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FDA's Role in the Regulation of Vaccines

Statement of

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Good afternoon Mr. Chairman and members of the Committee, I am Jesse L. Goodman, M.D., M.P.H., Director of the Center for Biologics Evaluation and Research (CBER) at the United States Food and Drug Administration (FDA). I am also a practicing infectious diseases physician and a microbiologist. CBER is the Center within FDA that is responsible for the regulation of most biological products, including vaccines, blood and blood products, and cellular, tissue and gene therapies. Thank you for the opportunity to discuss FDA's role in the regulation of vaccines including those intended for use in response to a threat to our national security.

At CBER, enhancing the nation's preparedness is one of our highest priorities, whether it is protecting the safety of our blood supply from emerging threats like West Nile Virus or facilitating the development of vaccines needed to face natural threats or potential deliberate threats, from pandemic flu to smallpox to anthrax. It is essential to do all we can to assure that such products be safe, and that they work. Therefore, while working closely with many partners to achieve our nation's and our global preparedness goals, our most critical and unique responsibility is to also do all that is possible to provide an objective, scientific assessment of the safety and efficacy of these and other biologic products. To help provide perspective, I am going to discuss relevant issues in vaccine development that illustrate the opportunities and challenges faced in developing these important products. As you know, under applicable laws and regulations, information provided to FDA concerning a specific investigational product is not available for public disclosure prior to licensure of the product.

Vaccines are different from most drugs in several respects and achieving the highest quality in manufacturing can be especially challenging and critical. Vaccines production frequently utilizes living cells and organisms, as well as complex growth conditions and materials often derived from living sources. The manufacturing process for vaccines usually includes many steps and requires frequent in-process monitoring of the product and components to assure that the product is safe, pure, and potent.

The production of most vaccines requires the growth of the immunizing agent (i.e. bacteria, virus, etc.) or the genetically engineered expression, in living cells, of recombinant immunizing proteins derived from that agent. The conditions for accomplishing this are complex and subtle, and even undetected or poorly understood changes in process or materials can significantly affect the composition of the vaccine and its safety, efficacy, or both. Thus, the process must be well controlled and monitored, and produce a consistent and well characterized product prior to its licensure. Even after licensure, manufacturers conduct a series of tests on the bulk, intermediate and final vaccine products and typically are required both to meet all product and process specifications and to submit the results of key tests, along with samples of the product to CBER for evaluation prior to CBER's approval of lot release and administration of vaccine. The tests performed on the final product may include those for sterility, identity, purity, and potency to assess immunogenicity and/or antigen content and, depending on the nature of the vaccine and its manufacturing process, additional tests as required by CBER to assure vaccine safety and quality.

Unlike drug products that are most often used to treat an existing illness or condition, vaccines are generally administered to large numbers of healthy individuals in order to prevent infectious diseases. Therefore, the potential adverse effects of vaccines, even if the events are rare, present unique risk-benefit considerations and may give rise to heightened concerns in the public health context.

From a regulatory perspective, there are four major stages in vaccine development. These stages include:

- The preclinical stage which consists of the development and testing of the product prior to the product being tested in humans. Early in the product development process, sponsors test candidate vaccines *in-vitro* (e.g., in laboratory assays, studies in cell lines, etc) and in animals. These early nonclinical studies give an indication of whether studies would be reasonably safe to proceed in humans and may also provide information regarding the potential effectiveness of the product.
- The Investigational New Drug (IND) stage consisting of multiple phases where the investigational product is studied in human subjects under well-defined conditions and with careful monitoring. In certain cases where studies to demonstrate efficacy in humans are not ethical or feasible, sponsors may conduct studies to demonstrate efficacy of the product in appropriate animal models.

- The license application stage is when manufacturers submit data and information regarding the results of the clinical and nonclinical studies, as well as complete information regarding the product and its manufacturing process to FDA for a complete review of product manufacturing, safety and effectiveness in support of licensure.
- Finally, for products that are approved, FDA continues its oversight during the post licensure stage to include review of post-marketing safety information from adverse event reports, periodic reports, post-marketing studies, review of lot release information and testing, and inspections of manufacturing facilities.

