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Gene Therapy: Development, Design of Studies, and Approval Process - BLOG

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ABSTRACT

Genome editing can be applied to various areas of medical diagnosis and treatments. Gene therapy pre-market applications comprise of systematically assessing a product's design controls, manufacturing process controls, and proposed protocols for post-marketing surveillance. Quality risk management principles have been described in various FDA regulatory guidances for several aspects of good manufacturing practices (GMPs) such as several stages of process validation and verification in the genome product's life cycle including critical quality attributes (CQAs) and monitoring critical process parameters (CPPs). A CPP is defined as a process parameter whose variability has an impact on a CQA of genome product and, therefore, should be monitored or controlled to ensure that the manufacturing process produces an end product of the desired quality. FDA's mission is to facilitate the premarket review and evaluation of new genomic products for clinical use. The FDA guidances emphasize a quality management approach to the design of studies by providing oversight and objective review based on risk-benefit analysis of new genomic products. FDA reviews, evaluates, verifies and validates the implementation of the regulatory design-control requirements which are applied to the control genomic product's quality throughout the total product life cycle (TPLC) [1-5].

INTRODUCTION

One of the primary functions of a genomic firm's research project team is to coordinate the various literature references necessary for the successful development of the genomic product under consideration. This coordination is usually accomplished by preparing a detailed genomic drug development plan and process controls. This requires analyzing, evaluating and constructing study design as they relate to the proposed genomic product's chemical entity for disease therapy (i.e., Cardiovascular, cancer, CNS indications, diabetes, etc.). This includes types and duration of therapies (i.e., acute or chronic situations with one or a few doses adequate for treatment modes. It's also important to consider routes of administration (i.e., intravenous, or infusion or non-intravenous such as oral, pulmonary, subcutaneous, intramuscular, dermal, etc.). The timelines for the various studies and their integration into a formal therapeutic drug development plan are compound specific and dependent on the availability of resources within the various departments of the sponsor firm and approval of sponsors management. At the same time, the designation of pertinent milestone events and the critical path are genomic compound specific and firm-specific. Additionally, studies, such as bioavailability for a candidate therapeutic compound may

be necessary. Other studies, such as potency, immunogenicity, toxicity, side-effects may be required. The formation of various project-related teams requires coordination for the successful development of a genome therapeutic product for premarket applications submitted to the FDA [1].

Development and Guidance for Genomic Products

Sponsors of genomic medical products shall establish and maintain plans that describe or reference the design and development activities and describe responsibility for developmental implementation. The design plans shall be periodically reviewed, updated, and approved as the product's design and development evolves. The sponsor shall establish and maintain procedures to ensure that the regulatory design control requirements relating to the genomic product are appropriate and address the intended clinical use of the product, including the needs of the user and the patient. The design input requirements shall be documented and shall be reviewed and approved by the organization's designated individual (s). The sponsor shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements. The design output criteria shall ensure that those design output elements are addressed for the proper functioning of the genomic product. The sponsor shall establish and maintain procedures for verifying the product's design. The design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design method (s), and the individual's responsibility performing the verification are documented in the design history file (DHF). Design validation shall be performed under defined operating conditions on each designated production unit, lots, or batches, or their equivalents. Design validation shall include software validation and risk analysis, where appropriate. The sponsor shall maintain procedures to ensure that the genomic product's design is correctly translated into production specifications. The DHF shall contain or reference the records essential to demonstrate that the design was developed in accordance with the approved design plan and the requirements of the regulatory design controls are met [2].

The genomic research teams should carefully review and evaluate the prototype design studies for the candidate therapeutic product as to how it is similar or different (i.e., DNA/RNA based sequences products based on genomic and specific nuclease applications). Currently, pandemic disease eradicating genomic products with single dose or multiple dose applications are developed and proposed for respective safety and effectiveness criteria. These genomic editing and therapeutic products should address the scope of the disease outbreak considering factors such as population susceptibility, effective doses, incubation period, modes and prevention of transmission, mortality rate, effectiveness of treatment interventions and population migration. Environmental studies have included the detection of epidemiological agents such as bacteria, virus, etc. in indoor and outdoor settings. Testing technology products are being developed and used for these types of agents based on real-time polymerase chain reaction (PCR).

