admired sectors in America. It's not where we should be, so what are we going to do about it?
- Risk management and a better understanding of drug benefits;
- Post-marketing commitments which are part of the public dialogue about the reputation of the industry;
- Biosimilar product approval which is also related to how the public sees the industry;
- What to expect from PDUFA.

What is our reputation? Consumers in America cannot believe the current cost of drugs. They're unhappy about it and are not willing to pay the prices. They think of this not only as industry's issue but also that FDA is part of the process and problem. And, particularly, they think that when FDA and industry fight the importation of drugs from other developed countries such as Canada that they are being denied access to drugs, which are just as good as American products. They don't understand why the industry and Agency take a position against imports.

Another issue we must contend with is that American consumers are offended by TV Direct-to-Consumer advertisements. They don't distinguish between innovator industry drug ads and those they see or hear on the radio for dietary supplements. Almost daily or weekly they read in the paper about liability trials for pharmaceutical products. The prevailing theme of plaintiff's bar is that the industry has acted in a greedy and perfidious way, which is interpreted by the public as meaning that companies are more concerned about profits than about patients. Members of industry don't believe that for a minute. While we are in business and recognize the need to make a return for our shareholders, we are very focused on concern for the patients taking our drugs. But that's not what is seen out there.

State attorneys- and inspectors-general also repeatedly bring lawsuits against the industry, again convincing the American public that there is something deeply wrong with it. When they see the business reports of record industry profits, they doubt our motivations. And then there is this issue of User Fees. When they see that more than half of the drug

More importantly is the big issue with public perception of safety, such as the fall-out from the *Vioxx* incident. It's a huge concern. Even FDA recognizes that concerns with safety could slow the Critical Path Initiative. There are some people who believe the FDA has failed in doing its duty. While I don't think most of the public believes that, there are people in powerful places who do. There are also issues involving intellectual property, which may seem unrelated to Regulatory Affairs and Critical Path, but, as I'll soon discuss, a part of the Food and Drug Act talks about product/data exclusivity and runs parallel with patents and is very important in terms of fostering innovation.

Critical Path is not the only topic that I plan to address today. There are actually three parts to the "puzzle" that I mentioned in the title to this speech. Here is a quote from a 500-page report published by the National Academy of Sciences in January 2006 dealing with technology and innovation in our country, including the pharmaceutical industry: *"There is no single formula for innovation. There is instead a multi-component environment that collectively encourages or discourages innovation."*

In her speech, Dr. Shirley Murphy defined Critical Path, but I think FDA is being much too modest. I look at the Critical Path at FDA as being their night job. Their day job is that they have applications to review. As much as industry wants to support the Critical Path, they want their applications reviewed on time. And, CDER, particularly, has User Fee deadlines that must be met, since they are evaluated by their completion, both individually during Personnel Performances and also by Congress. They have to put out a report to Congress every year, so they must meet those needs. They must also address Congressional questions arising about drug safety, which include an unending number of hearings that are enormously time-consuming. PDUFA IV also demands that key people at the Center such as Dr. Jenkins must spearhead their negotiations with the pharmaceutical industry, which also takes a lot of time. Shirley also mentioned about getting companies to share information. When this started two years ago, it was a bigger deal. Industry felt it just wasn't going to happen, since the industry has a very long history of keeping trade secrets. Under the capitalist system, when you discover something, you certainly don't give it away, if you don't have to. Dr. Woodcock has been particularly successful at telling industry that there must be pre-competitive areas, where information can be shared, because if it isn't, industry will never get out of this thing. The industry is often complaining that FDA does not use enough surrogate end points, does not use biomarkers, etc. When I worked at FDA, I always thought it was strange that industry would think FDA has the resources, money or time, to do this. Dr. Woodcock has said, there is no one person who is responsible for biomarkers. There is no one place you go to get your biomarker validated and used in a clinical trial. It's a problem facing industry, NIH, and FDA.

Shirley went over the milestones. I would say of the many things in the Critical Path report that just came out, which industry is very happy to see, are the seventy-six projects that are broken into a number of categories. Clearly the development of biomarkers and clinical trial design are at the top of the industry's list. That's my perception. For this talk I didn't go to the pharmaceutical trade association and ask, "Does everyone agree with this?" This is mostly my perception and the perception of some of my colleagues at Abbott, plus what I picked up from talking to other pharmaceutical companies.

be squeaky-clean safe, before FDA is willing to approve it. Whereas with lung cancer, there are very few options, so a greater degree of risk would be tolerated to get the product on the market, if it promised some degree of benefit to the patient population.

