Where Have We Been and What Have we Learned from the Past 26 Years of Biologic Drug Development

“I miss back when…”

pharmtox

genzyme
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1982...

- Gallon of gas: 91 cents
- US postage stamp: 20 cents
- First issue of USA Today published
- First implant of a permanent artificial heart
- First CD player sold in Japan
- “Ebony and Ivory” at the top of Pop music charts
- Weather Channel airs on cable for the first time
- Tylenol capsules laced with cyanide kill 7
- Time Magazine’s Man of the Year is the Computer
- St. Louis Cardinals win the World Series
- Actor John Belushi dies
- Leonid Brezhnev dies
- Michael Jackson releases “Thriller”
- *Ghandi* wins the Academy Award for Best Picture

- First commercial use of genetic engineering is launched when human insulin is marketed
The History of Insulin

- 1921: Banting, Best, Macleod and Collip discover insulin
- 1922: Pancreatic extract from dogs administered to a 12 year old boy
- 1936: Protamine was used to develop a slow-acting insulin
- 1950: Isophane NPH (neutral protamine Hagedorn) insulin developed (long-acting)
- 1951: “Lente” insulins developed
- 1956: Antidiabetic oral drugs came on the market
- 1974: Chromatographic methods led to highly purified animal insulin
- 1975: Fully synthetic insulin synthesized by Ciba-Geigy
- 1978: E.coli production of human insulin at Genentech
- 1980: Recombinant human insulin tested
- 1982: Eli Lilly receives approval for Humulin R (rapid) and Humulin N (NPH) in the US from the division of Metabolic and Endocrine Drugs in CDER
Where Have We Been…?

The Ghost of Christmas Past....
Where have we been?

- Alle Ding sind Gift, und nichts ohn Gift; allein die Dosis macht, daß ein Ding kein Gift ist.
- "All things are poison and nothing is without poison, only the dose permits something not to be poisonous."
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.
Putting the “pre” in preclinical

- The overall purpose of preclinical safety program is three-fold
  - Hazard identification
  - Hazard characterization
  - Risk assessment

- With the outcome being the ability to prepare for a safe first in human clinical dose AND to predict the possible negative sequelaes
- Need to balance the risks against the benefits
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 lead to the first regulation of Biologics in 1902.
History of Biologics Regulation

- 1901: 10 children died following administration of a horse anti-diphtheria antitoxin (due to tetanus)
- 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 an 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
International Conference on Harmonization

- The birth of ICH took place at a meeting in April 1990, hosted by the EFPIA in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the USA met, primarily, to plan an International Conference but the meeting also discussed the wider implications and terms of reference of ICH.

- ICH S6 (1997)
  - Guidance document covering development of biotherapeutic products
Alle Ding sind Gift, und nichts ohn Gift; allein die Dosis macht, daß ein Ding kein Gift ist.

"All things are poison and nothing is without poison, only the dose permits something not to be poisonous."
Is evolution necessary?

- (R)evolution in toxicity testing...
  to improve efficiency and predictions
  - International harmonization of guidelines
    - Standardization and flexibility
  - Validation and acceptance of alternative methods
  - Computational toxicology
  - Major technological advances
    - “Omics”, non-invasive/minimally invasive imaging, stem cells etc.
  - Use of non-traditional animal species/models
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
Campath...an example of evolution

- **2001 for oncology**
  - Safety package was limited
    - small #'s...
    - nothing chronic
    - Clinical indication drove the science

- **2008 for IMD**
  - Safety package requires significant overhaul
  - Clinical indication driving safety
  - Relevant animal species a problem
  - Transgenic animals available?
    - Comparability?
    - Reproductive studies?
ERT History of Development

- Ceredase/Cerezyme
  - 1991
- Fabrazyme/Replagal
  - 2001
- Aldurazyme
  - 2001
- Myozyme
  - 2006
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

- **Good scientific thinking**
  - This is really the key to success
  - Totality of the data
ICH S6: Guidance for Biologics

FDA Guidance: Estimating The Safe Starting Dose In Clinical Trials For Therapeutics In Adult Healthy Volunteers. July 2005

EMEA Guideline: Guideline On Strategies To Identify And Mitigate Risks For First-In-Human Clinical Trials With Investigational Medicinal Products. September 2007
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.
Challenges in development

- **Selection of relevant species**
  - Generally limited species reactivity
  - Relevant = pharmacologically active

- **Tissue cross reactivity**
  - What does it provide? Something?! Nothing?!

- **What should the relationship be of test material and formulation used in IND-enabling safety/toxicology studies to Phase I/II clinical material?**
  - Length of EARLY studies impacting this
  - Must be decided early

- **Appropriate toxicology studies**
  - How to design the most informative safety package
Challenges in species selection

- Limitations
  - Animal numbers, variability

- Specificity
  - Absolute equivalence of antigen density or affinity for the mAb, however, is not necessary for an animal model to be useful. Differences in binding, for example, may be compensated for by alterations in the dose or dosing frequency. Potency is important.
  - Receptor expression, kinetics
  - Sequence homology

- Predictability
  - How useful is the selected species toward predicting safety in man
  - Specific biological differences
  - Appropriate pharmacology
  - How homologous is the target human vs. animal
Using/defining the relevant \textit{in vivo} species

\begin{itemize}
  \item \textbf{Number of species}
    \begin{itemize}
      \item When is one enough?
      \item How far down the evolutionary tree do you go?
        \begin{itemize}
          \item What are the expectations for a “tox species?”
        \end{itemize}
    \end{itemize}
  \item \textbf{Pilot work}
  \item \textbf{Multiple NHPs}
\end{itemize}
Why do something different?