Currently, available testing products are being developed and used for detecting pandemic biological agents or their breakdown products (i.e., virus particles). The ideal diagnostic product is dependent on accuracy, sensitivity, and specificity of the testing methodology dependent on efficiency of the sample collecting locations, and placement of the monitors, and the concentration of the organism in the air sampled by the collector. Rapid and accurate diagnosis of potential viral agents is important for detecting and lessening the impact of a potential infectious disease agent threat/risk in global pandemic situations. The most important situation is to enhance diagnostic capacity of the Laboratory Response Network (LRN), established by the Center for Disease Control (CDC). Current emphasis is placed on development and availability of testing systems using PCR-antibody-conjugating methodologies/products which have greater sensitivity and specificity. These types of clinical applications requires detailed knowledge of the pathophysiology of the disease and the pharmacological applications of gene-therapeutic products facilitating the design of clinical trials in order to determine the essential data needed for the US FDA's approval process [2,3]. For gene-therapeutic products, preclinical (non-clinical) pharmacodynamic studies can be important if there exists adequate data as precursors for the design of studies. Such studies may also include dosing, route of administration and efficacy. Additionally, availability of clinical pharmacokinetics and pharmacodynamics of the proposed gene-therapy product are helpful in submitting FDA's premarket approval application (PMA) [3].

Preclinical Development

The genomic product candidate is subject to a number of preclinical studies to establish and characterize its safety profile. New medical applications must be shown to be safe and effective before FDA approval. The manufacturer must show that the product is safe and effective in human subjects. The genomic sponsor must first convince CDC that the product is reasonably safe to use in humans to evaluate safety and efficacy in clinical studies. This is established through preclinical laboratory

testing (i.e., bench testing including any suitable animal applicable models, referred to as FDA's regulatory "preclinical/non-clinical studies"). Preclinical studies of the new genomic product help establish boundaries for the safe use of the intended treatment when human applications or "clinical trials" begin. The sponsor of the new genomic product submits a protocol as "Investigational New Drug (IND)" application to the FDA requesting permission to initiate clinical trials. The IND allows the use of an investigational medical product in human subjects for the sole purpose of conducting clinical trials [4].

Good Laboratory Practice (GLP)

GLPs are the FDA regulations for the nonclinical laboratory studies to support investigational new drug applications (INDs). FDA regulations applicable to GLPs are provided in 21 CFR, Part 58. GLP regulations require protocols for standard methods, facilities, equipment, test controls, records and reports, audits and inspections to be used in conducting preclinical and nonclinical laboratory studies that are used to assure the quality and integrity of data provided in INDs. Nonclinical studies include in vitro and in vivo experiments for the new genomic products safety profiles. GLP standards relate to both the design and the projected use of the product and the qualifications of the personnel and facilities involved with the intended use of the product. The purpose of GLP regulation is to assure the integrity of the nonclinical safety data, such that the evaluation of the study quality and interpretation of the study results may be done with confidence. FDA's guidance documents related to GLPs are recommended along with ICH (International Conference on Harmonization) documents. The GLP sponsor provides genomic quality assurance or QA monitors and checks the results from the studies to ensure that the experiments are conducted in compliance with the FDA regulations [4,5].

Good Clinical Practice (GCP)

FDA regulations applicable to GCPs are provided in 21 CFR 312. FDA has published a consolidated guideline of GCP in conjunction with the ICH guideline {E6, 62 Fed. Reg. 25692(1998)}. The consolidated guideline for GCP is intended to provide a unified standard for conducting clinical studies. These standards apply to all aspects of clinical trials, from protocol design, monitoring and auditing, to recording, analysis, and reporting of clinical data presented in new product applications to the FDA. The overall aim of GCP is to protect public health and the rights, welfare, and confidentiality of study participants. The GCP process is intended to ensure that all data and reported results are credible, accurate, and evidence-based. While GCP places emphasis on the clinical accuracy of results, it also deals with the importance of the processes used to conduct clinical trials and embracing GCPs as a part of total quality system approach to new medical product development and approvals. According to this requirement, GCP refers to the collection of regulations and requirements that must be complied with while conducting clinical trials [4,5].

Principles and Procedures for New Genomic Product Applications

The FDA's new genomic drug approval process begins with research plans involving basic research, laboratory testing, and projected utility. This initial stage includes design concepts, discovery and development of prototypes involving preclinical and clinical studies of new genomic product materials to be reviewed and approved by an institutional review board (IRB). These IRBs exist in hospitals, university medical centers, and private clinical research institutions at which clinical trials take place. Before a clinical trial is initiated, foreseeable risks are weighed against the anticipated benefits for the individual trial subject and the intended clinical population. Generally, a clinical trial is initiated and continued only if the anticipated benefits are feasible. The FDA filing and premarket applications consist of the following categories:

1. Investigational new drug application (IND)
2. New drug application (NDA)
3. Abbreviated new drug application (ANDA)

For a genomic drug manufacturer to introduce a product in the market for human use, multi-face procedures will be required. These procedures begin with a number of preclinical or prior-to- human applications, followed by three phases of human studies. New genomic drug products may be also subject to a fourth phase, known as post market surveillance, which may require additional trial data. FDA has published detailed guidance on the new drug development and approval process available on their website. The emphasis is placed on the interactions between the various stages of investigational studies and the continuing dialogue with the FDA review status throughout the development and completion of premarket application [4-6].

