



Risk assessment of 'traditional' biologics

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What is a Biologic?

- From PHS Act of 1944
 - A biologic is any virus, toxin, antitoxin, therapeutic serum, vaccine, blood, blood component or derivative, allergenic products or analogous products or trivalent arsenic compounds such as arsphenamine applicable to the prevention, treatment or cure of diseases or injuries to man



The St. Louis Tetanus Epidemic...where it all began

- Diphtheria-a was a dangerous infectious disease
- Diphtheria antitoxin was a formidable weapon
- Poor supervision of antitoxin production had many concerned.
- Federal oversight was not taken until tragedy in St. Louis, MO
- 13 children died of tetanus after receiving diphtheria antitoxin
- Jim, the horse which had provided the antitoxin for three years was found to have tetanus
- This led to the first regulation of Biologics in 1902.



History of Biologics Regulation

- 1902: Biologics Control Act (Public Health Service Act)
 - Regulates the sale of viruses, serums, toxins, analogous products,
 - authorized biologics regulations
 - Required licensing of manufacturers and establishments
 - Provided inspection authority
- 1906: Food, Drug and Cosmetic Act passed
- 1930: PHS Hygienic Lab became NIH
- 1937: NIH reorganized, Hygienic Lab became Division of Biologics Standardization
- 1955-1972: Biologics regulated within NIH, Division of Biologic standards
- 1972: DBS transferred to FDA, Bureau of Biologics
- 1982: FDA merged the Bureau of Biologics and the Bureau of drugs into the Center for Drugs and Biologics
- 1988: CDB separated into CBER and CDER
- 2006: Certain responsibilities for biologics development reorganized into CDER



What is a “traditional” biologic

Usually generated from recombinant DNA, using biomolecular engineering

- Human growth hormone
- Biosynthetic human insulin
- Erythropoietin
- Granulocyte colony-stimulating factor
- alpha-galactosidase A
- alpha-L-iduronidase
- glucocerebrosidase
- N-acetylgalactosamine-4-sulfatase
- Tissue plasminogen activator
- Interferon
- Rebif
- Interferon beta-1b
- Insulin-like growth factor 1



The Case of Orphan/Ultra Orphan Development

- Regulations
 - Kefauver-Harris 1962
 - Orphan Drug Act of 1983
 - Rare Disease Act 2002
- 350 million people worldwide affected with a rare disease (prevalence)
- 5,000 to 7,000 distinct rare diseases exist,
- Only about 400 rare diseases have therapies and about 80% have a genetic component
- About 30 percent of children with rare diseases will die before reaching their fifth birthday
- Should these be regulated the same?



Biologic Development Program

Risk vs. Uncertainty

- Risk is directly related to uncertainty
 - The more uncertainty the greater the risk
- Every new biologic begins with uncertainty and would therefore be considered high risk
- Risk is reduced with knowledge and good science
- No way to have complete risk prevention with targeted therapeutics
- Reduce the uncertainty and you reduce the risk
- Risk mitigation plan is key to forward motion

