Review of USFDA, EU and SG5 Clinical Requirements

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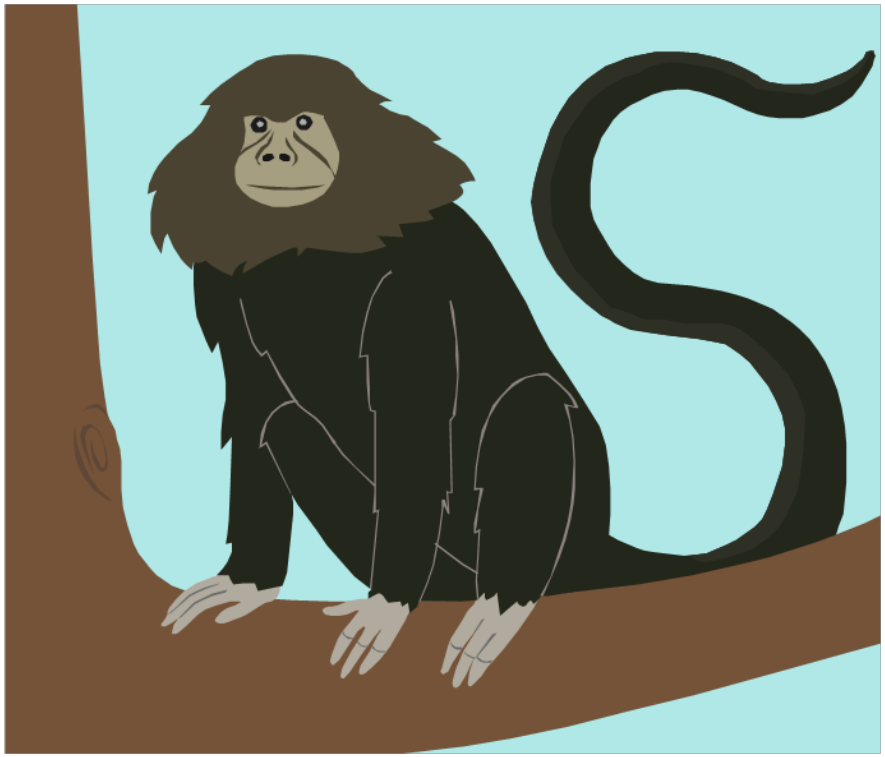
Hello!



Objective

- To demonstrate the parallels between the requirements for USFDA review of premarket clinical data, EU requirements and GHTF SG5 guidance for clinical evaluation
- To enable conformity assessment bodies and regulatory authorities that recognize the EU requirements and SG5 guidance to accept FDA premarket clinical data as supportive of compliance with the Essential Principles of Safety and Performance

Discussion Points

- Premarket approval
- FDA standard for review
- EU clinical requirements
- GHTF-SG5
- Clinical evidence
- Clinical evaluation
- Parallels between FDA, EU and SG5 requirements

Premarket Approval

- “Truly new”, breakthrough medical devices must be approved by FDA before being sold in the US
- Most medical devices are marketed through the 510(k) route which requires a demonstration of substantial equivalence
- Less than 2% of all medical devices go through the premarket approval (PMA) route
- PMA typically is the route to market of last resort because it is long and expensive
- Majority of “truly new” medical devices require clinical investigation

FDA Standard for Review

- Medical devices must be determined to be **safe and effective**
- There must be a reasonable assurance that device is safe based on **valid scientific evidence**
- Clinical data allows FDA to **weigh any possible benefits against probable risks** of injury or illness from use of device
- Effectiveness of device is to be determined on basis of **well-controlled investigations by qualified experts**
- Advisory panels consisting of experts in a particular area of medicine are engaged by FDA when FDA lacks the relevant knowledge or experience on the particular device

Medical Device Directive

- The Medical Device Directive (MDD) 93/42/EEC, as a general rule, requires that evidence of the clinical **performance and safety** of a medical device be provided by means of clinical data
- Clinical data can come from a number of sources, including the scientific literature and clinical investigations
- The evaluation of clinical data is the process by which the **data is assessed, analyzed** and deemed appropriate and adequate to establish conformity of the device with the pertinent essential requirements of the MDD
- The outcome of this process is a report which includes a conclusion on the **acceptability of risks and side effects when weighed against the intended benefits** of the device

EU Clinical Investigations

- Clinical investigations must be perfromed on the basis of an appropriate plan of investigation
- Clinical investigations must be performed in circumstances similar to the normal conditions of use
- All the appropriate features, including those involving the safety and performance of the device, and its effect on patients must be examined
- The investigations must be performed under the responsibility of an **authorized qualified person** in an appropriate environment
- The written report must contain a **critical evaluation** of all data collected during the clinical investigation