Clinical Trials

Clinical trials are an integral part of new gene-therapy drug discovery and development and they require review and evaluation by FDA before the new gene-therapy drug products can be brought to market. Before submitting an NDA, the sponsor must conduct preclinical and clinical studies designed to demonstrate the safety and efficacy of the drug product. Clinical trials involve studies of human subjects where the protocol-designed studies provide information and data to support the NDA submission to FDA. Clinical trials may be classified by their stage and phase in the product life cycle and are generally classified into three phases (phases 1, 2, and 3). Clinical trials require careful planning and consideration of the types of subjects to be enrolled.

The main purpose of clinical trials design objectives is to test a hypothesis and ultimately to reach a conclusion as to whether the gene-therapy product has any effect on the human body and the disease condition in which it is being tested. Additionally, the gene drug product improves the subject's health or quality of life, has an advantage over the current treatment available for that disease or condition, and can be administered safely to that subject. Sponsors of gene-therapy product studies are required to control risks to clinical trial participants. It is critical that all personnel involved in clinical trials understand the FDA and CDC regulations and guidelines that govern the protection of human subjects while evaluating the efficacy of the product. Generally, clinical trials for new drugs consist of three phases (Phase 1, Phase 2, and Phase 3). Phase 1 involves a relatively small number of subjects intended to gather initial safety information. Its purpose is to determine a safe dose range in which the drug can be administered, metabolized and pharmacologically effective with minimum toxicity.

The results of the Phase 1 studies are used to develop Phase 2. Phase 2 involves a large number of subjects who have the disease or condition the genomic drug product is intended to treat. Phase 2 may be divided into two subparts: Phase 2a is a pilot study which is used to determine initial efficacy, and Phase 2b uses controlled studies on several hundred patients. At this point, the sponsor and the FDA usually confer to discuss the data and plans for Phase 3 studies. Phase 3 studies are considered "pivotal", designed to collect all of the essential data to fulfill the safety and efficacy criteria that the FDA requires to approve the new therapeutic drug application for the US marketplace. Phase 3 studies are usually very large, consisting of thousands of patients usually double blind, randomized, and controlled studies that are often conducted at multiple sites. In this Phase, detailed data are gathered about the effectiveness of new therapeutic drug product in comparison to control subjects. Subjects are followed to evaluate side effects and safety. Phase 3 studies establish effectiveness of final dose, indications for clinical use, labeling, application claims, product's stability, packaging and storage conditions. Upon completion of Phase 3, the sponsor submits an NDA to the FDA for premarket approval in order to make it available for final clinical use in the prescribed patient population [4-6].

FDA's Good Manufacturing Practices (cGMP's) and Pre-Approval Inspections (PAI's)

Current Good Manufacturing Practices (cGMP's): Pharmaceutical cGMP's (Title 21 CFR 210 & 211) are the part of quality assurance practices which ensure that the new genomic drug products are consistently produced and controlled in conformance with the FDA's quality standards. They are known as current manufacturing practices, processing, packing, or holding of genomic therapeutic drugs (the ICH Q10 adopted by the US in 2009). The FDA guidance," Quality Systems Approach to Pharmaceutical GMPs" describes the aim of the agency to help manufacturers implementing modern quality systems and risk management tools to meet the requirements of the agency's current approaches to cGMPs. The implementation of ICH Q10 throughout the product life cycle facilitates and strengthens the link between drug development and manufacturing activities. In addition to ICH Q10, the FDA adopted industry sponsored guidelines for continuous quality improvement (ISBN 0273-3099). The FDA is committed to support ways to promote drug development and accommodates NDA sponsors to use improved quality management approaches to foster innovations and improvements. These approaches help enhance the consistency and coordination of the FDA's drug quality regulatory programs, in part, by further integrating enhanced quality systems approaches into the Agency's regulatory processes concerning review and inspection activities. In reference to New Drug Applications (NDA's), cGMPs include quality system approaches whereby the sponsor addresses the specifications of the drug product and the manufacturing process controls from the prototype design to the production and release of the finished product.

The FDA's cGMP regulations do not prescribe in detail how the manufacturer must proceed as it designs and manufactures specific drug product. Instead, a framework is presented requiring the manufacturer to develop and follow procedures and to fill in the appropriate details for a particular drug. However, the most important point behind GMP regulations is that quality must be designed and built into a product. As development proceeds, the active drug substance and dose form must be

manufactured at large scales. This scale-up may introduce variations in the manufacturing steps of a drug product. Thus, it is critical to monitor the drug substance and product for variations during development and manufacturing processes. The emphasis of design controls drug GMPs should be on products that conform to defined user needs and intended clinical uses. For NDA applications, it is essential to have data showing that the product and active drug substance have documented stability in the packaging that will be used for shipping and ultimate clinical use. FDA GMP regulations require information about all the steps of the manufacturing process from incoming materials to final distribution of the product.

