Science at CBER: Why, How, and What?

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This presentation will discuss science and, in particular, the research programs at the Center for Biologics; why CBER thinks they are so integral to the regulatory mission; and how CBER makes sure they remain integral to the regulatory mission. The latter part of the presentation will provide some examples of the research done at CBER, so that you'll have a concrete understanding of how the research is tied to CBER's regulatory work

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This slide emphasizes the complexity of the products that CBER regulates. These are, for the most part, living entities, live viral vaccines, for example; living cells and whole blood; and cell therapies. Now CBER is looking at stem cell-derived therapies; xenotransplantation, the use of non-human cells, tissues, or organs. And some of these products are used in combination with devices or drugs, so they become combination products raising a whole next level of complexity. It is the complexity of the products that CBER regulates which really drives the need for using cutting-edge science to understand the regulatory issues these products raise, and the ability to face and solve those problems in the regulatory arena.

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CBER's approach to regulation is to work within the framework provided by the specific laws, importantly the Food, Drug, and Cosmetic Act, and the Public Health Service Act, combined with the regulations that are promulgated under those acts. CBER combines active research with external discussion, review of data submitted by sponsors to the FDA, and internal discussion.

Notably, the research is a critical part of that process, from data derived from research programs, which contributes toward rational policy and regulatory decisions.

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So how is that done? The CBER researcher is called a "researcher regulator". These researchers comprise about 10 percent of the staff and are integrated with the review process. The researcher regulators do all the same functions that a full-time reviewer would do. So that means they review submissions, such as INDs, BLAs and PMAs.

They go out on inspections, either pre-market or biennial inspections. They write policy documents. They participate in organizing or presenting at advisory committee meetings.

They are integral to CBERs regulatory mission and review the same products as the full-time reviewers. It means that CBER has the right expertise at the right time to identify scientific concerns in a regulatory application or a product class, and applies research and expertise to solve problems in the laboratories or, in the case of biostatistics and epidemiology, at the computer.

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So how does CBER manage the research programs to make sure that research is relevant to the regulatory work? This is an iterative process where you could really start anywhere, but let's start here, with the identification of regulatory and public health needs. Each year, CBER looks at the products that are currently in-house; the types of public health concerns that are driving product development; and does what is called "horizon scanning", this looks forward at what is new in terms of scientific technology and new products that are likely to be developed in the coming years to address public health needs.

From that, research priorities are derived. Offices within the Center then derive their own research priorities in alignment with Center-wide priorities. They develop plans, including strategic planning that incorporates horizon-scanning to identify areas of expansion, should increased resources become available.

Each primary investigator, or PI, submits a list of past accomplishments and future plans on a yearly basis. The research programs are evaluated on an annual basis for their relevance, productivity and quality in terms of these plans and priorities. And, of course, newly identified regulatory and public health needs often come out of the research programs themselves.

The use of external review and input is integral to this entire cycle. CBER has external site visits. Advisory committees are used. And there are other mechanisms to obtain external input into the research programs.

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To give you a more specific idea of Research Priorities, they were developed in Fiscal Year 2009 with the Research Leadership Council. This is a committee comprised of both research regulators as well as full-time reviewers and management.

In all cases, CBER research should meet the following goal: To ensure the safety, efficacy, and availability of biologic products and the use and development of appropriate regulatory pathways.

This goal is met through one of a variety of different priority areas:

- Development and evaluation of methods, reagents, and standards.

- Evaluation, development, integration of novel scientific technologies and preclinical models for use in product regulation.

- Facilitation of the development of new biological products for control of high priority public health threats, including pandemic influenza, emerging infectious diseases, and agents of bioterrorism.

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Also,

- Developing and analyzing novel approaches to evaluate biologics that reduce, refine, or replace use of animals (the 3R's).

- Improving clinical trial design and evaluation, including adaptive design approaches.

- Enhancing risk management, risk assessment, and risk communication sciences.

- And building on CBER pilots with CMS, CDC, VSD, and others to enhance and extend active population-based safety surveillance, by developing improved analytical tools and accessing large databases, including support of Sentinel Initiative.

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Each office performs an annual review of research programs, which is used to allocate research resources. These programs are looked at for their relevance to the Center and office priorities; for how one's unique expertise and perspective is being used; for productivity, for example, how many publications and the type of journals where it is being published; for patents or number of patents filed; and for regulatory guidance or other output related to the research. Quality can be measured by things like impact factor of the journal, invited presentations, or other means of recognition by scientific peers.

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In addition, there is external peer review by an outside committee of experts in the same field. That is done every four years for each scientist within the Center.

