Good Regulatory Practices for Biotech CEOs

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OR

How to avoid jail time, fines, sanctions,

costly delays and shareholder backlash

while

developing a novel product

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OR

Mistakes that can kill your product
before you even get started
or as you approach the finishing line

No animals were harmed in the preparation of this presentation
With apologies to the athlete who suffered only minor injury

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Regulatory Planning and the Implications for Strategy and Financing

- Develop the Product Development Plan with regulatory expectations in mind

Good Regulatory Practice

- Understand your product through good science
- Understand how the regulatory requirements apply to your product

- A well thought out and scientifically justified product development plan aimed at meeting the regulatory requirements will minimize problems

The Basic Regulatory Requirements

- Laws and Regulations
  - 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
  - International harmonization - ICH guidelines

Penalties apply – costly additional work, development delays, lack of interest from investors, shareholder wrath

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:
  - New viruses or adventitious agents identified
  - Pharmaco-vigilance identifies safety signals
  - Similar products in development set new precedence

U.S. Food and Drug Administration
Protecting and Promoting Your Health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Who Regulates Medicines?

Therapeutic Goods Administration
Australia's regulatory authority for therapeutic goods

MHRA

BfArM

afssaps

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How to get product into clinical development

- Prior to any clinical studies - 3 key issues to address

  - **Efficacy / Quality / Safety**

But FDA and international agencies are mostly concerned about safety

How to get product into clinical development

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

- Demonstrate adequate **quality** of product
  - Reproducibly manufacture product
  - Demonstrate purity
  - Formulate into “medicine” – solution, tablet, capsule

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

Planning

- Start with an end in mind
  - Product for marketing or
  - Proof of concept

- Develop a basic Target Product Profile
  - Indication
  - Target population
  - Dosage
  - Presentation

Planning

- Outline plan for your pivotal trial (Phase 3 or proof of concept)
- What Phase 1 and intermediate studies would be required
- Preclinical studies
- Manufacturing
- Regulatory interactions and requirements.

Early clinical programme

Phase I studies

- Healthy volunteers (not for cytotoxics!)
- Ascending single dose to establish safe dose, basic kinetics
- Repeated dosing at safe level to investigate tolerability, expand kinetics

- Use results from Phase I studies to revise the TPP

Phase II studies

- First studies in patients
- “Proof of principle”- indications of efficacy in disease condition
- Clinical end-points, surrogate effects
- Target - establish efficacious and safe dose (hope they are the same!)
- Understand clinical performance in order to allow Phase 3 studies to be designed – sample size, clinical endpoints, populations

Typical non-clinical package

- Single and repeat dose toxicology
  - Minimum 14 days toxicology, rodent and non-rodent species
- “Special” toxicology - local tolerance, sensitisation
- Mutagenicity
  - Bacterial mutation *(in vitro), c*hromosomal aberration **or** lymphoma assay
- Safety pharmacology
  - Major body system effects – cardiovascular, respiratory, CNS
- Efficacy pharmacology
  - Demonstrate mode of action from *in vitro / in vivo* models of activity
- Absorption, Distribution, Metabolism, Excretion
  - Compare metabolic fate *in vitro*
  - Demonstrate lack of accumulation

Regulatory interactions and requirements.

- Informal advice from friends at FDA
- Consultants and advisors
- Guidelines – and there many
- Formal meetings with regulatory agencies

- However be aware of regulatory creep

US Regulatory Meetings.

- Formalized program
- Guideline
- Some variation between review divisions

- Pre-IND
- Post Phase 2
- Pre Marketing Application

US versus non-US development

- European Community
  - Clinical trials are approved by national agencies
    - UK – MHRA, Sweden - MPA
    - Meetings can be arranged to discuss product development issues
    - Usually face to face meetings
  - In general, products are approved for marketing by EMA
    - Scientific advice from EMA on development issues such as the design of Phase 3 trials

US versus non-US development

- Australia
  - TGA is the regulatory agency
  - TGA approves products for marketing
  - Clinical trials
    - Approval system (CTX)
    - Notification system (CTN)
- India/China
  - India –DCGI
  - China -SFDA
- South Africa

Acceptability of foreign clinical data

- ICH (adopted by FDA) has a guideline
  - In general foreign clinical data is acceptable but with caveats
  - Data may not be acceptable due to
    - Different medical practice and medicines
    - Different nutritional background
    - Different genetic backgrounds
  - FDA and other agencies have indicated that human data is not a substitute for comprehensive preclinical assessments

Issues that need to be considered or which will challenge biomedical research managers.

