PK/PD Study Strategies for Biopharmaceuticals: Is Bigger Better?

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New Drug Approvals and R&D Spending

Despite use of adaptive trials, improved project management, and increased reliance on global partners, the cost of drug development remains stubbornly high. Among the reasons behind this is growing protocol design complexity, which leads to longer clinical time. For example, while average approval time in the U.S. has declined in recent years, total development time (clinical plus approval) has remained relatively flat, averaging 8.6 years since 2002.
Trends in Total Cost per Drug

Industry Duration

Source: NCE (Dimasi, Parexel 2002); mAbs and Proteins (Reichert, Parexel 2002)
Development Cost Per Phase

Monoclonal Antibodies in Development

MORE mABs IN DEVELOPMENT PRESAGES MORE MARKETING APPROVALS

*Therapeutic Monoclonal Antibodies Entering Clinical Study or Approved, 1995-2007*

Expanded development of monoclonal antibodies worldwide supports projected global sales growth of 14% per year through 2012. While the number of new mAb approvals has remained essentially flat in recent years, annual approvals are set to increase — one mAb has been approved in 2008 and four are undergoing FDA review.

*Note: mAbs studies data presented as 2-year moving averages*

*Source: Tufts Center for the Study of Drug Development*
Future of Monoclonal Antibodies

Market introduction of monoclonal antibodies will continue to increase as drug sponsors become more adept at development and drug regulators become more familiar with evaluating this product class.

- The recent trend of more candidates entering clinical study each year enhances prospects for new monoclonal antibody (mAb) approvals.
- Development programs will increasingly include innovative antibody fragments such as single chains and domain antibodies. Nearly 20 fragments are now in clinical study, although most are in early stage development.
- With 22 mAbs currently available in the U.S. and more than 200 in the pipeline worldwide, regulatory agencies will emphasize a ‘quality-by-design’ approach to manufacturing.
- Merger and acquisition (M&A) activity—with large pharmaceutical firms acquiring antibody-focused biotechnology companies—will expand. Despite initial concerns over the potential for clashing cultures and priorities, evidence suggests that recent M&As have not resulted in diminished productivity.
Why Large Molecules?

- Around 60% of revenue growth forecast to come from biologic products (therapeutic proteins and monoclonal antibodies):
  - By 2010, annual sales of biologics will have increased by $26bn, compared to a $13bn increase for small molecules.

- Within the Big Pharma peer set, the revenue growth rate to 2010 forecast for biologics is a robust CAGR of 13.0%, outstripping the near-static CAGR of 0.9% predicted for small molecules. The small molecule growth rate is depressed by continued exposure to intense generic competition.

- Big Pharma has assumed a strong position within the antibody market, a major attraction of this product type being the total absence of generic risk.
Definition of Biopharmaceuticals

FDA – Biologics: Any virus, therapeutic serum, toxin, antitoxin or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man

- Includes proteins, peptides, their derivatives or products of which they are components

  (Section 351 of PHS Act, 21 CFR 600.3(h))

European Union – Biological Medicinal Product: a protein or nucleic acid–based pharmaceutical substance used for therapeutic or in vivo diagnostic purposes, which is produced by means other than direct extraction from a native (nonengineered) biological source
What is a Drug?

Section 201(g)(1):

- Recognized in USP or other compendia
- **Intended** to diagnose, cure, mitigate, treat or prevent disease
- **Intended** to affect structure or function
- **Intended** as component of these
- Exceptions for foods and supplements
Historical Perspective of Biological Regulations

- 1902 Biologic Control Act/1906 Pure Food Drug Act
- 1972-Transfer of Biologics Regulation to FDA’s Bureau of Biologics (prior regulated by NIH)
- 1982-Bureau of Drug and Biologics Merged
- 1987-Center for Biologics Separated from Center for Drugs
- 1993 Center for Biologics Re-organization into Review Divisions oriented toward product type
- 1995 REGO-Biologics Regulations Brought into Line with Drug Regulations
- 2003 CBER’s incorporation of therapeutic proteins into CDER
- 2005 full integration within CDER review divisions
Relative Size of Small Molecules and Proteins

Size & Complexity – Small Molecule Drugs & Proteins

<table>
<thead>
<tr>
<th>Size</th>
<th>Large Molecule Drug</th>
<th>Large Biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>hGH</td>
<td>IgG Antibody</td>
</tr>
<tr>
<td>21 atoms</td>
<td>~3000 atoms</td>
<td>~25,000 atoms</td>
</tr>
<tr>
<td>Bike</td>
<td>Car</td>
<td>Business Jet</td>
</tr>
<tr>
<td>~20 lbs</td>
<td>~3000 lbs</td>
<td>~30,000 lbs (without fuel)</td>
</tr>
</tbody>
</table>
## Comparison of Small Molecules and Biologics