In addition, every four years there is an internal peer review by CBER's Promotions and Conversions Evaluation Committee. This includes review of the report from the external review, called a site visit report; outside letters of recommendation; and an intense evaluation of the quality of the regulatory work.

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To summarize, this graphic illustrates the cyclic nature of the way CBER manages research resources, and ensures they are relevant to the regulatory mission.

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You may have heard of the Critical Path Initiative.

The underlying premise of this Initiative is that FDA has an important and unique role to play in facilitating the development of safe and effective products past the basic research stage, through final approval, and even post-marketing in terms of safety surveillance.

This part of the product development life cycle can be considered its "critical path."

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During each of these stages, problems may arise that FDA is uniquely suited to identify because of its ability to look across a whole class of products and see things that other people may not see. FDA can identify stumbling blocks to the development of products that others may not see, and then work to solve those problems to keep things moving on this path. And so these images were used to signify that the path is not going to be straight, it's not going to be smooth, it's going to be bumpy, winding, and difficult. But again, CBER's research programs are one way to address these difficult problems in order to facilitate development of safe and effective products.

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CBER products are complex because of the nature of biologics products and because there are always new products being developed.

Therefore,
it requires that the science base of CBER be at the cutting edge so there is an understanding of the issues arising from these complex,
new products.
And 'new knowledge' integration is needed to facilitate development of safe and effective products.

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To highlight that, this talk will show a few examples of a primary research program from each of CBER's major product areas -- cell and gene therapies, vaccines, blood and blood products -- and also post-marketing safety surveillance.

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In the area of cell therapies, a promising new class of products is derived from stem cells. To respond to the numerous regulatory questions driven by this novel product class, CBER has enhanced ongoing research through a collaborative program with different investigators within the Division of Cell and Gene Therapy. These investigators have the right expertise at the right time to come together

and develop an animal model that can help CBER start looking at some of the regulatory issues posed by these types of products.

The CBER scientists designed a research project using mesenchymal stem cells. These are adult stem cells that can differentiate into a variety of different tissues. The project involves the clinical investigation of these cells in the treatment of hind limb ischemia, using a mouse model genetically engineered to express GFP under the control promoters of various genes that are associated with responses to injury or repair, to evaluate and understand the host response.

Prior to infusion, these cells will be characterized for a variety of different phenotypic characteristics, including cell signaling pathways, cell surface markers, chromatin status, and so on. These are also labeled with a fluorescent red marker so that the cells are tracked in vivo after they go in. So you can look at what happens to the fate of these stem cells after they are put in vivo, and also look at the host animal response to these cells. CBER is hoping this type of approach will allow for the correlation of the markers that are associated with in vivo outcomes, either the optimal outcomes, in terms of actually curing the hind-limb ischemia, or undesired outcomes, such as toxicity or other undesired outcomes.

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In addition, the Division of Cell and Gene Therapy has developed a variety of reference materials to improve characterization of cell and gene therapy products.

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Here's an example from the realm of gene therapy. While reviewing regulatory submissions using adenoviral vectors to target metastatic cancer cells, staff realized that most of the vectors in these clinical trials did not reach the target cancer cells, and therefore had to be given at very high doses. At high doses toxicity from the vector was observed, so they wanted to understand why the vectors were getting cleared rapidly. They identified scavenger receptors in Kupffer cells in the liver as the mechanism for clearing this vector so quickly. This discovery may allow others to develop methods to block this pathway, and to allow vectors to reach the intended target cells using lower, safer doses.

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Another example that is relevant to many of CBER's products is mycoplasma testing. Many of you probably know that the gold standard for mycoplasma testing is a culture-based assay. However, the assay is cumbersome and can take as long as 28 days.

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Staff in the Office of Vaccines developed a new strategy which relies on a short enrichment step in cell culture, followed by DNA isolation, and amplification of the

ribosomal genes or other genetic markers. Then the PCR amplicons are screened against a microarray that allows one to identify if a mycoplasma contaminant is present. The sensitivity is comparable to traditional assays, and it reduces a 28-day assay to less than 1 week. This is really important, especially in the context of new products like cell therapies, where for technical or clinical reasons, sponsors may not have the ability to freeze the cells and wait 28 days before administering to patients.

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Also from the realm of vaccines is work published in the Journal of Virology, describing an improved assay to detect vaccine efficacy for vaccinia virus, a surrogate for small pox. Using genetically engineered vaccinia virus that expresses the luciferase gene, viral replication is monitored by in vivo bioluminescence, allowing in-life measurements over time.

