Regulatory Submission: Applying GLP in Surgical Efficacy Studies

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Welcome to Toxikon
Toxikon is a preclinical contract research organization. We contract and partner with biotech, pharmaceutical and medical device industries to deliver exceptional product development services.
Experience

- More than 30 years in the R&D, Analytical Chemistry, *in-vitro* & *in-vivo* services
  - Material Qualification
  - Medical Devices
  - Combination Products
  - Packaging / Bioprocessing Support
  - Pharmaceutical Drug Product
  - Biologics
  - Excipients
Quality Credentials

- **GLP** - Supporting applications for research or marketing permits (IND, NDA, IDE, BLA, PMA, 510K)

- **Non-GLP** – For pilot studies, efficacy studies, and research and development and screening of materials
Quality Credentials and Certifications

» ISO/IEC 17025: 2005 Accredited

» AAALAC Accredited

» FDA Registered

» USDA Registered

» OLAW Assurance

» MSPCA Permit

» Nuclear Regulatory Commission (Radiolabel)
The Markets We Serve

- BIOTECH
- PHARMA
- DEVICES
- CUSTOM
Preclinical testing of medical device and drug candidates provides critical insights into their human safety and therapeutic profiles.
ARE WE CRAZY??

"SO HAVE YOU FILLED OUT YOUR ORGAN DONOR CARD YET??"
Application of the Standard

» Conducting Nonclinical Laboratory Studies That Support Or Are Intended To Support Application Of Research Or Marketing For Products Regulated By The FDA

» Includes:
  • Food
  • Food Additives
  • Animal Food Additives
  • Human and Animal Drugs
  • Medical Devices For Human Use
  • Biological Products
  • Electronic Products
What is Efficacy?

» No shortage of definitions
» Efficacy vs. Effectiveness vs. Benefit
Efficacy

4 Critical Factors:
- Benefit to be achieved
- Medical problem giving rise to the use of the technology
- Population affected
- Conditions of use under which technology is applied
Efficacy

» Benefit:
  • Technology’s efficacy depends heavily on its benefit is simple…
  • …But what outcomes represent benefits?
    • Curative technology has direct relationship to patient outcome
    • Diagnostic technologies?
      • Technical Capability
      • Accuracy
      • Impact
      • Therapeutic Impact
      • Patient Outcome
        » Longevity
        » Relief from symptoms
Efficacy

» Medical Problem
  • Seems simple but…
  • Can lead to controversy
    • Cost?
    • Outpatient vs. inpatient?

» Population Affected
Efficacy

» Conditions of Use

• Partially determined by the skills/knowledge/abilities of health personnel

• Average conditions of use
  • May differ between hospitals/physicians etc.

• Valuable to have measures of outcome that are not dependent on differing variables inherent in average conditions of use
So What is Efficacy?

» Efficacy: The probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under ideal conditions of use.

» Efficacy vs. Effectiveness
  • Effectiveness is concerned with the benefit of a technology under average conditions of use
R&D: Testing Your Idea

» Animals vs. Humans
  • Efficacy often requires a complaint patient
  • Size Does Matter!
  • Reproducing Medical Problems
    • Academia vs. Real World
Efficacy and the FDA

» **Effectiveness**: “There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide **clinically significant results**.” 21 CFR 860.7
» **Safety:** “There is reasonable assurance that a device is safe when it can be determined based on valid scientific evidence that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks.” 21 CFR 860.7

» **Clinical Significance vs. Risk**
Why perform preclinical development studies?

Product Expansion:
Additional claims can be supported by clinically relevant studies.

Differentiation:
Products are being evaluated and selected based on the strength of their demonstrated properties.

Competition:
When evaluating products – whether competing or stand-alone – physicians recognize the value of quantitative data that has been generated in a biologic system.

Submissions:
Scientifically valid and clinically relevant data is needed to support safety and efficacy claims.
FDA Device Classification: Risk-Based Approach

- **Class 1: Common, low-risk devices**
  - General controls
  - Most exempt from pre-market submission

- **Class 2: More complex, higher risk**
  - Special controls
  - Pre-market notification [510(k)]

- **Class 3: Most complex, highest risk**
  - (Devices which support or sustain human life; devices which pose potential unreasonable risk of illness or injury)
  - Comprehensive data needed
  - Pre-market application [PMA]
Pre-market Notification vs. Pre-market Approval

» **Pre-market Notification 510(k)**
  • Requires:
    • Demonstration of Substantial Equivalence to Predicate Device(s)*
    
    "As safe and effective as the predicate device(s)"
    • Classes: I, II, some III

» **Pre-market Approval**
  • PMA Requires:
    • Demonstration of Reasonable Safety and Effectiveness Class: III
Designing Efficacy Studies

- **Is there guidance?**
  - Talk to the FDA

- **Never under estimate the power of a pilot study!**
  - Can save time and money
  - Non-GLP

- **Do your home work**
  - Established animal models?
  - Species?
  - Academic studies vs. what is needed to show efficacy
  - Controls
    - Predicate vs. Negative Controls vs. Both

- **Keep them separated**
  - Safety= Risk
  - Efficacy= Clinical Significance
Designing Efficacy Studies

» Animal Numbers

» Knowing your device can save you money
  • Participation in your studies?

