Evaluation of Biological Product Safety Throughout the Lifecycle at FDA's Center for Biologics Evaluation and Research

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In this presentation, safety surveillance for biological products throughout their lifecycle will be described. This safety monitoring is comprehensive and pertains to products as they are used for approved indications as well as for other diseases or even risks from overdoses or drug abuse.

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Let's begin with a look at the overall lifecycle of a product, beginning well before a product is licensed. This lifecycle consists of successive pre-licensure trial stages, followed by approval, and finally the post-licensure safety surveillance stage. The FDA, along with the sponsor, is monitoring safety at all of these phases. As needed, risk management strategies, or what are now called REMS - risk evaluation and mitigation strategies - are developed to control certain identified risks. Safety surveillance of a product is a comprehensive process across this lifecycle.

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Let's go through the goals and principles of the safety surveillance at the Center for biologics evaluation and research, known as CBER, what biological products are covered, and the methods and approaches utilized. As presented in other portions of this program, the licensed biologicals at CBER include vaccines, blood, and blood products.

CBER also regulates tissue and cell products, many of which are not subject to licensure or have not yet been licensed. Tissues as a class of product are regulated under different legislation. CBER still monitors their safety, but with special focus on infectious risks.

A variety of resources and mechanisms are used to monitor safety, but a principal one is passive safety surveillance: Anecdotal case reports of suspected side effects are received by FDA from the public, from doctors, patients or their parents, pharmacists, nurses, neighbors, grandmothers, and anyone else who cares to submit a report. Active analysis of external databases is now increasingly being used in addition to this passive surveillance system. Some examples of both approaches will be shown.

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CBER assures the safety and efficacy of these listed, licensed, or otherwise regulated products, which include preventive, diagnostic, and therapeutic products; if and when successful licensure occurs in the future, CBER will also manage gene therapies.

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There are differences and similarities between biologicals and drugs, and for the purposes of safety surveillance both the differences and the similarities are important. Biologicals have traditionally been prophylactic. Think about vaccine products to prevent common diseases. These biologicals are given to people who are healthy to prevent the future threat of a target disease. Often vaccines are given to a very large fraction of the population. Therefore, in contrast to many therapeutic drug products, a very high benefit-to-risk ratio is required. Drugs are typically therapeutic, given to people often who are already sick. Think about chemotherapy for a cancer treatment, for example. Substantial serious drug side effect risks are often clinically acceptable in the context of the anticipated therapeutic benefits.

But this distinction between biologicals and drugs is not hard and fast. While most vaccines are still preventive and require exceptional benefit-risk ratios, as one counterexample, there is the BCG vaccine originally licensed to prevent tuberculosis, but which can now also be used therapeutically for bladder cancer. Substantial morbidity from side effects of BCG when used this way as a therapeutic agent are considered acceptable in the context of the target disease, bladder cancer, against which BCG can stimulate an immunologic response.

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Post-licensure safety surveillance for biologicals and drugs share similar philosophies, but there are more variables for biological products than typically for small molecule, chemically well-defined, drug products. An important reason is that biologicals are produced in ways that have more vulnerability to variations between batches or "lots."

After licensure, the regulations that are specific to biologics require that the sponsor submit details about the testing of each individual lot to CBER for approval before the manufacturer can begin to distribute that lot. This lot release procedure or protocol has exceptions: The manufacturers can get a waiver so that they may only submit data and not actual specimens for independent testing by CBER, a waiver which can be revoked if concerns arise.

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Now, what are the limitations of safety data before licensure when all one knows about the product is from the clinical trials? Pre-licensure clinical trials are primarily sized and designed to demonstrate efficacy of the new product against a particular target disease. It is efficacy that is the primary hypothesis that drives the sample size calculations. A lot of factors limit one's confidence in the safety findings from these trials. Among others, the sample sizes are often too small and the observation periods typically much too short to provide confidence that all important side effects will be detected.

Other factors also constrain confidence in safety findings from these clinical trials prior to licensure. Enrollment exclusions often are more stringent than the prescribing controls after licensure. Consequently, one can't generalize the results to a larger population. You may exclude from a clinical trial, for example, a patient who is already on a certain drug or simultaneously has another disease. So a variety of factors mean that a much larger and more diverse population is going to receive the product after licensure. These considerations refer to drugs as well as biologicals.