Drug Product Life Cycle (DPLC): The design phase of drug product life cycle is the most important developmental stage in regard to the genomic drug products approvals. It is at the initial design phase that the inherent safety, efficacy of the genomic drug product is established. The review and periodic management of design and processes involved in the genomic drug product's manufacturing are essential to maintain the genomic drug's built-in quality towards completion of the product's specifications. Design maintenance activities during the development process ensures that design outputs are verified as suitable for manufacturing before becoming final production specifications. The flow diagram for GMP inspections represents the process flow for FDA's inspections for design control regulatory requirements. The FDA investigator verifies and validates that the formulation, manufacturing or processing methods are consistent with descriptions described in the section of the PMA-NDA application. Manufacturing process flowcharts provide road maps to FDA investigators. They provide a detailed view of the process and increase understanding of how the process flows. With a process flowchart, FDA investigators can identify critical control points of the genomic product's manufacturing processes.

Genomic Product's Risk Assessment & Monitoring: The DPLC for genomic NDA is an integrated development and manufacturing framework. The DPLC can be divided into the following three categories.

1. Early- genomic product cycle (concept, prototype)
2. Mid-genomic product cycle (pre-clinical, clinical, manufacturing)
3. End product cycle (intended clinical use, application of FDA's continuous quality monitoring standards)

All segments of DPLC are interconnected to every other phase with the final end product providing built-in quality and process improvement steps learned from one segment of the life cycle into another segment of the life cycle as it proceeds to the next generation of genomic products. The essential components of DPLC are composed of management responsibilities, quality assurance, and genomic drug design monitoring units. The ICH quality system approach requires sponsors of NDAs to establish and maintain procedures to control the design of the genomic drug product in order to ensure that specified requirements are met. The intrinsic quality of the genomic NDA drug product and its safety and efficacy are established during the design phase. The appropriate drug design controls are observed and maintained during production stages of development so that finished drug products are safe and effective for their intended clinical use and points of disposals. Process validation (PV) is a requirement of the FDA's cGMP regulation and typically, the drug industry approach to PV has been to evaluate prospective batches incorporating risk analysis in regard to complexity of the manufacturing process and dosage form unit operations including critical control points monitoring during entire DPLC.

FDA's 21 century cGMP and ICH initiatives (such as Q8, Q9, and Q10) are part of regulatory requirements for new genomic product's NDA approval process. Risk management is applicable to several areas of PV, from early stages of product design / development, manufacturing and end stage of the product's release. Some of the benefits of total genomic drug product's risk management approaches during DPLC are as follows:

- Benefits process understanding by proactive identification of failure modes (hazards) and managing the identified risks as early on in the product life cycle
- Enables that high risk, critical aspects of the process are well recognized by appropriately designed studies
- Monitoring of risks reduces product and process failures

It is important to assess the risks in each manufacturing process step. The assessment starts by identifying the potential risks in each manufacturing process step. The assessment starts by identifying the potential risks, then controlling them to an acceptable level to ensure that the genomic product consistently meets FDA approval quality standards. FDA's Quality by Design (QbD) guidances provides a sound framework for design controls from product development to the final manufacturing end processes and for post-development changes and optimization. The QbD concepts are outlined in ICH Q8, Q9, and Q10 guidelines. These ICH documents are already adopted by FDA. The QbD approach can be maintained throughout the life cycle of the genomic product to facilitate continuous quality improvement. In contrast, previously, traditional pharmaceutical manufacturing relied heavily on end product testing, and the process typically lacked the flexibility needed to respond to variables encountered during manufacturing processes. The application of Hazard Analysis Critical Control Points (HACCP)

principles identifies critical control points (CCPs) in the manufacturing process that require quality control monitoring because of detection of out-of-limits or drifts when they occur. The HACCP system provides a focus on the CCPs most likely to control product safety. This approach allows FDA reviewers and investigators to evaluate CCPs over time by examining a firm's monitoring and corrective action records. Investigators can verify the HACCP application by confirming that significant product safety hazards are properly identified, and the appropriate controls are in place [4-6].

CONCLUSION

New genomic drug applications are reviewed primarily for safety and efficacy with regard to their claims for intended clinical use. The FDA's mission is to facilitate the development of the premarket review and evaluation of INDs and NDAs. A central theme over the past few years has been a standardized approach to evidence-based review and evaluation. The FDA emphasizes the Quality System approach to genomic product's design of studies by providing oversight and objective review by setting thresholds for new product's safety and effectiveness by ensuring that organized data and appropriate labeling are present in support of the new medical product's intended and clinical use [6].

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