- Species specificity of your development product limits information that CAN be acquired

- Targeted therapeutics are being developed for more than JUST oncology
  - Chronic safety required for chronic patient population
  - Population specific indication (sensitive populations)
    - Women of child bearing potential, children, etc

- Need to reduce the uncertainty
Borrowing from ICH S6 (sec 3.3)

When no relevant species exists…

- **Use of Homologous proteins**
  - May differ from product intended for clinical use
    - Production process, range of impurities/contaminants, pharmacokinetics, and exact pharmacological mechanism
    - Relevance of surrogate to clinical material

- **Transgenic animals expressing the human receptor**
  - If similar physiological consequences as expected in humans
Challenges of Developing a Homologue

- Cost and resources
- Production capabilities
- Specificity of new molecule/animal to clinical candidate
  - Isotype differences from mouse to NHP to human
- Similarity of new molecule/animal to clinical candidate
  - Key product attributes
- Bioanalytical analysis available
  - What is the criteria for “quality”
    - What constitutes comparability for the surrogate?
    - Biochemical/physical, pharmacology, PK, immunogenicity and safety?
Use of a homologous protein

Pro’s

- May reduce uncertainty
- Helps to reduce animal (NHP) use
- May be most useful reagent for certain toxicology studies

Con’s

- Not the clinical candidate
- It needs to be well characterized
- Comparability during the development process can be challenging
- Might bring into play “second species” questions
- Co-development pathway
- Assays!
Homologues may be useful to understanding pharmacological properties of your human drug
  • Particularly if the target is not well understood

Homologues should continue to be considered as there may be specific instances where the use in toxicology studies is acceptable

However...

Homologues may not be useful (predictive) for assessment of safety of the clinical product for a number of physiological, biological and practical reasons
When no relevant species exists…

- Use of homologous proteins
  - May differ from product intended for clinical use
    - Production process, range of impurities/contaminants, pharmacokinetics, and exact pharmacological mechanism
    - Relevance of surrogate to clinical material

- **Transgenic animals expressing the human receptor**
  - If similar physiological consequences as expected in humans
Challenges in using transgenic animals

- Characterization is key
- Biological relevance needs to be evaluated
- Pharmacology?
- Immunogenicity is still a concern
- Remember though, that a “mouse is just a mouse”...so understand the limitations of your model.
Transgenic animals

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

**Con’s**
- How relevant is relevant
- Immunogenicity
- More variability
- Biology and physiology may impact outcome
Some Key Thoughts

- Understand the differences
  - There is utility in exploring a homologous protein or a transgenic animal for safety information. But be prepared to explain, understand and characterize the differences adequately to make the data useful.

- Accept your limits
  - Remember that it will be the totality of the data that drives your safety assessment. The goal of safety evaluation is to identify the hazards and characterize them adequately. Homologous proteins and transgenic animals can go a long way to filling in the blanks.

- The totality of the data will drive your considerations for FIH
  - Don’t assume NOAEL if MABEL is better
First in human dose selection

- **Therapeutic Pharmacology**
- **Adverse Pharmacology**

Graph showing:
- **Effect** vs **Dose or Exposure**
- Min Effective Dose (MED)
- Therapeutic Range
- NOAEL
- Unacceptable Toxicity

Legend:
- Blue line: Therapeutic Pharmacology
- Red line: Adverse Pharmacology
First in human dose selection

- Dose or Exposure
  - 10 100 1000 10000
- Effect
  - 0 20 40 60 80 100

- NOAEL
- Min Effective Dose (MED)

- Therapeutic Pharmacology
- Adverse Pharmacology
First in human dose selection

Dose or Exposure:
- 10
- 100
- 1000
- 10000

Effect:
- 0
- 20
- 40
- 60
- 80
- 100

NOAEL

Min Effective Dose (MED)

Therapeutic Pharmacology

Adverse Pharmacology
First in human dose selection
Introducing “MABEL”

- MABEL vs. NOAEL

![Graph showing dose-effect relationship for MABEL and NOAEL](image)

- Therapeutic Pharmacology
- Adverse Pharmacology

- MABEL
- NOAEL
- Min Effective Dose (MED)
- Therapeutic Range
- Unacceptable Toxicity
What Have We Learned…?

The Ghost of Christmas Past…again…

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What have we learned?

- *Alle Ding sind Gift, und nichts ohn Gift; allein die Dosis macht, daß ein Ding kein Gift ist.*
- "All things are poison and nothing is without poison, only the dose permits something not to be poisonous."
What have we learned!

- **Need to understand the science!**
  - Decisions on the safety of first-in-man studies need to be science-based and take into account all data (PK/PD, in vivo and in vitro)
    - employ use of “experts” and initiate communication early in development

- **Need to define “biological effect”**
  - Different for each molecule
  - Relevant to clinic (need to understand MOA and differences between animals and humans)

- **Need early biomarkers of pharmacological activity (and assays to measure this activity)**
  - Include pharmacology measurements in toxicity studies?

- Will be established on a “case by case” basis
“Where key events shaped his life and character”
“Where key events shaped his life and character”
Where are we going?

- **Present**
  - New targeted therapeutics
  - Gene therapies
  - Oligonucleotides and siRNA technology
  - Cell therapies
  - Vaccines

- **Future**
  - Challenges will always exist
  - It’s the “spirit” that you don’t know that you fear the most
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