Another consideration is that CBER undertakes numerous comparisons of the clinical trial data for safety observations during its evaluation of a licensure application. In so doing, CBER is not just looking at the hypothesis of efficacy. Instead, CBER really examines whether any of hundreds or thousands of possible adverse events has occurred more often in the treated group than in the placebo group. It is not unexpected in these comparisons to see apparently significant results by chance alone in some small subset. And, of course all of these comparisons of the clinical trial data for safety observations are post hoc. These factors limit the inferences that one can draw and mean that the findings from clinical trials have to be viewed as provisional. So the absence of risks from a clinical trial is not definitive, and the identification of an apparently increased risk in the test group often has to be viewed as tentative until corroborated with independent data.

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There are some notable historical examples that argue the case for product safety surveillance. These episodes go back over a century.

In 1901, contaminated diphtheria antitoxin killed 13 people with tetanus.

A half century later, in what is known as "the Cutter incident," many patients contracted infections and developed paralytic polio from poorly inactivated virus during vaccine production. Seven different lots were involved.

As recently as 1996, there was an episode in the U.S. involving human serum albumin that had already completed manufacturing and had met all of its quality control criteria. As it was being shipped out, pallets of the product packaged in glass vials were dropped by a forklift operator. No one's standard operating procedure had a provision for forklift operator mishaps. This was an unanticipated complication. Many of the vials broke, as evidenced by a lot of broken glass, but some of the vials looked good. So the personnel in this shipping department hosed off the material to salvage the good vials.
They did not anticipate what in fact occurred, that some of the apparently intact vials had non-apparent cracks. Rinsing with non-sterile hose water introduced the bacteria Enterobacter cloacae, and thereby contaminated at least one lot.

This came to the FDA's attention because a patient developed bacterial sepsis

with shaking chills during the infusion. It was a spontaneous report that brought our attention to this very important matter.

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So safety surveillance is essential despite the fact that CBER imposes very stringent quality controls in the manufacturing of biological products. CBER has to be alert for any surprises in the area of safety after licensure.

In this process, CBER strives to monitor safety comprehensively. CBER does not limit its concern to the use of a product for the purpose as described in its license.

That is, once a product is licensed for one indication, physicians may use it for other indications, and this is considered the legitimate practice of medicine. This use is known as "off-label use." Think about cancer. The approval of a product to treat cancer is often for a specific malignancy, but oncologists have a very strong track record of systematically evaluating the usefulness of new products for related and other malignancies. The results of this clinical evaluation and use do not come to the FDA for approval. So when safety findings emerge from off-label uses, FDA pays the same kind of attention to them as with the use of products for the labeled indications in its comprehensive approach to safety surveillance.

Let's take a moment to clarify some terms. Notice the word "off-label." The "label" refers to the professional package insert, the leaflet that accompanies most medication vials, not the sticker on the vial. In pharmaco-epidemiology, a "labeled" adverse event refers to a definite or possible side effect that appears on the label. This could be listed in the package insert's adverse events section or perhaps in a warning or other safety-related section. In contrast, an "unlabeled" adverse event is a potentially new risk, a possible side effect that is not included in the package insert.

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What are CBER's roles and goals in this kind of safety surveillance?

CBER works with manufacturers to evaluate the need for pharmacovigilance plans, the Phase 4 studies. CBER often assists with the design of the studies, and then later reviews the results from these studies. But most additions to safety data after licensure are from spontaneous reports.

CBER has several specific objectives for safety surveillance. To detect new risks, that is, something entirely unanticipated, such as a medication error with a mix-up between two products that nobody realized might confuse people.
And to discover new or additional information about previously known risks, such as a greater incidence rate or a higher degree of medical severity or specificity than previously appreciated. CBER watches for potential transmission of infections, particularly for tissue products.

CBER is also looking for pertinent pre-existing conditions that might represent risk factors that could guide future prescribing for safer use of these products. And, of course, CBER monitors for patterns of adverse events by production lot.

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CBER has three safety teams which are interdisciplinary, inter-office communication groups.
They facilitate coordination among the offices of:

- Biostatistics and Epidemiology
- Compliance and Biologics Quality
- Communication Outreach and Development, and the
- Center Director's office;

With the pertinent review office from the:

- Office of Blood Research and Review or
- Vaccine Research and Review or
- Cellular, Tissue and Gene Therapies.

