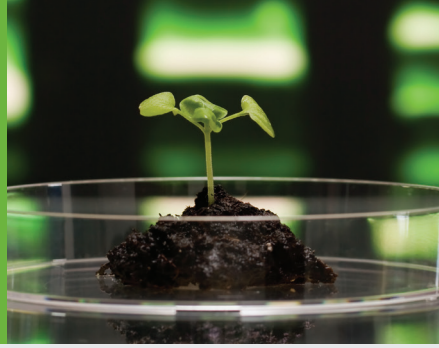
FDA Regulatory and Compliance Monthly Recap



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KEY FINDINGS

FDA draft guidance explains benefit-risk considerations for IDE applications

The regulator is clarifying the "principal factors" it will take into account with assessing the benefits and risks of IDE applications for human clinical study, and describing risk mitigation measures, in a bid to improve review process predictability and patient access to new devices.

The document Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions (IDEs) is primarily aimed at spelling out the factors considered during the assessment of risks and anticipated benefits for IDE studies, and how to offset uncertainty using risk mitigation measures. According to the FDA, using the benefit-risk framework in an IDE application will make it easier to incorporate evidence and knowledge from different domains – clinical, nonclinical and patient – to support a "comprehensive, balanced decision-making approach," as well as improve the predictability, consistency and transparency of the IDE application review process.

The guidance goes over the informed consent process and the standard for IDE decisions, calling the former a "key tenet" to the FDA's IDE benefit-risk framework by way of being a key principle of human subject protection in clinical investigations. Regarding IDE decisions, the guidance further clarifies assessment of risks and benefits associated with a device use proposed in the application, and inadequacy or uncertainly about the data from prior studies; the proposed study; the manufacturing, transport and storage of the device; or monitoring of the study. With three main decision categories on IDE applications, the FDA may grant approval, approval with conditions or disapproval. The FDA also notes it will consider study design, which has a "direct bearing on the knowledge that can be gained from that study."

The FDA also explains IDE application evaluation in the context of a device development pathway, stating that during IDE benefit-risk assessments, it considers the stage of device development, the maturity of the technology, and the availability of nonclinical testing to accompany or substitute clinical testing. Given that device investigations at different stages of developments are usually associated with different types of risks and levels of uncertainty, the assessment should be tailored to the device development stage. The guidance also states nonclinical data plays a key role in determinations throughout all stages of development, noting that in certain cases nonclinical testing can reduce the need for additional clinical testing.

As stated in the guidance, because IDE applications have a more limited level of evidence than do marketing applications, decisions related to the former are made in settings that involve greater uncertainty and less evidence. However, this uncertainty can be offset by tailored risk control/mitigation measures. In taking into account benefits of investigational research, the FDA weighs direct benefits to the subjects and benefits to others – either indirect benefits to subjects or the gain of important knowledge.

When the FDA assesses benefits and risks for an IDE application, it also considers the contextual setting in which the study is being proposed, including characterization of the disease or condition being treated or diagnosed, the availability of alternative treatments or diagnostics, and the risks associated with them. Information about subject tolerance for risk and perspective on benefit may also be useful in terms of context – when it's available.

The FDA also dedicates a section of the guidance to outline its approach to assessing benefits and risks of IDE studies, recommending that sponsors include a summary of the key considerations. These are listed as patient preference as it relates to the participants in the study, and a description of the investigational device as well as a risk analysis related to its use. The risk assessment of IDE subjects should involve the description of the relationship between a hazard and harm, whose extent is determined by types of risks – including severity, likelihood or probability – and duration. Also considered are residual risk evaluation and risk management, with the FDA noting that risk controls that can be applied to IDE studies include safety by design, protective measures and communication of safety information.

The guidance also describes assessment of other risk considerations of investigational studies, including those related to study data, benefits of gained knowledge and risk to others, as well as of direct benefits to study subjects and to others. The FDA concludes with several appendices, including one that includes recommendations related to the benefit-risk summary and what it should address, one that provides hypothetical examples for illustrative purposes, one that goes over the investigational device description and one that provides a glossary of risk management terms.

Allergan warned by FDA over unapproved marketing of SERI Surgical Scaffold

The regulator sent a letter to the company warning it for promoting the surgical mesh – which is approved to support and repair soft tissue and reinforce deficiencies – for breast surgery applications, which falls outside the scope of its approved indication.