» Animal model relevance to real world application
  • How far do you really need to go?

» Analysis and Endpoints

  • Quantitative vs. Qualitative
    • Histomorphometry
    • MicroCT
  • Other testing?
    • Biomechanical
Designing Efficacy Studies

» Moving Safety and Efficacy
  • Where to begin?
  • Combination products

AND LASTLY……..

» GLP vs. Non-GLP
  • GLPs and surgical efficacy studies
What are the GLPs?

» FDA 21 CFR Part 58 Good Laboratory Practice for Nonclinical Laboratory Studies
Application of the Standard

» Intent: To Assure The Quality And Integrity Of The SAFETY Data

» Safety vs. Efficacy
  • Safety Data ALWAYS GLP
  • But What About Efficacy?
What Does This Really Mean?

» 3 Day Course
» Why Do It Yourself, When You Can Hire Someone To Do It For You?
  • Hire a Consultant
» GLPs May Be Written In Black And White But Really…..
» GLPs Are About…
  • Managing
  • Organizing
  • Documenting

…To Assure The Integrity Of The Data And To Be Able To Reconstruct The Entire Study.
The Basics

» Overhead In Managing A GLP Program Is More Than Some Universities And Start-up Companies Can Afford
The Basics: The People

People

• The Three MUST Haves:
  • Management
  • Quality Assurance Unit (QAU)
  • Study Director
• Three Separate People
• Defined Reporting Structure
  • Organizational Chart
• Defined Responsibilities
The Basics: The People

» Management
  • Overall Responsibility For GLP Testing
  • Assures Study Director Has Resources

» Study Director (SD)
  • Overall Responsibility For The Conduct Of The Study
  • HUGE Responsibility

» QAU
  • Monitors For Compliance (Protocols/SOPs)
  • Reports Findings To Management And SD To Make Corrective Actions
The Basics: The People

» Technical Staff
  • Perform The Studies Or Perform Tasks To Support Studies (Animal Care)
  • Education, Training, And Experience
  • Training Records And Job Descriptions
The Basics: The Facility

» Facility

- Suitable Size
- Animal Care Facilities
  - Separation Of Species (Test System)
  - Isolation Of Studies
  - Separation Of Sick Animals
  - Routine And Specialized Housing
- Separate Storage Of Supplies
  - Food/Bedding
- Separate Area For:
  - Storage Of Test Article
  - Prep Of Test Article
- Archives
The Basics: The Equipment

» Equipment
  • Appropriate Design For Its Intended Purpose
    • Validation
    • Calibration
    • Maintenance
    • SOPs
The Basics: Operations

Operations

• SOPs
  • Equipment
  • Defined Activities
  • Used To Confirm Conformance To Standards- GLPs, USDA, OLAW Etc.

• Reagents
  • Traceability
  • Verification Of Suitability
  • Includes Support Drugs And Fluids
Animal Care

- SOPs For ALL Activities (Yes, ALL Of Them)
- Vendor Selection And Qualification
- Ordering Of Animals
- Receipt
- Inspection
- Verification Of Health Status
- Quarantine/Acclimation
- Individual Unique Identification
- Separation Of Species
- Husbandry Practices
- Food/Bedding Analysis
- Pest Control
Test and Control Articles

» Characterization Of Test And Control Articles
  • How Is This Done For Devices?
  • Still A Bit Of A Mystery With The FDA
  • The Study Director Should Know:
    • How It Was Made
    • How Stable Is It?
    • What Is It Made Out Of
    • Labeling (Lot/Batch)
  • Documented By Testing Facility
  Or The Sponsor

» Management Of The Device
  • Handle If It Were A Controlled Substance
    • ID
    • Security
    • Accountability (Total Received/Used/Final Disposition)
Test and Control Articles

» Documenting Use Of Other Products
  - Carriers
  - Supporting Materials/Delivery Devices
The Paperwork

» Protocols
  • Content Is Responsibility Of The Study Director
  • Amendments- Planned Changes
  • Deviations- Errors In Execution
  • Unplanned Events- Unforeseen Circumstances
  • All MUST Be Clearly Documented

» SOPs
  • Used To Fill In The Finer Details Of The Protocol
  • More Specific Description Of All Aspects Of GLPs

» Conduct
  • Data Recorded Clearly/Descriptively/Detailed
  • Recorded At The Time Of The Event
The Paperwork

» Reports
  • Includes Elements Of The Protocol
  • Includes Objectives And Procedures
  • Include Amendments/Deviations/Unforeseen Circumstances
  • Summary Of Data
  • Conclusions

» Archiving
  • Study Director’s Responsibility
  • ALL Data MUST Be Archived
  • Send To Archives When Final Report Is Signed
» What If I Did Not Follow an Aspect of the GLPs?

- Study Could Be Rejected
- You Cannot Make GLP After The Fact
- GLP Exemptions
  - Study Director And QA Can Make Statements As To:
    - What Sections Were Not Compliant
    - Why It Was Not Compliant
    - What Risk That Has On The Integrity Of The Study
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References