All of these offices have representatives on the teams. Team representatives get together regularly to compare notes. Epidemiologists from OBE often participate in these safety team efforts and other ad hoc work groups.

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For pharmaco-epidemiologists, passive safety surveillance is our bread and butter but it has both strengths and limitations. Case reports of adverse events that are submitted to one of several FDA systems can be viewed as "open-ended"; that is, they offer the potential to learn about any kind of risk, not just concerns or issues previously suspected. They can let one discover new or rare side effects. They can be timely. They have a great deal of geographic diversity.

But there are limitations. It is common to see missing and inaccurate data, under-reporting, and absence of control or comparison groups and denominators. CBER often doesn't know how many people were exposed to a particular product lot when first looking at new case reports. In general, causation cannot be inferred from these suspected side effect reports, although there are exceptions. And, of course, there's a very low likelihood that a long latency adverse event would culminate in a spontaneous report. For example, a late malignancy, years after exposure to a drug, probably would not arouse suspicion or concern on the part of the patient or the physician and lead to submission of an adverse event

report.

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Let's look now at safety surveillance specific to vaccine products.

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CBER has an integrated approach to post-licensure vaccine safety monitoring. This includes using a variety of tools, including pharmacovigilance plans, the Vaccine Adverse Event Reporting system, which is a passive surveillance system known as VAERS, and the Vaccine Safety Datalink, a collaborative effort with the CDC, and other research tools.

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First, the "pharmacovigilance plan", in its current form, is a product of the ICH process.

ICH is the International Conference on Harmonisation, a long-standing initiative to harmonize regulatory guidance between Japan, Europe and the US, as well as other parties. Once harmonized, an ICH guideline becomes an FDA guidance. FDA implemented the ICH E2E Pharmacovigilance Planning guideline in April of 2005.

The pharmacovigilance plan discussed in this guidance can be submitted with a biologics license application or BLA. If the sponsor does not do so, the Center may choose to communicate that a pharmacovigilance plan would be useful, with a description of where the sponsor can read about the format for these plans.

The pharmacovigilance plan is now commonly the basis for Phase 4 studies. It attempts to include important identified risks, potential risks, and key missing information. The manufacturers are supposed to consider actions designed to address any of these concerns. This format gives OBE a basis to engage in constructive discussion with the reviewers in the product review offices, as well as with the sponsors of new product applications.

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CBER also monitors vaccine safety through the Vaccine Adverse Event Reporting System. VAERS was created by the National Childhood Vaccine Injury Act of 1986, or NCVIA.

In those days, some vaccine manufacturers were dropping out of vaccine production because of lawsuits associated with vaccine associated adverse events. It was increasingly no longer financially viable for them to continue producing vaccines. The NCVIA established a form of no-fault insurance system to reduce the manufacturers' vulnerability.

VAERS centralizes surveillance for safety by accepting reports of adverse events

or suspected side effects from any party for any adverse event after any vaccine. VAERS does this even though only a subset of vaccines requires adverse event reports and even then only under certain circumstances.

The Health Resources and Services Administration or HRSA, is one of FDA's sister Public Health Service agencies in the U.S. HRSA administers most of the NCVIA program, particularly its Division of Vaccine Injury Compensation. If a person has a side effect to a vaccine, the concept is that the person deserves compensation, because he or she accepted vaccination on behalf not only of himself, but also of the larger society. There is a set of vaccines and recognized possible adverse events linked to those vaccines that are contained in what is known as the Reportable Events Table. This table is published and periodically updated. If a physician sees a patient with one of these specified adverse events, in principle, the physician must report that adverse event to VAERS. In practice, there is no enforcement mechanism. Therefore, we generally interpret the reports to VAERS as fundamentally spontaneous adverse events, though in principle there is a subset of them that are stimulated by this legal compulsion. Think about vaccine-associated paralytic poliomyelitis. The oral polio vaccine is a live virus product which very rarely does provoke polio disease in the recipient or immunosuppressed contacts of that recipient. It's a good example where causality is well established. It's possible to clarify that a given patient with polio really does have the vaccine strain of virus causing the illness, and thus likely able to succeed in making a claim for injury compensation.