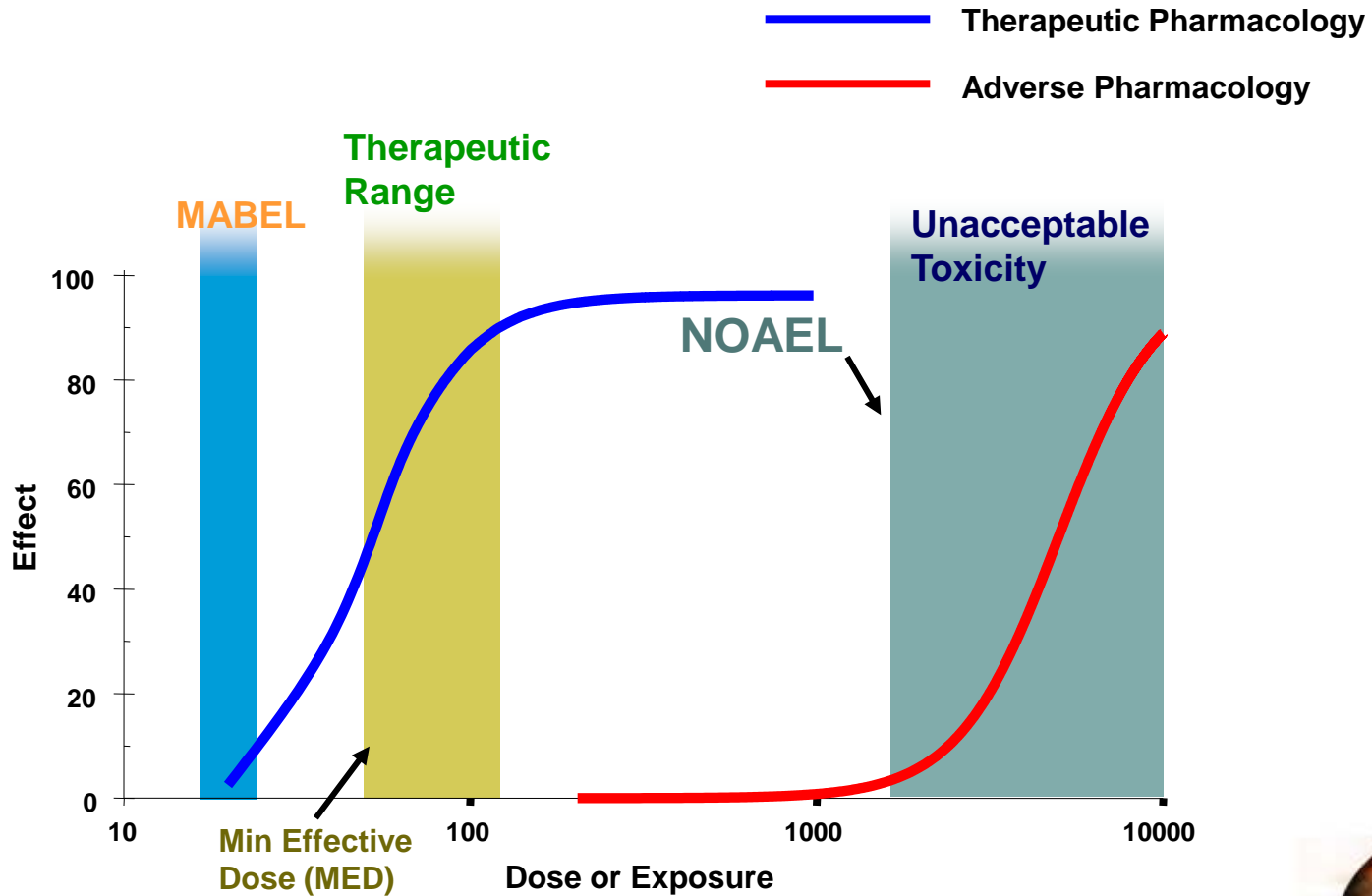


How to reduce the uncertainty

- The overall purpose of preclinical safety program is three-fold
 - Hazard identification (screening, ID tox)
 - Hazard characterization (dose and dosing regimen)
 - Risk assessment (relationship to clinic)
- With the outcome being the ability to propose a safe first in human clinical dose
- Need to balance the risks against the benefits



First in human dose selection



How do we get there?

- History
 - Similar class information
 - Other products with similar mechanism of action
- Regulatory guidances
 - Use these as a place to START your thought process
 - Don't END with these as there are often creative alternatives
- Good scientific thinking
 - This is really the key to success
 - Totality of the data
- Case-by-Case



Biologics and ICH S6...what does it mean

- Safety evaluations should include the use of **relevant** species
- A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope.
 - Knowledge of receptor/epitope distribution can provide greater understanding of potential in vivo toxicity
- Safety evaluation should **normally** include two relevant species
- Toxicity studies in non-relevant species may be misleading and are discouraged.
 - Transgenic animals expressing the human receptor may be used if similar physiological consequences as expected in humans



What Does “Case-by-Case” Mean?

- The pharmacology of the biopharmaceutical should provide the scientific rationale and justification for the appropriate nonclinical tests.
 - Only species that are pharmacologically responsive should be used in safety studies
 - ICH S6 principles should drive consistency of “case-by-case” approach
- Judicious use of animals is critical
 - Appropriate studies, appropriate time in development
 - Not “just because it can be done”
 - Neither “that’s the way we have always done it”



Molecules do not act if they do not bind...BUT binding does not mean they act!

