Preclinical Data Required for an IND

Revathi Tirughana ACRP-CP,PMP
Regulatory Affairs Specialist
Office of IND Development and Regulatory Affairs

Overview

- Definitions
  - Preclinical data required
    - Product development
      - Preclinical animal studies
        - Tips for Good Preclinical Data
          - Key Takeaways

Definitions

- **Good Documentation Practices (GDP)** are methods for recording, correcting and managing data, documents and records, to ensure the reliability and integrity of information and data throughout all aspects of a product's lifecycle
  - "Attributable, legible, contemporaneously recorded, original or a true copy, and accurate **(ALCOA**)"
- **Good Laboratory Practice** (**GLP**) is a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. (21CFRPart 58)

Preclinical Study Data Required

- Product Development
  - Product characterization
  - Manufacturing platform development
- Preclinical Animal Studies
  - To assess product safety
  - To assess product potency or efficacy

Product Characterization

- Conduct extensive characterization studies
  - "Know thy product"
  - Use similar class reference, FDA guidance docs
- Identify product's quality attributes (QAs) and potential impact to product potency
  - chemical, physical, biological and microbiological attributes
- Identify key product specific assays to be used for product release testing or biomarker assays to be used in clinical studies.
  - Potency assay development

Manufacturing Platform Development

- Establish manufacturing platform parameters
  - Identify cell culture conditions, limitations, and susceptibility
  - Consider scale-up and new technology in the future
  - Qualification runs
- Identify critical reagents and back-up sources
  - Research vs GMP grade products
  - Performance comparability, cost, & reliable supplier
- Assess how the product will be used
  - Product administration, concentration, formulation, and delivery systems

Preclinical Animal Studies

Types of Animal Studies Required

- Proof of Concept/ Efficacy data (Pharmacology)
- Biodistribution (Pharmacokinetics)
- Safety/toxicology data (GLP)
- Tumorgenicity

- Key Considerations
  - Model selection: Species, disease type, tumor burden, Biological system compatibility
  - Study design comparability: Treatment regimen, Dosing

- Product used in the in-vivo studies should be manufactured and tested as per the proposed investigational product to support product safety/efficacy.

TIPS for Good Preclinical Data

- Identify studies that may support a future IND application and incorporate GDP prospectively.
- Strong **data integrity** = strong **data quality.**
- Incorporate quality by design (QbD) as much as possible when planning preclinical studies.
- Practice transparency in preclinical research reporting.
- Any data that supports an IND application is subjected to critical review by the FDA.
- Consider using Laboratory Information Management systems (LIMS), Electronic lab notebook, or databases which allow for controlled document storage.

Why Does Preclinical Data Matter?

U.S. FOOD & DRUG

FDA STATEMENT

Statement on data accuracy issues with recently approved gene therapy

For Immediate Release: August 06, 2019

Statement From: Director - Center for Biologics Evaluation and Research (CBER) Dr. Peter Marks M.D., PhD.

As a public health agency, we believe that it is critical to facilitate the development of innovative safe and effective medical products, like the cellular and gene therapy products that have shown enormous potential to treat previously untreatable diseases. As part of the approval process for biological products, the agency reviews extensive information submitted by manufacturers, including details of how the product is made in a reproducible manner, how it has been tested in animals, and how it has been investigated in human clinical trials to demonstrate its safety and efficacy.

H

FDA Says Some Preclinical Data was Manipulated for Novartis' $2.1 Million Gene Therapy Drug

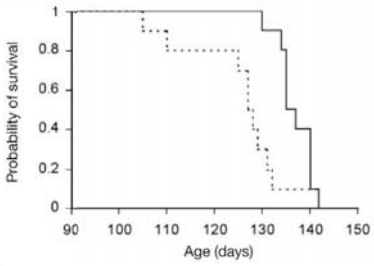
Published: Aug 07, 2019 | By Alex Keown

In May, the U.S. **Food and Drug Administration (FDA) approved Novartis'** gene therapy Zolgensma as a one-time treatment for spinal muscular atrophy. On Monday though, the regulatory agency revealed that **data manipulation was involved** in the preclinical process but

FDA Statement excerpt:
" However, the integrity of the product testing data used in the development of the product's manufacturing process is still a matter that we are continuing to evaluate and take very seriously."

Why Does Preclinical Data Matter?

- Animal data showed some promise.
- Clinical trial was completed with 412 patients in a randomized placebo controlled study.
- Patients treated with investigational product failed more rapidly than those on placebo. (Gordon et al, 2007)
- Alluded to issues with transgenic mouse model selection



All data that is used to support an IND may have an impact on human subject.

Key Takeaways

- Robust preclinical testing serves a fundamental role in characterizing the potential risks associated with an investigational product.
- Recognizing pitfalls and addressing them earlier on in drug development will pay off in the long run.
- Quality of preclinical data is integral in translational research and subsequently has real life implications.

References

1. Gordon, P., Moore, D., Miller, R., Florence, J., Verheijde, J., Doorish, C., Hilton, J., Spitalny, G., MacArthur, R., Mitsumoto, H., Neville, H., Boylan, K., Mozaffar, T., Belsh, J., Ravits, J., Bedlack, R., Graves, M., McCluskey, L., Barohn, R. and Tandan, R. (2007). Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomised trial. *The Lancet Neurology*, 6(12), pp.1045-1053.
2. US-FDA, CBER Directors (2019) https://www.fda.gov/news-events/press-announcements/statement-data-accuracy-issues-recently-approved-gene-therapy
3. US-FDA,(2018). *Section 1. Modernize Toxicology to Enhance Product Safety*. [online] U.S. Food and Drug Administration. Available at: https://www.fda.gov/science-research/advancing-regulatory-science/section-1-modernize-toxicology-enhance-product-safety-strategic-plan-regulatory-science [Accessed 5 Dec. 2019].
4. Keown, A. (2019). *FDA Says Some Preclinical Data was Manipulated for Novartis' $2.1 Million Gene Therapy Drug | BioSpace*. [online] BioSpace. Available at: https://www.biospace.com/article/some-preclinical-data-was-manipulated-in-novartis-2-1-million-sma-gene-therapy/ [Accessed 5 Dec. 2019].