A warning letter was sent to Allergan after the FDA reviewed the company's www.seri.com website and found the SERI Surgical Scaffold was being marketed without an approved PMA or IDE application for the device "as described and marketed," rendering it adulterated. The commercial distribution of the mesh with "major changes or modifications" to its intended use without the submission of new PMA notification also renders the SERI Surgical Scaffold misbranded, according to the letter.

The FDA specifies in its letter that the SERI Surgical Scaffold received clearance under K123128 with the indications for use as a "transitory scaffold for soft tissue support and repair to reinforce deficiencies where weakness or voids exist that require the addition of material to obtain the desired surgical outcome." Included is the reinforcement of soft tissue in plastic and reconstructive surgery, as well as general soft tissue reconstruction.

However, Allergan is promoting the SERI Surgical Scaffold as though it were intended for breast surgery applications, listing breast revision surgery, breast reductions, muscle flap reinforcement, and mastopexy with or without augmentation as procedures that "may benefit from using the SERI Surgical Scaffold." The letter states this would constitute a "major change or modification to its intended use" for which Allergan doesn't have approval or clearance.

The FDA wrote surgical mesh wasn't cleared for use in breast reconstruction using a tissue expander or implant – which means the aforementioned indications aren't included in the scope of the company's intended use.

The letter also notes the specific breast reconstruction surgery indication changes the intended use of surgical mesh that's cleared with a general soft tissue reinforcement indication.

FDA provides guidance on assessing potential risks to embryo/fetal development posed by drugs used by men

The regulator's guidance document contains recommendations for evaluating what the potential is for API exposure in males to adversely affect offspring development.

In its guidance Assessment of Male-Mediated Developmental Risk for Pharmaceuticals, the FDA is making recommendations for assessing risks to embryo/fetal development that could result from investigational API administration to males via an effect on male germ cell or seminal transfer of an API.

While there's guidance related to the need to assess pharmaceuticals' potential for genetoxic and embryo/fetal developmental toxicity before their administration to pregnant women, there's a lack of consistency in the design of clinical trial protocol when it comes to pregnancy risks for a sexual partner of a man being administered an API.

When a clinical trial with an investigational drug is being designed, nonclinical studies are likely the only source of information about potential risks to male reproduction or the development of offspring. The guidance states when a trial involves exposure to a potential reproductive or developmental toxicant, investigators should consider issues of risk characterization, informed consent and contraceptive options. In designing a clinical study that involves male subjects, investigators must consider the potential for adverse effects on the conceptus of a sexual partner who is or may become pregnant, the FDA wrote. Due to a lack of clinical information, nonclinical data will be used to assess risk and to inform decisions about the need for appropriate precautions during clinical trials.

Specifically, the FDA is advising sponsors on how to examine what the potential is for API exposure in males to adversely affect offspring development based on three considerations, including the evaluation of studies on mechanisms of action, genetoxicity, reproductive toxicity and developmental toxicity; known effects of API or pharmaceutical in animals or humans; and assessment of possibly embryo-fetal exposure through the transfer and vaginal uptake of reproductive toxicants that secrete into seminal fluid.

The document also goes over factors that investigators should take into account when they test new APIs in males and risk mitigation recommendations.

The FDA lists the reproductive and developmental toxicity of the pharmaceutical; the cytotoxic or genotoxic properties of the drug; pharmacologic properties suggesting risk; and the absorption, distribution, metabolism and excretion properties of the drug as factors to consider when evaluating the potential for developmental toxicity.

The regulator wrote that it intends to consider the totality of provided evidence to support recommendations on the need for male contraception during trial design or to support labeling requirements during drug approval. Contraceptive use recommendations apply to reproductively competent men and vasectomized men, unless existing data shows that only germ cells are affected.

The regulator recommends male subjects in clinical trials take precautions to prevent pregnancy and exposure of a conceptus throughout and following pharmaceutical exposure if an API's genetoxicity and reproductive and developmental risk potential is unknown or if it was identified as having genotoxic, reproductive and/or developmental effects in nonclinical studies.

The guidance document also lists nonclinical studies applicable to the assessment of drug-induced male-mediated developmental effects in animals, including in vitro studies such as pharmaceutical effects on sperm, in vivo studies such as general toxicity with semen analysis in adult males, and ADME information.