Wrapping up the second part of the component, we feel ("we" being myself and others at Abbott) it would help if CDER adopted a more structured and transparent approach to drug assessment, which needs to be one that permits discussion on what the methodology is, which primarily FDA is in a position to discuss. It should allow comparison of new drugs with existing therapies. Perhaps PhRMA and BIO need to assume a role in this, just as they need to educate patients about benefit-risk and create better tools at least for patient education, if not for the mass public. This would avoid the extreme statements that FDA is too slow in approving drugs or FDA is reckless in approving, and some of the drugs that come out are unsafe.

The last piece of the puzzle is what I call new regulatory, intellectual property, and liability pathways. Those things are not necessarily in the purview of FDA (some parts are), but they do influence innovation. I perceive this as a business problem, more than an FDA or societal one. What happens in industry — this is based on reading a number of articles — is that the regulatory pathway is not entirely clear; there can be a tendency to push companies to go after compounds and markets which have already been studied. In similar compounds the profits may not be as great, but the regulatory requirements are clearer, so the prospect of approval is better. Compare that to going into some highly unmet medical need area where the regulatory pathway is ill defined. Safety issues can kill it before it even gets to FDA. So there will be a reluctance to start a clinical program. It's not one way or the other. Companies do both. I think there is pressure for companies who have to answer to shareholders to look at incremental innovation, instead of quantum innovation, which is what we need.

One way of approaching this is to develop a predefined list of high-priority diseases that have unmet needs, and then to focus on them, significantly modifying the requirements for the clinical trials. This is not new. Dr. Ray Woosley, head of the Critical Path Institute in Tucson, published an article in January 2005 with somewhat similar ideas of getting products to market on a sort of gradual roll-out, avoiding a situation of having multiple adverse events. This might require fewer patients in clinical trials. By looking for strong signals through Phase II and giving greater focus to biomarkers that show activity, and, then based on that, an agreed upon threshold for efficacy and safety, drug companies might be granted a provisional approval which would foster getting these drugs to patients who really need them. FDA does have mechanisms in place already (Subpart H) that allow patients to get access to medications under development by allowing approval of drugs with surrogate end points. But as you know, it's tough to come up with surrogate end points. Something like this would be potentially much easier to administer and make it easier on patients and physicians. I'll continue this thought in a minute.

The U.S. Food and Drug Act allows five years marketing exclusivity for a new chemical entity. When I was working in FDA generic drug program, I thought that was plenty long. I've now come to decide that the ten-year European approach is much better. Under the five-year exclusivity, a product comes out, usually has one indication, and if the

Fast Track status, even though adrenal insufficiency is itself a very serious condition. Similarly a condition like urinary tract infection in and of itself is generally not a serious, life-threatening medical condition. But if you develop *urosepsis* or renal failure from chronic urinary tract infections, those outcomes are clearly serious, so a product that affected those outcomes might get Fast Track designation.

Clinical development programs must be designed to seek improved clinical outcomes for serious manifestations or sequelae of the treated condition. The Fast Track guidance specifically states that this is not limited to therapeutic products *per se*: it could also include diagnostic or preventive agents. Again, the goal is better treating or minimizing the likelihood of serious outcomes in patients.

Fast Track is a designation given in the context of having an IND. To have an IND, inherently you have to be talking clinical studies, so you would not be able to get a Fast Track designation before you have an IND. The earliest you could have a Fast Track designation would be when you have an IND. It can be based on promising pre-clinical science that suggests your product may be useful, even though you have zero clinical data. But, again, the argument can be made at any point in the clinical development process, and the Fast Track designation can be granted at any point. Operationally it doesn't make sense to look for it at the very end, but it is available at any time at or after the initiation of IND, if you can make the case. That gets you into consideration for the CMA Pilot Programs.

The CMA I Program is the rolling submission. That's when the program is nearly done, and it's just a matter of getting the marketing submission in and reviewed as efficiently as possible. The CMA II Program is done typically after the Fast Track designation has occurred. If you look at the guidance, it pertains typically at an end-of-Phase I Meeting, so it's not at the start (when clinical studies have not yet been performed). You do need to have some clinical data to support your CMA II application. The guidance does contemplate that that could happen earlier: for example, if you have non-U.S. clinical data to provide support for going for a CMA II application.