After immunizing at weeks two to three, the test animals are challenged with this genetically modified virus, and followed each day, for 10 days, for bioluminescence. Lethality, or survival, is used as a marker for vaccine protection. The slide shows an example in the animals that are not vaccinated. As you can see, the blue spots indicate where vaccinia virus is replicating.

By measuring the extent of bioluminescence, it was shown that 100% of the animals that are challenged with no vaccine die by day 8, and those that had received the vaccine survive. To correlate this with the new biomarker, they show that all the vaccinated animals have transient expression in the nasal cavity and the lungs, but in all the animals that survived, it eventually is cleared and all mice that die sustained high levels of bioluminescence.

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To summarize, this shows that, in addition to lethality as an endpoint for vaccine protection, time course of detection of bioluminescence is a more accurate prediction of lethality in vaccinia virus-infected mice than the traditional marker of weight loss. So this provides a new preclinical model that may allow for evaluation of new vaccines.

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Another example of applying new technologies to old problems is some work in the Office of Blood. Stored platelets lose their ability to function over time. Currently, the only way to measure this is to conduct clinical trials. That is, platelets are stored for a certain period of time and then given to people to determine their in vivo half-life. So the research regulator in the Office of Blood hypothesized that there may be an in vitro marker that could be used to correlate the in vivo activity, and chose to analyze whether a new class of small, non-coding, single strand RNAs, called microRNAs, may provide that marker. Because microRNAs are critical in a variety of biological processes, one of which is apoptosis, it was thought that by looking at a variety of apoptotic-specific

microRNAs, you might find one that correlated with the decrease in activity in platelets over time.

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It was found that four microRNAs seem to show a clear trend in the stored platelets compared to fresh ones. This may lead to development of an improved in vitro method to look at the quality of stored platelets.

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CBER also evaluates novel technology in the context of blood screening assays, for example, to detect HIV.

Using a nanotechnology-based method, one scientist in the Office of Blood has shown that you can detect HIV p24 about 150-fold more sensitively than conventional EELISA, which is used currently to screen blood. And furthermore, in a look back at donors in terms of their known time of exposure to HIV, the new assay, shown here in the white bars, compared to the conventional assay, shown in the black bars, demonstrated that you can pick up a signal with the new assay approximately three days earlier. So this has important implications in terms of improving the safety of the blood supply.

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In terms of post-marketing surveillance, CBER is also trying to improve the ability to detect low-frequency adverse events in populations after biologics have been approved. As a proof of concept, in 2006, the Office of Biostatistics and Epidemiology analyzed the Medicare/Medicaid database, which contains approximately 40 million records from individuals 65 years or older. Using this database, they analyzed in real time the frequency of Guillain-Barre syndrome following the seasonal flu vaccine.

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What they were able to show is that while there was an initial peak, in fact, they did not see any increase in Guillain-Barre syndrome rates during that season.

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To finish, let's highlight the role that CBER scientists played in the preparation of the pandemic H1N1 vaccine in 2009. This was a team effort from scientists in the Division of Viral Products and the Division of Product Quality.

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CBER was among the first to provide human serology data, which supported selection of the vaccine strain.

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CBER also used reverse genetics to develop a reference virus strain, which was distributed to manufacturers for evaluation as a candidate vaccine strain.

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CBER prepares the reagents that are used for vaccine standardization and lot release testing. The hemagglutinin is purified from the candidate vaccine strain, and used to immunize sheep. Those antisera are then used to determine potency of the vaccine lots. The vaccine strain-specific antisera are distributed to all the manufacturers and used for reagent calibration.

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CBER also tests the seed viruses developed by manufacturers, as well as potency testing, independent of the manufacturers. And then, of course, the Center reviews and releases the vaccine data.

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CBER has also used its science to be proactive in thinking through possible future crisis situations. For example, what impact could an influenza pandemic have on the blood supply? CBER looked at a worst-case scenario, one not likely to happen, where 50 percent of the blood donations would be decreased over 3 months.

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CBER was able to show that if you can proactively define parameters to control the use of blood, though you will still have a dip in the blood supply, it will recover fairly quickly compared to non-restricted use. Under normal conditions, the modeling showed it would take a much longer time to reinstate the blood supply to normal levels.

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To close this presentation, here is a quote from the FDA Science Board Subcommittee on Science and Technology, which speaks to the strength of the CBER research program. It states that "CBER has a rigorous process for establishing priorities and the impact of the research on regulation.
In particular, CBER science is integrated into the review and manufacturing site inspection process, and the external peer review is the norm rather than the exception."

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This concludes the presentation, "Science at CBER: Why, How, and What?" and we would like to acknowledge those who contributed to its development. Thank you.