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And research is conducted. A major resource for such research is the vaccine safety datalink or VSD. The VSD is built upon a contractual arrangement between CDC and several health maintenance organizations to provide access to their enrollment and pharmacy and hospital discharge diagnosis and other data systems.

The primary purpose is to allow vaccine safety hypothesis testing studies, including, in recent years, methodologic adaptations for the proactive "rapid cycle analyses." In rapid cycle analyses you are looking proactively at a small number of predefined potential risks, such as Guillain Barré syndrome with influenza vaccines. The CDC conducts such rapid cycle analyses often in collaboration with CBER.

In addition to these collaborative studies with CDC, CBER also refines and tests hypotheses that emerge from the spontaneous reports, and develops external data systems to refine signals and, selectively, to test hypotheses.

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Here are a few examples of recent vaccine safety issues investigated by CBER with weblinks where you can learn more specific information concerning them. It is important to highlight the fact that CBER provides such information in an

open way.

CBER is committed to transparency in its vaccine safety communications to the public and healthcare providers, because it is paramount that they maintain their confidence in the safety of vaccines.

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A bit more on our vaccine safety communications. FDA employs a range of modalities and settings for such communications in addition to the kind of information referenced in the last slide. They include printed formats, particularly labeling revisions, changes in the professional package insert, letters to health care providers, articles in the Morbidity and Mortality Weekly Report,or MMWR, which is issued by the CDC, and other medical literature. FDA can also use the internet, as when it posts a Public Health Notification on its web site. And FDA talks to the public with presentations at various conferences, advisory committee meetings, and meetings or conference calls with vaccine manufacturers.

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Let's focus now on the class of blood and blood products. Blood is complicated in the United States. You will appreciate in a moment that we have a matrix of systems to make sure that blood collection is safe for the donor and that the resulting transfused or derivative products are safe for the recipients.
In some ways, the situation is much more complex than vaccine manufacturing and monitoring.

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How do we assure the safety of blood and blood products? The regulation of blood and blood-related products is covered in detail in a separate presentation so the focus here will be on surveillance generally and associated reporting systems. As just noted, the safety assurance for blood, blood products, donors and recipients involves multiple interconnected and overlapping domains and systems. There is a reporting system for deaths which will be discussed in a moment, another reporting system for "biological product deviations" -- previously known as "errors and accidents" --, a reporting system for adverse events in product recipients, and a reporting system for medical errors.

There is another system for device malfunctions. CBER regulates blood related devices, including test kits to screen donors and products for infectious diseases, equipment and software for plasmapheresis and whole blood collection, and anticoagulant bags and tubing for storage of blood components. So, you can see it's not a simple situation.

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Blood safety reporting has mandatory and voluntary elements. Mandatory reporting is by the blood manufacturers. Manufacturers have to report to CBER immediately when a complication of blood donation or transfusion is confirmed to

be fatal. And then they have to file a follow-up report within seven days. Required reporting for product failures include biological product deviation reports to CBER and device problem reports that come to a similar system at CDRH, the FDA's Center for Devices and Radiological Health. As of the date of this presentation in 2011, manufacturers of blood and blood components do not have to report non-fatal adverse events.

Voluntary reports of adverse events come to AERS and VAERS. The FDA's Adverse Event Reporting System, or AERS, is the counterpart to the Vaccine Adverse Event Reporting System. Both of these systems accept reports from any source. Medical errors are mainly reported through the hospital system rather than to FDA. The CDC operates a National Nosocomial Infections Surveillance system, the NNIS, which has become part of a broader National Healthcare Safety Network, or NHSN, which in recent years added a hemovigilance component for hospital reporting to CDC about various blood-related incidents and adverse events.

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Let's turn now to human tissue and cell products.

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Again, other presentations in this program address the regulatory framework for human tissue and cell products in detail, but this safety surveillance discussion will note that their regulatory framework differs. It is a tiered risk approach that begins with the foundation of FDA's authority to prevent the transmission of infectious diseases. Tissue allograft products are not licensed. The primary focus on allograft-attributable infections is on the risk of a contaminated cadaver donor or a living donor of cells. Contamination can also occur through the processing steps that the tissue processors perform. In the effort to monitor and follow up on individual case reports, FDA collaborates closely with the CDC as they are responsible for surveillance of a range of infectious diseases.