- Biological characteristics of the investigational agent should be considered in devising and accepting a pathway that will ultimately be informative of **pharmacological** and **toxicological** properties
- Primary consideration should be given to receptor mediated activity in designating a test animal species



The BEST Case

Safety studies with the human therapeutic drug (clinical candidate) performed in the most pharmacologically relevant species provide the greatest probability to reveal potential toxicity in humans



What are the challenges with traditional biologics

- Species selection
- Study length
- Dosing regimen
- Patient population
 - Repro
 - Juvenile studies
- Immunogenicity



Challenges in species selection

- Limitations
 - Animal numbers, variability
- Specificity
 - Differences in binding, for example, may be compensated for by alterations in the dose or dosing frequency. Potency is important.
 - Receptor/epitope expression, kinetics
 - Sequence homology
- Predictability
 - How useful is the selected species toward predicting safety in man
 - Specific biological differences
 - Appropriate pharmacology
 - *Especially with respect to safety pharmacology*
 - How homologous is the target human vs. animal



Transgenic animals

Pros

- May be readily available
- Reduces NHP use
- Less variability
- Likely using the clinical candidate for development

Cons

- How relevant is relevant
- Immunogenicity
- More variability
- Biology and physiology may impact outcome



An example of why species selection is so important...



The therapeutic and the tools

- Biologic Therapeutic
- Consistent with other approved class of therapeutics
- Significant safety history with class
- Prior safety programs of class products conducted in normal animals

- Development plan was similar to previous class products utilizing normal animals, 2 species, relevant endpoints, length of study, dose and dosing regimen consistent with clinical program, high dose in safety studies at least 10x above highest anticipated clinical dose



IND-enabling safety studies

- Normal Mouse
 - Acute and Repeat dosing
- Hemolysis of human whole blood
- Acute Rat study
 - Single dose
 - NOAEL = highest dose administered
- Acute Dog with Safety Pharmacology
 - Single dose
 - NOAEL = highest dose administered
- Repeat dose in rats for 26 weeks
 - NOAEL = same dose from acute rat and acute dog studies



Pharmacology studies

- Conducted in the KO mouse at range of doses with significant and sustaining efficacy
- One target organ not affected by single low doses
- Study conducted in KO mouse to affect target tissue



- Result
 - Significant and dose dependent mortality in the KO mouse at doses considered safe in normal animal



What Studies Do You Do... And When?



Pilot Work First...

- Short term, multi-dose NHP study (4 doses total)
- Resulted in chronic study with an elimination of one dose group
- Single species, 6 month study conducted prior to IND to support market approval.



Some thoughts on DART work

- For traditional biologics two species HAS been utilized
 - Rats/mice/rabbits
- Biggest challenges are immunogenicity especially in rabbits
 - Resulting in effects on dams
- There are ways around this with creative dosing strategies



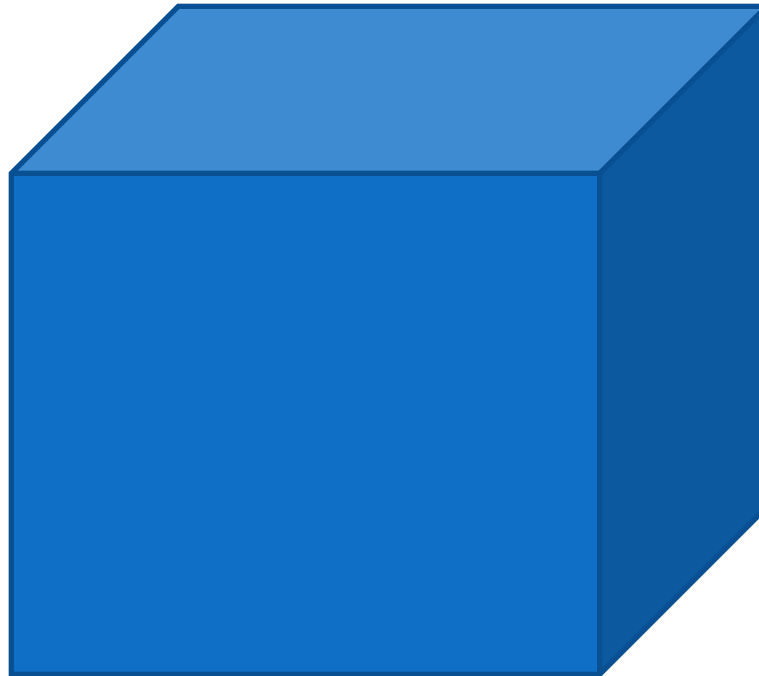
Enzyme Replacement Therapies

- Ceredase/Cerezyme
- Fabrazyme
- Aldurazyme
- Myozyme/Lumizyme

What was the value of the preclinical program to predicting clinical safety outcome?



Time to think outside the box.



Thank you for attending

