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 at FDA's Center for Biologics Evaluation and Research, known as CBER, 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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CBER assures the safety and efficacy of those products under its jurisdiction which includes products that are licensed, that is, vaccines, blood, blood products, and advanced therapeutics such as stem cells and gene therapy 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 infection risks. CBER also assures the safety and efficacy of medical devices involving its regulated products.

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The Office of Biostatistics and Epidemiology has a key role in the safety surveillance activities of CBER. It is composed of two divisions: the Division of Biostatistics and the Division of Epidemiology. Each division has two branches. Within the Immediate Office of the Director are additional teams. These include the Analytics and Benefit Risk Assessment Team, the High-Performance Integrated Virtual Environment Team, also known as HIVE, and the Business Management Team.

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The Division of Biostatistics provides statistical evaluation of study protocols for scientific soundness, comprehensive statistical review for medical product applications, and development and evaluation of novel study design approaches. The Division of Epidemiology analyzes adverse event information and epidemiology studies, assesses applicant Pharmacovigilance Plans, and determines the need for post-market studies and risk mitigation. The Analytics and Benefit Risk Assessment Team provides Benefit-risk assessments and management, data mining, bioinformatics and genomics, and Real World Evidence, such as effectiveness studies.

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Safety surveillance at CBER is facilitated through a number of safety teams and groups which are interdisciplinary, inter-office communication groups.

These groups facilitate coordination among the offices of:

· Biostatistics and Epidemiology

· Compliance and Biologics Quality
· Communication Outreach and Development,
· and the Center Director's office and representatives from review offices, such as:
· the Office of Blood Research and Review or,
· the Office of Vaccine Research and Review or,
· the Office of Tissue and Advanced Therapies.

Team representatives get together regularly to compare notes. Epidemiologists from the Office of Biostatistics and Epidemiology participate in these safety team efforts and other ad hoc work groups.

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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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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 surveillance 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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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. These limitations include instances of 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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As already noted, CBER conducts safety surveillance throughout a product's lifecycle. What do we mean by "lifecycle?" The overall lifecycle of a product begins well before a product is licensed. The 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 evaluation and mitigation strategies, also referred to as REMS, are developed to control certain identified risks in the post marketing phase. Safety surveillance of a product is a comprehensive process across this lifecycle.

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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 means that a much larger and more diverse population is going to receive the product after licensure. These considerations apply to drugs as well as biologics.

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 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. CBER carefully reviews all available data when determining a product's safety profile.

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Let's now turn to the post-licensure setting. Post-licensure safety surveillance for biologics 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 biologics are produced in ways that have more vulnerability to variations between batches or "lots."

After licensure, CBER maintains a lot distribution database and monitors adverse event reports for possible lot-specific patterns.

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What are CBER's roles and goals in the post-licensure setting?

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

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There are differences and similarities between biologics and drugs, and for the purposes of safety surveillance both the differences and the similarities are important. Vaccine products to prevent common diseases are biologics which 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, they have to be very safe so that the benefits outweigh the risks. 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 biologics and drugs is not hard and fast. While most vaccines are still preventive and require exceptional safety, 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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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, the Vaccine Safety Datalink, a collaborative effort with the CDC, safety studies performed in partnership with the Centers for Medicare and Medicaid

Services, also referred to as CMS, 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 Council for 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.

Prior to the NCVIA, 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.

The FDA and CDC co-administer the VAERS program.

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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 one can look proactively at a small number of predefined potential risks, such as Guillain Barré syndrome with influenza vaccines. CBER performs similar vaccine safety hypothesis testing studies through its own research within the Sentinel Post-Licensure Rapid Immunization Safety Monitoring program, also known as PRISM. Sentinel will be further described later in the presentation.

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A bit more on our vaccine safety communications. FDA employs a range of modalities and settings for such communications. 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. 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.

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CBER also regulates therapeutic blood-derived products such as antihemophilic factors (plasma derived or recombinant), coagulation factors, fibrin sealants, and immune globulins. Voluntary reports of adverse events come to FAERS the FDA's Adverse Event Reporting System, which is the counterpart to the Vaccine Adverse Event Reporting System. Both of these systems accept reports from any source. Safety studies for blood-derived products can also be performed within Sentinel, or in conjunction with the Centers for Medicare and Medicaid Services.

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Let's turn now to human tissue, cell products, and gene therapy 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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Safety surveillance processes for gene therapy products are similar to those for vaccines and therapeutic blood-derived products. Pharmacovigilance plans for each product is reviewed, safety is monitored as per the Code of Federal Regulations, FAERS provides passive surveillance, and active surveillance studies can be performed within Sentinel and the Centers for Medicare and Medicaid Services. Additionally, there is FDA guidance for longer term observation of studies for delayed adverse events.

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Let's move on now to describe FDA's Sentinel Initiative and CBER's Division of Epidemiology.

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The FDA Amendments Act of 2007, section 905, required that FDA establish an active post-market risk identification and analysis system.

The objective of this system is to enhance FDA's capability to identify and investigate safety issues in a reasonable amount of time and to be able to estimate a measure of association between medical products exposure and adverse outcomes.
The main data source includes claims and administrative data with a small proportion from electronic health records all of which are provided by private insurance companies.

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CBER has its own Sentinel program. The CBER Sentinel Program consists of 3 components: First, the Post-licensure Rapid Immunization Safety Monitoring, or PRISM, component focuses on the vaccine surveillance. Second, the Blood Safety Continuous Active-surveillance Network, or BloodSCAN, focuses on surveillance of blood and blood-derived products. And, third, Surveillance of Tissues and Advanced Therapeutics performs surveillance on tissues and advanced therapeutics.

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CBER's Division of Epidemiology partners with other agencies and leverages new technologies in order to enhance product safety. Examples include the development of advanced text mining systems, as well as partnering with the Centers for Medicare and Medicaid Services to develop capabilities to rapidly detect potential safety concerns.

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Division of Epidemiology reviewers have access to advanced text mining capabilities through the Office of Biostatistics and Epidemiology's development of the "Event-based Text-Mining of Health Electronic Records", or ETHER.

Pilot projects are underway within the Division to harness technologies with the potential to recognize and evaluate potential safety concerns more efficiently; including a current project that is underway utilizing IBM-Watson.

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The Division of Epidemiology collaboration with Centers for Medicare & Medicaid Services is able to use billing data from approximately 58 million persons in the United States. Recent collaborative projects have included surveillance of Guillain-Barré Syndrome following seasonal influenza vaccine, and the duration of effectiveness of Herpes Zoster Vaccine in the elderly.

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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.