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Let's move on now to legislative changes and initiatives that have moved, and continue to move, FDA beyond passive safety surveillance - notably the FDA Amendments Act of 2007, the FDA's Sentinel Initiative, and CBER's Analytic Epidemiology Branch, known as AEB.

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The Food and Drug Administration Amendments Act of September 2007 gave the FDA some new responsibilities and authorities. Under the act, known as FDAAA, the FDA may require manufacturers to conduct safety studies or clinical trials at the time of product licensure. Another provision says that FDA must develop a post-market risk identification and analysis system to link and analyze safety data from multiple sources with at least 25 million persons in place or available for study by 2010, and 100 million by 2012. The Sentinel System

described next is, in part, a response to that FDAAA requirement.

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The Sentinel Initiative incorporates FDA's effort to develop an active electronic safety monitoring system to strengthen our ability to monitor post-marketing performance of medical products, not just safety, but also efficacy. It's designed to augment, not replace, the existing safety monitoring systems. It will enable the FDA to access existing automated health care data resources by partnering with the data holders or owners, such as insurance companies that have large claims databases, owners of electronic health records, Health Maintenance Organizations, or others. The data are planned to remain outside of reach of the FDA. The owners will still hold their data, keeping their data behind existing or better firewalls in the future. But the data owners will run queries that the FDA requests. The FDA might ask, for example, do you have any reports of intussusception with this new vaccine? Then the results from those queries will come back to FDA. Only the results of the queries will come back to the FDA, and strict privacy and security safeguards will be preserved.

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CBER's Analytic Epidemiology Branch, or AEB, was created in 2008 and is in some ways similar to the Sentinel Initiative. It is a unit within the Division of Epidemiology, devoted to the expansion of capabilities for biological product safety surveillance, signal strengthening or refinement, and hypothesis testing within defined population databases, such as the claims data of Health Maintenance Organizations and electronic medical records. AEB and the Sentinel Initiative build on two decades of collaborative experience with CDC's VSD.

AEB's early experience mainly employed claims data files from CMS, the Centers for Medicaid and Medicare Services. One project using these data is evaluating the data files for tissue allograft safety and utilization. The Analytic Epidemiology Branch collaborates with the Department of Defense, the Veterans Health Administration, the Indian Health Service, and a British system, the General Practice Research Database.

These kinds of approaches certainly present challenges. By employing independent data, that is, not relying on the spontaneous reports in AERS and VAERS, one can ask questions and legitimately test product safety hypotheses. The hypotheses often originate in AERS or VAERS with a series of case reports about patients with the same kind of adverse event who had all received the same vaccine or other biological product.

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As noted, the AEB also uses some CMS data, usually data from the Medicare system, the part of CMS that serves people over the age of 65. Smaller fractions of Medicare beneficiaries are younger than 65 years old, qualifying on the basis

of end-stage renal disease or other chronic disabilities. There are about 45 million people, a huge number, currently enrolled in this CMS system. They include about 38 million elderly and about 7 million others with disability or end-stage renal disease. Individual health utilization data are available for the 85 or 90 percent of these patients who are enrolled in the fee-for-service part of the Medicare system. A prescription drug benefit component began a few years ago, and we are working to get data from that system as well. Much of the AEB work with CMS data is coordinated with the Sentinel Initiative in the FDA's Office of the Commissioner in a program known as the SafeRx program.

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In 2008, AEB issued a set of request for proposals with a number of safety goals:

To develop a capacity for response to vaccine, blood, and tissue product safety concerns.

To conduct collaborative mission-oriented pharmaco-epidemiologic research to refine and test hypotheses on vaccine, blood, or tissue product safety and effectiveness issues, including those arising from adverse events reported to the FDA.

And, to develop improved methods for rapid detection of adverse events from biological products in large U.S. population-based data sources. Work is currently underway in these areas.

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To summarize, the diversity of biological products regulated by CBER requires multiple surveillance and safety assurance strategies. Open-ended safety surveillance is essential for the earliest possible discovery of unanticipated hazards to the public health. New authorities and technologies offer important promise for more robust capabilities to recognize signals earlier and to evaluate them systematically more efficiently and quickly.

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This concludes the presentation, "Evaluation of Biological Product Safety Throughout the Lifecycle at FDA's Center for Biologics Evaluation and Research."

We would like to acknowledge those who contributed to its development.
Thank you.