Preclinical Data and Regulatory Considerations.

Jim Ackland

Regulatory 101

- **Regulatory agencies administer laws and regulations**

- **Why have laws and regulations?**
  - Prevent ineffective or unsafe products entering the market place
  - Products are developed which have an acceptable risk benefit profile (safe and effective)
  - Ensure products are reasonably safe to proceed into clinical investigation

- **Regulatory agencies are conservative by nature**

The Basic Regulatory Requirements

- Laws and Regulations
  - High level
  - Country specific

Penalties apply - fines, sanctions, imprisonment

The Basic Regulatory Requirements

- Guidelines and guidance
  - Often generic in nature
  - Interpretation required for particular applications
  - Change as technology advances
  - Different standards and procedures in different regions

Penalties apply – costly additional work, development delays, loss of financial support

Regulatory Changes/Regulatory Creep

- Major regulatory changes occur after disasters:
  - Dangerous medicines - Safety
  - Ineffective medicines - Efficacy
  - Contaminated medicines – Quality

- Minor regulatory changes occur constantly with technology and knowledge:
  - NexGen Sequencing
  - New viruses or adventitious agents identified
  - Pharmaco-vigilance identifies safety signals
  - Similar products in development set new precedence

Regulatory Perspectives

- Regulators and Sponsors/Developers have different perspectives on product development

Regulatory Perspectives

- Sponsors view
  - Regulators will tell us what to do
  - Regulators inhibit development
  - Too conservative, risk averse and impose unnecessary delays
  - The world needs an AIDS vaccine –lets get on with it

Regulatory Perspectives

- Regulatory agency view
  - Sponsors expect us to tell them what to do
  - Sponsors don’t understand the risks associated with this product
  - More data is needed to define the risks
  - We want to minimize the risk of harming someone

Safety is Always Primary

"FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety."

IND Regulations [21 CFR 312.22 (a)]

Risk-Benefit Assessment

- At various steps there is a risk-benefit assessment by regulatory agencies (and companies) involving
  - Quality
  - Safety
  - Efficacy
- Initial clinical trial application
- Subsequent clinical trial applications
- Prior to marketing approval
- Post approval pharmacovigilance

Risks for Novel Vaccines

- Predictable potential risks
  - Chemical or microbial contamination, inadequately characterized product and impurities, lack of stability
  - Toxicities leading to local or systemic adverse reactions
  - Virulence, attenuation, reversion and transmission for replicating vectors

- Unpredictable risks
  - Rare adverse events such as immune mediated diseases
  - Increase in susceptibility to HIV or other diseases

Risk identification and mitigation

- By product design – design safety into products
- By GMP manufacture – eliminate concerns of contamination, heterogeneity and instability
- By GLP preclinical safety assessment – understand basic toxicities
- By careful well controlled Phase I clinical trials – generate real safety data

How to get product into clinical development

- Demonstrate potential clinical usefulness (**early preclinical efficacy**)
  - In vitro and / or in vivo (animal) models of disease

- Demonstrate adequate **quality** of product
  - Design product with safety in mind
  - Manufacture product under controlled conditions - GMP
  - Characterise in terms of identity, purity, impurities, quantity/potency, freedom from adventitious agents

- Demonstrate adequate **safety**
  - In vitro and in vivo safety studies
  - Characterize toxicity
  - Justify starting dose and proposed maximum dose

Design in safety

- If possible avoid
  - Novel adjuvants with no clinical safety data
  - Neurotropic or cardiotropic viruses
  - Cell lines which have not been used in vaccines
  - Novel excipients or raw materials
  - Raw materials derived from animals
  - Novel process steps
- Be able to defend the safety of your product based on the design.

Manufacture

- Qualified GMP manufacturing contractor or facility
- Documentation, documentation, documentation!

- If it is not documented then it did not happen or does not exist.

GMP manufacture

- Good quality raw materials – USP, NF, EP
- Qualified cell banks
- Qualified virus seeds
  - including genetic stability
- Defined processes and in process controls
- Facilities and procedures which minimize risk of contamination
- Product characterization
- Stability
- Qualified assays

Animal Studies

- 21 CFR, Part 312.23(a)(8)
  - Pharmacologic & Toxicologic Studies
    - "…adequate information about the pharmacological & toxicological studies…on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, & scope of animal and other tests required varies with the duration & nature of the proposed clinical investigations."

Typical vaccine non-clinical package

- Proof of rationale
  - Immunogenicity
  - Efficacy
- Repeat dose toxicity study
  - GLP - 21CFR Part 58
  - Susceptible species (rabbits) – immunogenicity, permissive if a replication virus
  - NHPs are not a default
  - Two species are not a default
  - Novel adjuvants – will need a comprehensive assessment

Vaccine repeat dose toxicity

- Full human dose preferred
- Proposed number of doses in clinical study plus 1 extra
- Can use an accelerated schedule
- Adequate number of animals (5-6 per sex per time point for rabbits, 10/sex per time point for mice/rats, 3-4 NHPs/sex per time point)
- Acute and recovery safety assessments
- Clinical pathology – hematology, blood chemistries, coagulation)
- Full necropsy
- Full histopathology

Regulatory expectation and interactions

- Informal advice from friends at FDA
- Consultants and advisors
- Guidelines – and there many
- Formal consultations/meetings

- However be aware of regulatory creep

Overview

- Importance of consultations/meetings with regulatory agencies
  - Engage RA in development process
  - Validate strategies
  - Differences in RA meeting procedures between European and US countries
  - Sound scientific approach with good understanding of guidelines and product
  - Consider your audience and their expectations

FDA Consultations

- Formal structured approach
- Procedure – Guidelines
- Critical meetings (Type A)
- Prescribed meetings (Type B)
- Non-critical meetings (Type C)

US Meetings/Consultations

- Pre-IND (Type B)
  - Validation of initial clinical strategy and proposal
  - Feedback on adequacy of preclinical safety
  - Comment on manufacture and control of the product

- Pre-pre-IND (Type C)
  - Early advice in advance of pre-IND
  - Novel cell line, virus, process
  - Complex development program

Advice and practical experience

- Adequate preparation is vital
- Timing is very important
  - Questions – think carefully about the questions
  - Information Package – what data is needed to allow an adequate informed response to the questions

Advice and practical experience

- Conduct of the meeting (not usually a meeting)
  - Bring the right company personnel
  - Use scientific evidence to defend positions
  - Respond honestly to questions, don’t guess

- Meeting minutes
  - Take your own notes
  - Share with agency
  - Respond to any discrepancies in agency minutes

Conclusion

- Engage regulatory agencies in development process
- Understand limitations, challenges and expectation of Regulatory Agencies
- Be well prepared
  - Educate the audience
  - Know the existing guidelines
  - Base discussions on science

Good Regulatory Planning

- Understand your product
- Understand the regulatory expectations

- Develop the Product Development Plan with regulatory expectations in mind

- Get good advice early!

Summary

- Design and develop your product/process with potential risks in mind
- Predict and address potential safety issues early in development by GMP manufacture and GLP toxicity studies
- Validate the program through interaction with regulatory agencies

- Understand your product in terms of
  - potential and real risks
  - potential and real benefits

Thank you