EU Clinical Data Requirements

- Clinical data in CE marking process required to demonstrate device is **safe, performs as intended by manufacturer, and benefits outweigh risks**
- Specific requirements for clinical evaluation of most devices are not available in established guidance
- In the absence of specific requirements, the manufacturer must decide which data are sufficient for CE marking (e.g., number of subjects, endpoints, patient follow-up period, etc.)
- Majority of CE marking trials are nonrandomized, single arm, feasibility studies involving less than 100 patients for which the primary objective is to demonstrate safety
- CE marking protocols rarely include a study hypothesis and statistical sample size rationale in spite of its requirement by the European Standard (ISO 14155-1&2)

US Approach

- To receive approval to market a Class III high-risk (and some Class II) medical device in the US, a manufacturer must demonstrate that the device is **reasonably safe and effective**
- Typically requires a prospective, randomized controlled, adequately powered clinical trial involving hundreds of patients
- The EU approval process does not require an evaluation of effectiveness for medium- to high-risk medical devices

Differences Between US and EU

- **Example:**

  US

  FDA required 800-patient, multicenter, randomized trial comparing distal protection to usual care (no protection)

  EU

  GuardWire device CE marked on basis of 22-patient, single arm study to demonstrate safety and performance for aspirating material during stenting

GHTF – SG5

- Promote convergence of regulatory requirements for generation and presentation of clinical evidence
- Essential Principles of Safety and Performance require that **known and foreseeable risks and any undesirable side-effects are minimized when weighed against the benefits of intended performance**
- The clinical safety and performance of many technologies are well-characterized
- Other devices utilize new, state-of-the-art technology with little or no human application
- Assessment of what is acceptable clinical evidence must be undertaken on a case-by-case basis

Clinical Evidence

- GHTF – SG5/N1R8: 2007 Guidance
- Clinical data and clinical report
- Important component of the technical documentation needed to demonstrate conformity with Essential Principles
- May be submitted in part or in total to and reviewed by conformity assessment bodies and regulatory authorities
- Used to support marketing of the device, including any claims made about the safety and performance, and labelling of the device

Clinical Evaluation (Basics)

- GHTF – SG5/N2R8: 2007 Guidance
- Assessment and analysis of clinical data to **verify clinical safety and performance**
- Important for **demonstration of risk-benefit profile**
- Manufacturers can draw on any one or combination of data sources, including published literature, clinical experience on comparable devices or data from clinical investigations
- Medical devices with little or no human experience likely require clinical investigation

How is Clinical Evaluation Performed?

- ***Identification*** of documentation/data from clinical investigations, including investigation plan
- ***Appraisal*** for understanding merits and limitations of clinical data
- ***Analysis*** for determining if data collectively **demonstrates clinical performance and safety**
- Basis should be considered for demonstration of performance as intended and **acceptable risk-benefit profile**
- **Should be conducted by suitable qualified individual(s)** with knowledge of device, research methodology, and conditions to be treated by device

Clinical Evaluation Report

- Outlines scope and content of the evaluations, clinical data, appraisal and analysis
- Documents conclusions about **safety and performance** of the device in question
- Outlines technology on which the medical device is based, intended use and any clinical performance claims
- Where clinical data is relied on for a comparable device which has been the subject of an earlier clinical evaluation (for which the manufacturer holds the evaluation report), the data from the earlier report can be cross-referenced

Parallels Between USFDA, EU and SG5 Requirements

- Submission of valid scientific evidence/clinical evidence
- Demonstration of clinical safety and effectiveness/safety and performance
- Risk-benefit analysis
- Well-controlled investigations/clinical evaluation should be performed by qualified individuals
- FDA review of premarket clinical data comparable to assessment of clinical evidence

Conclusions

The parallels between the requirements for USFDA review of premarket clinical data, EU requirements and the GHTF SG5 guidance for clinical evaluation should enable conformity assessment bodies and regulatory authorities that recognize the SG5 guidance to accept FDA premarket clinical data as supportive of compliance with the Essential Principles of Safety and Performance

Conclusions

The requirements by the USFDA for demonstrating reasonable safety and effectiveness represents a more stringent standard than the EU and SG5 requirements for demonstrating safety and performance.

Consequently, clinical data from FDA-approved clinical investigations should be accepted in lieu of additional clinical trials


The End

Thank You!

Questions?