FDA calls on generic drugmakers to make tablets, capsules physically similar to reference drugs

The regulator issued guidance on the size, shape and other physical attributes of generic tablets and capsules, recommending that the physical characteristics of generic drugs closely resemble those of their reference drugs.

The agency is concerned variations in the physical characteristics of generic drug products – for example, in tablet sizes and shapes – could "affect patient compliance and acceptability of medication regimens" or result in medication errors. The FDA is thus recommending that manufacturers of generic drug products take physical attributes into consideration when developing QTPPs for generic product candidates. The guidance applies to ANDAs and their supplements for additional strengths submitted to the OGD, but not to approved ANDAs already on the market, the FDA notes.

The regulator is making recommendations based on published literature on patient experiences swallowing tablets and capsules, as well as agency experience with NDAs and ANDAs submitted for oral tablets and capsules.

The document provides guidance regarding the size, shape and other physical attributes of tablets and capsules, in addition to biowaivers. With regard to size, the FDA recommends that generic oral tablets and capsules meant to be swallowed intact be of a size similar to that of the respective reference listed drug (RLD). Manufacturers are similarly recommended to ensure the drug products have a similar shape, or to have a shape found to be easier to swallow in comparison to the RLD's shape. The FDA notes evaluating and comparing the "largest cross sectional areas" of the generic product and the RLD is one way to quantify shape changes, recommending spatial imaging or the use of computer models. The guidance document covers other physical attributes that should be considered as far as how they affect ease of swallowing, including tablet coating, weight, surface area, disintegration time and propensity for swelling.

FDA guidance describes implementation of the USP Salt Policy for naming prescription drugs

In a final guidance document, the regulator explains the USP naming and labeling policy for drug products

containing salt as an active ingredient, and how the CDER is implementing it, in a bid to eliminate discrepancies between the established name and strength on labels.

The regulator issued guidance explaining how the CDER's implementation of the United States Pharmacopeia's (USP's) Salt Policy will affect drug products containing an active ingredient that's a salt. The FDA notes it exclusively applies to the monograph title for drug products, and not for drug substances.

According to the FDA, adhering to the USP Salt Policy will "help reduce medication errors" resulting from a disparity between the established name and strength on the label of drug products that contain a salt.

The FDA says the policy, "Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations," affects the development of new drug products because most of the time, a USP monograph title for a new drug product serves as the nonproprietary or "established" name of the related drug product. If a drug product's label or labeling bears a name that's inconsistent with the applicable monograph title, it risks being misbranded.

In the document, the FDA goes over the policy, breaking it down into five main points, including that the monograph title for a drug product containing salt as an active ingredient will bear the name of the active moiety rather than the name of the salt when creating a drug product monograph title, and that the strength is expressed in terms of the active moiety rather than salt strength equivalent.

The FDA also explains how the CDER is applying the policy, noting it is being applied to prescription drug products under development for which companies are seeking approval. It's recommended that the established name of the drug products as determined under the policy be consistently used in all contexts where the established name is used. The document also covers how the CDER is applying exceptions, describing procedures and conditions, and encouraging early communication for a potential exemption.

The regulator goes on to explain how to implement the USP Salt Policy as it relates to product development and labels and labeling information, and notes its nonimpact on active ingredient requirements. The document lists three steps sponsors should follow when developing a drug for which the USP Salt Policy may be relevant, including considering whether the product contains an active ingredient that's a salt; considering whether the product qualifies for an exemption, and if so, contacting the CDER for preliminary feedback; and developing the product in a way that the name and strength are in accordance with the policy. The FDA also notes the application of the policy doesn't affect statutory and regulatory requirements for drug products, listing a number of factors to consider when creating labels and labeling, including that the established name of the drug product and the active ingredient should be "correctly displayed throughout the labeling." Also highlighted are locations in the PI where sponsors should be particularly attentive to the language, including the Highlights section, the Dosage Forms and Strengths section, and the Description section.

For more information on any of these FDA regulatory and compliance updates, please contact Scott S. Liebman at sliebman@loeb.com.

Loeb & Loeb LLP's FDA Regulatory and Compliance Practice

Loeb & Loeb's FDA Regulatory and Compliance Practice comprises an interdisciplinary team of regulatory, corporate, capital markets, patent and litigation attorneys who advise clients on the full spectrum of legal and business issues related to the distribution and commercialization, including

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