OR

Things that keep you awake at night during product development

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What can wrong

- Murphy's law - What can go wrong will go wrong at the worst possible time.
  - But experience helps identify what should be done when and how
  - Cutting corners

- Manufacturing - GMP
- Preclinical Safety -GLP
- Clinical - GCP
- Regulatory

Manufacturing

- GMP
  - Some concessions for early clinical trials
  - Need a qualified experienced person to assess compliance requirements
- Manufacturing contractors
  - Compliance with GMP
  - Qualify contractors by audit
  - Monitor activities
- Examples of horror stories
  - Sterility tests on Master and Working Cell banks
  - Use of animal products
  - Poor documentation

Preclinical safety

- Contractors
- Compliance with GLP
- Need for monitoring
- Examples of what can go wrong
  - High AST/ALT levels
  - For cause audit
  - Poor sample handling
  - Contractor retested at their expense
  - Results no elevation of AST/ALT
  - 12 month delay in the program

Clinical

- Clinical Research Organizations (CROs)
- De-barred Investigators
- FDA audits
  - Falsification of qualifications
  - Source data verification
  - Not following inclusion/exclusion criteria
  - Adequate oversight of CRO by Sponsor
- Post hoc analysis of results

Clinical

- And things can go wrong

- BIAL Clinical Study BAI 10-2474
  - Novel pain medication
  - 128 Healthy volunteers
  - Single and Multiple Ascending Dose design
  - One participant died in the multiple high dose group
  - Five other serious AEs

BIAL Study

- Animal toxicology indicated no particular concerns
- All approvals were obtained
- Clinical protocol was followed
- Daily dosing
- One volunteer after 5th dose of the highest dosage hospitalized in the evening
- Clinic staff continued next day with dosing other volunteers without checking the condition of the hospitalized volunteer

Findings

- Animal pharmacology was limited and needed to establish a dose response curve
- A neuropsychological assessment should have been conducted for this type of product
- In FIH studies doses should be to be adjusted according to the data collected in volunteers already having been exposed during the trial.
- Volunteer safety should take precedence over any practical, economic or regulatory considerations.
- Dose escalation strategies in first-in-human and Phase 1 trials should take account of considerations based on common clinical and pharmacological sense.

FDA Probing Death in Targeted Genetics Corporation Gene Therapy Trial

- SEATTLE, WA--(MARKET WIRE)--Jul 26, 2007 -- Targeted Genetics Corporation (NasdaqCM:TGEN - News).

NIH RAC Meeting on Death in AAV trial

- Evidence points to the AAV gene therapy product not being directly involved
- Immunosuppresive drugs (prednisone, methotrexate and systemic anti-TNF) allowed disseminated histoplasmosis
- Possible infection caused an aneurism in a blood vessel which led to a massive bleed and organ failure
- Unable to identify and control the source of the bleed and control the infection led to the subsequent death.

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CEO of Controversial Gene Therapy Company 'Talked From Both Sides of Her Mouth'

- By Brandon Keim _July 30, 2007

- The death of a person involved in a gene therapy trial run by Seattle-based Targeted Genetics has recalled the tragedy of Jesse Gelsinger, who died in 1999 while receiving an experimental treatment for liver disease at the University of Pennsylvania.

Impact of bad results

- Lots of addition work (time and money)
- Bad publicity
- Funding and financing
- Potential litigation
- Program termination
- Flow on to other programs

Good Regulatory Planning

- Understand your product
- Understand the regulatory expectations
- Develop the Product Development Plan with regulatory expectations in mind

- Check everything and everyone.
- Get advice from independent experienced people early and often!

Thank you