<table>
<thead>
<tr>
<th>Small Molecules</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low MW</td>
<td>Large MW</td>
</tr>
<tr>
<td>Mostly well defined physicochemical properties</td>
<td>Complex physicochemical properties (e.g. tertiary structure, glycosylation)</td>
</tr>
<tr>
<td>Chemically synthesized</td>
<td>Biotechnology produced from host cell lines and isolated from culture media</td>
</tr>
<tr>
<td>Generally stable</td>
<td>Both heat and shear sensitive (aggregation)</td>
</tr>
<tr>
<td>Single entity, high chemical purity, purity standards well established</td>
<td>Often heterogeneous mixture, broad specifications that may change during development, difficult to synthesize</td>
</tr>
<tr>
<td>Rapidly enters systemic circulation through blood capillaries</td>
<td>Larger molecules (&gt;15-20 kDa) primarily reach circulation via lymphatics, subject to proteolysis</td>
</tr>
<tr>
<td>Oral administration often possible</td>
<td>Usually parenterally administered</td>
</tr>
<tr>
<td>Distributes to multiple organs/tissues</td>
<td>Distribution often limited to plasma and/or extracellular fluids</td>
</tr>
<tr>
<td>Metabolized to active and non-active metabolites</td>
<td>Catabolized to endogenous amino acids</td>
</tr>
<tr>
<td>Specific toxicities (Not associated with pharmacological effect)</td>
<td>Mostly receptor mediated toxicity, including exaggerated pharmacological effects</td>
</tr>
<tr>
<td>Non-antigenic</td>
<td>Usually antigenic (MW &gt; 10 kDa)</td>
</tr>
<tr>
<td>One bioanalytical method for PK studies</td>
<td>Several bioanalytical methods (drug, antibody) for PK studies</td>
</tr>
</tbody>
</table>

Baumann, Current Drug Metabolism, 2006
Utility of PK and PD in Drug Research and Development

**Research**
- Optimize dose regimen in animal models
- Select Lead Molecule

**Preclinical**
- Minimize unnecessary studies
- Optimize dose for tox studies
- Predict safe/efficacious clinical doses (therapeutic window)
- Understand ADME and impact on PK/PD

**Clinical**
- Provide pivotal decision making information (eg, dose regimen)
- Support Go/No Go decisions
- Reduce risks in clinical trials

*These are the same for small molecules and large molecules. However....*
PK of Biologics

- Absorption
- Distribution
- Metabolism
- Elimination
- Analytical Assays
Absorption of Biologics

- **Molecular Weight (MW):** \( \uparrow MW = \uparrow T_{\max} \)
  - Absorption via capillaries MW < 1,000 Da
  - Via lymphatic MW > 16,000 Da
- **Route of Administration (IV, SC, IM)**
- **Absorption kinetics may be non-linear**
  - May produce different \( C_p \)
- **Immunogenicity may differ based on route**
  - SC > IM > IV
Absorption of Biologics

Fig. 2. Correlation between the molecular weight and the cumulative recovery of rIFN alpha-2a (MW 19,000), cytochrome c (MW 12,300), Inulin (MW 5200), and FUDR (MW 246.2) in the efferent lymph from the right popliteal lymph node following s.c. administration into the lower part of the right hind leg. Each point and bar show the mean and SD of three experiments performed in three separate sheep. The line drawn is the best fit by linear regression analysis calculated with the four mean values. The points have a correlation coefficient $r$ of 0.998 ($p < 0.01$).
Distribution

- Approximate plasma volume (3-5% of TBW)
- Limited tissue distribution
- Binding proteins (endothelial binding sites, free or shed receptors, macroglobulins, and other circulating molecules)
  - Have limited binding capacity
  - Have inhibitory or stimulatory effects
  - Serve as transporters and activators
  - Affect therapeutic protein elimination (e.g., IGF-1 and binding proteins)
- Kinetics may be nonlinear
Metabolism

◆ Catabolic Processes
  – Degraded to small peptides and amino acids
  – Liver, Kidney, Blood, Site of Administration
◆ Highly dependent on
  – Structure (e.g., Glycosylation)
  – Charge
  – Size
  – Hydrophilicity/lipophilicity
Elimination of Biologics

◆ Elimination kinetics may be nonlinear

Immune-mediated clearance
- Anti-drug antibodies can increase or decrease clearance (clearing antibodies versus low-affinity antibodies that sustain Concentrations)

Receptor-mediated Clearance (Cl)
- Increases Cl at lower doses
- Decreases Cl as receptors are saturated

Catabolism
Renal elimination of molecules < 69 kDa
Increased half-life due to FcRn receptor and recycling
Analytical Assays

◆ Concentration of biologic
  – Immunoassays (ELISA, RIA)
    • Lack of specificity (active versus inactive, isoforms, endogenous versus exogenous)
    • Interference from binding proteins (e.g., IGFs), anti-drug antibodies
    • Cross-reactivity (e.g., rheumatoid factor)

◆ Assays for anti-drug antibodies
  – Screening assay
  – Binding assay
  – Neutralizing assay/bioactivity assay
Case Study

Bisphosphonates versus denosumab for Osteoporosis:
Inhibitors of bone resorption
Bisphosphonates

- **Absorption:** Poorly Absorbed, especially in the presence of food or calcium \((F = <1-10\%)\)
- **Distribution:**
  - 20 – 80% of absorbed dose taken up by bone;
  - Plasma half-life is 0.5 to 2 hours in humans;
  - Bone half-life is up to 10 years
  - Bisphosphonates should not be absorbed rapidly in large quantities as this can cause the formation of insoluble aggregates or complexes that can impair kidney function
- **Elimination:** Urinary excretion
Alendronate is one of the most potent bisphosphonates currently undergoing clinical investigation (>100-fold more potent than etidronate in vivo).