Just to reiterate, there's a guidance on the CMA I program on the FDA website: Fast Track Products. Generally it includes products that have been subject to an end-of-Phase II or pre-NDA/BLA meeting. Initial NDAs and BLAs are eligible. Re-submissions are not. CMA I guidance provides for submission of reviewable units, up to four. Traditionally people would think of doing a CMC submission and a pre-clinical science submission and then a clinical safety and efficacy submission as separate, reviewable units. That's again subject to agreement between the sponsor and the FDA. Then there's a discipline review letter for each reviewable unit, and the final decision comes after review of the final reviewable unit, and that's when the setting of the PDUFA date kicks in, when the final piece of the application has been submitted. The program provides for this pilot to be in effect through September 2007 with evaluation of the value, cost, and effectiveness after initial experience.

CMA II includes Fast Track products only. Here the guidance says these are products that have been the subject of an end-of-Phase I meeting or equivalent. You do not have to be at the end of Phase I based on U.S. data, if you have other ex-U.S. data that will provide the same kind of information. The applicant is required to specify two things: 1) The

Steering Committee

QA/RA Steering Committee

Industry Representatives

D. Bruce Burlington, MD
Executive Vice President
Business Practices and Compliance
Wyeth

Alexander R. Giaquinto, PhD
Vice President & Regulatory Advisor
Tunnell Consulting, LLC
and
President
ARG Consulting LLC
(Former Senior Vice President, Regulatory Affairs, Schering-Plough Corporation)

Peter Honig, MD, MPH
Executive Vice President of Worldwide Regulatory Affairs and Product Safety
Merck Research Laboratories

Mathias Hukkelhoven, PhD
Senior Vice President
Global Head, Drug Regulatory Affairs
Novartis Pharmaceutical

Clare Kahn, PhD
Vice President
U.S. Regulatory Affairs
Cardiovascular Metabolic
GlaxoSmithKline

Thomas J. Kirsch, MS
Former Vice President Global Research & Development, Quality Assurance
Johnson & Johnson Pharmaceutical Research & Development, LLC

Christopher Kowtna, MS, MBA
Associate Director
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, LLC

Joseph Lamendola, PhD
Vice President
Global Regulatory Sciences
Bristol-Myers Squibb Company

Tobias Massa, PhD
Vice President
Global Regulatory Sciences-CMC
Bristol-Myers Squibb Company

Susan Galle, MS
Senior Director & Head of Regulatory Affairs
Zelos Therapeutics

Kevin Malobisky, MS
Director, Drug Regulatory Affairs
Sanofi-Aventis

Jonathon Parker, RPh, MS
Director
Worldwide Regulatory Strategy
Pfizer Global Research & Development

Douglas Sporn
Divisional Vice President
Regulatory Intelligence/FDA Liaison Office
Global Pharmaceutical Regulatory Affairs
Abbott

Roy Sturgeon, PhD
Executive Vice President
Lachman Consultant Services

Annette Stemhagen, DrPH, FISPE
Vice President
Epidemiology & Risk Management
United BioSource Corporation

Christine Blumhardt, PharmD
Consultant

Temple University School of Pharmacy Representatives

Michael Borenstein, PhD
Associate Dean

Daniel J. Canney, PhD
Director, Graduate Studies

Peter H. Doukas, PhD
Dean

Wendy Lebing, MALD, MS
Assistant Dean
QA/RA Graduate Program

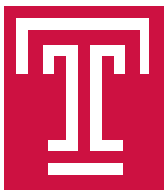
FDAAA Scholarship

The QA/RA Program extends its deep appreciation to the Food and Drug Administration Alumni Association (FDAAA) for establishing the FDAAA Centennial Scholarship Endowment in 2006.

To commemorate the 100th anniversary of the Pure Food and Drugs Act, the FDAAA established a scholarship fund to encourage academic training in regulatory and quality issues. After reviewing graduate programs of schools nationwide, the FDAAA selected the Quality Assurance/Regulatory Affairs Graduate Program of Temple University's School of Pharmacy as the recipient of the endowment. The QA/RA program is deeply honored to receive this prestigious award.

The FDAAA Centennial Scholarship Award is open to current and new students in Temple's QA/RA graduate program who are not eligible for tuition reimbursement at their organization. The scholarship is awarded every fall on the basis of financial need and academic merit.

Created in 2000, the FDAAA is a non-profit volunteer service organization whose mission is to educate the public about the ever-expanding public health mission of the federal Food and Drug Administration. Members are former Agency employees who continue to use their specialized technical, scientific, and institutional knowledge to perform public service related to the FDA.



Quality Assurance/Regulatory Affairs Graduate Program
Temple University School of Pharmacy
425 Commerce Drive, Suite 175
Fort Washington, PA 19034-2713

267.468.8560
www.temple.edu/pharmacy_QARA