FDA often provides guidance to sponsors, even prior to submission of an IND, in regard to both the types of preclinical studies needed and the design of the clinical trials needed to assess the intended use(s) of the product. FDA's guidance is intended both to help protect human subjects and to assure that the studies performed are designed in such a manner that the study results are likely to provide sufficient information to allow a determination of the product's safety and efficacy.

While all medical product development is challenging, vaccine development is especially complex, and we expect that new challenging issues will arise during the development process. The issues may arise in any number of areas, and may affect product potency, quality, and safety. Such issues can raise safety or study design concerns that may result in FDA placing an IND on clinical hold. A

clinical hold is an order by FDA not to initiate or continue clinical studies until the issues of concern have been satisfactorily addressed. It is important to note that most clinical hold issues are eventually resolved, allowing product development to proceed. I'd like to describe some of the more typical reasons for FDA to place a trial on hold. FDA may determine that study participants would be exposed to an unreasonable and significant risk of illness or injury. Or, the IND application may not have sufficient information for FDA to adequately assess the risk. For later phase studies, FDA may place an IND on hold if the study plan or protocol is deficient in design to meet its stated objectives. Clinical hold is an important human subject protection safeguard and also helps prevent the conduct of studies of investigational products that are unlikely to provide information that is useful in evaluating the product. FDA staff spends a considerable amount of time interacting with sponsors to resolve clinical hold issues.

FDA strives to develop processes that facilitate product development to meet emerging public health needs, such as protection from terrorist agents and prevention of pandemic influenza and other emerging threats. The regulation known as the "Animal Rule" provides a mechanism for FDA to approve medical treatments based on effectiveness data from animal studies when human efficacy studies are unethical and/or not feasible. Under the "Animal Rule," effectiveness would be evaluated in adequate and well-controlled animal studies that establish that the product is reasonably likely to produce clinical benefit in

humans. Such approvals also require the demonstration of safety in humans. These safety studies may be conducted concurrently with the animal studies.

An additional tool available to speed product availability is the ability for FDA to allow the use of unapproved products and unapproved uses (so-called “off-label” uses) of approved products, in a declared emergency, under the Emergency Use Authorization (EUA) provision of the Food, Drug, and Cosmetic Act. This authority was expanded under the Project BioShield Act. To authorize such emergency use, FDA would need to find that the agent can cause a serious or life-threatening disease or condition; that based on the available information it is reasonable to believe that the product may be effective against the disease or condition; that the known and potential benefits of the product’s use outweigh the known and potential risks; and that there is no adequate, approved and available alternative.

FDA works very hard to develop and define innovative and needed pathways and evaluation tools, and to provide technical assistance to facilitate development and availability of needed products that are safe and effective. One of our most critical and core roles is to protect human subjects and to provide an independent scientific assessment of the product, both during the development process, and in reviewing product applications and requests for EUA.

To protect and preserve our scientific independence and judgment, FDA does not involve itself in specific HHS contracting decisions to award or terminate contracts. FDA's longstanding practice is to recuse ourselves from HHS decision making in specific contracting decisions. This was our process at the time of HHS's VaxGen acquisition contract and it remains so today. FDA does provide scientific and technical expertise on various HHS-led interagency counterterrorism working groups, which among other things are involved in defining the needs for medical countermeasures being pursued by HHS for the Strategic National Stockpile. In addition, FDA may provide technical comments to HHS upon request on draft Requests for Proposals for such countermeasures.

At FDA, providing the American public with safe and effective medical products is our core mission. We base important decisions, such as to allow specific human studies of an investigational product, or to approve a vaccine or allow its emergency use, on the available scientific information and a careful evaluation of risks and benefits to patients. We also are fully committed and engaged in continuing to work with our federal partners and with product developers to provide an efficient product development pathway to achieve our nation's high priority public health preparedness goals.

Thank you again for this opportunity to discuss vaccine development with the Committee. I welcome your comments and questions.