After a 2-h intravenous infusion, plasma concentrations of alendronate decline rapidly to 5% of initial values within 6 h.

About 50% of a systemic dose is excreted unchanged in the urine in the 72 h following administration.

The remainder is assumed to be taken up by the skeleton.

After sequestration into bone, the elimination of alendronate is very prolonged. The terminal half-life was estimated to be greater than 10 years. Despite prolonged skeletal residence, the biological effects of alendronate begin to diminish post-treatment, since the duration of effect reflects factors besides dose and cumulative drug exposure.

When taken after an overnight fast, 2 h before breakfast, the oral bioavailability of alendronate averages 0.75% of dose with substantial variability (coefficient of variation 55%–75%) both between and within subjects.
AMG 162
“Denosumab”

- FULLY HUMAN monoclonal antibody to RANKL
- $\text{IgG}_2$
- High affinity for human RANKL ($K_d \ 3 \times 10^{-12} \ M$)
- Specific: does not bind to TNF$\alpha$, TNF$\beta$, TRAIL, CD40L
Denosumab Binds to RANKL and Blocks Osteoclast Activation and Function

- **Denosumab**
- **OPG**
- **RANKL**
- **RANK**

Growth Factors
Hormones
Cytokines

**Bone**

- CFU-M Colony-forming unit macrophage
- Prefusion Osteoclast
- Multinucleated Osteoclast
- Activated Osteoclast

**Osteoclast Activated**

**Osteoclast Formation, Activation, and Survival Inhibited**
PK in Preclinical Species

Rat

Monkey

Peterson, et al, AAPS 2004
PK Model: 2-Compartment

Non-Linear Clearance

\[ CL = \frac{V_{\text{Max}}}{(K_m + C)} + k^*V \]
PK Model Adequately Describes Monkey PK
Increased Clearance due to anti-AMG 162 antibodies

Animals that were Antibody Positive (■, ▲) On or Before Week 4 and Antibody Negative (●) up Through Week 6 Following Subcutaneous Administration of AMG 162 to Cynomolgus Monkeys.
PD of Biologics

- Effect can be direct or indirect
- PD generally associated with $C_{\text{min}}$ or AUC
- Both clinical efficacy and safety may occur at later times
  - E.g., Cardiac issues with Herceptin
- Often a prolonged duration of action
- Infusion reactions can occur due to cell lysis and cytokine release syndrome
  - E.g., Rituxan

Adapted from Zhao, AAPS 2008
PD of Denosumab in Monkeys
Indirect PD Model

Effect (NTx)

PD

$K_{\text{synthesis}}$

$K_{\text{degradation}}$

Inhibitory $E_{\text{max}}$

$PD \text{ Inhibition} = 1 - \frac{E_{\text{max}} C^\gamma}{IC_{50}^\gamma + C^\gamma}$
PD Model Adequately Describes Monkey Data
Serum Denosumab Concentrations: Phase 1
Predicted and Observed Serum Concentrations
Predicted and Observed Serum NTx
Other Issues to Consider in the Development of Biologics

- Surrogate Molecules
  - Alternative if molecule does not cross-react with other species
  - Use in reproductive toxicology studies to spare use of primates and increase “N”
  - Challenges of developing a surrogate
    - Cost
    - Time
    - Delay to other projects
Other Issues to Consider in the Development of Biologics

- **Immunogenicity**
  - “Most biotechnology-derived pharmaceuticals intended for humans are immunogenic in animals.” ICH S6
  - Anti-drug antibodies must be measured and characterized
  - Must assess effect on Pharmacokinetics
  - Must assess effect on Pharmacodynamics
  - Immunogenicity in preclinical species may not reflect humans
Other Issues to Consider in the Development of Biologics

◆ Impact of antibodies:
  – Clearing Antibodies
    • Decrease drug effectiveness
  – Sustaining Antibodies
    • Act as depot of drug
  – Neutralizing Antibodies
    • May Decrease drug effectiveness
  – Antibodies that cross-react with endogenous protein
    • May develop antibodies to endogenous compound

⇒ Pure Red Cell Aplasia secondary to anti-EPO antibodies
Summary: PK/PD Study Strategies for Biopharmaceuticals: Is Bigger Better?

- There is an industry trend towards large molecule drug development
- PK/PD can play a key role in development of large molecules
- Fit for Purpose: Advantages and disadvantages of small molecules versus biologics must be considered