Study Design Considerations for Biopharmaceuticals

Maggie Dempster, GlaxoSmithKline

Theresa Reynolds, Genentech

Study Design Topics

- Species Selection
  - Considerations for species selection
  - Justification of number of species
- Duration of Studies
  - Support for Single-dose Clinical Trials
  - Chronic Use Products: 6-months Sufficient
- Dose Selection
  - Application of PK/PD Principles
- Recovery Period
  - Reversibility and Dose Response
  - Immunogenicity
  - Value of Recovery Data

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SPECIES SELECTION

Considerations for species selection

Justification of number of species

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Species Selection - General Principles

[Addendum to ICH S6 (R1)]

"A number of factors should be taken into account when determining species relevancy"

- Comparisons of target sequence homology
- Cell based assays
  - Qualitative/quantitative cross-species comparisons
    - relative target binding affinities
    - Receptor/ligand occupancy & kinetics
- Functional activity assessment / PD Marker
  - In vitro / in vivo

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Species Selection - General Principles

[Addendum to ICH S6 (R1)]

"When the target is expressed at very low levels in typical healthy preclinical species (eg. inflammatory cytokines or tumour antigens), binding affinity and activity in cell-based systems can be sufficient to guide species selection."

"For monoclonal antibodies and other related antibody products directed at foreign targets (bacterial, viral, etc.), a short-term safety study in one species (to be justified) can be considered; no additional toxicity studies are appropriate.

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Species Selection Questions

- How novel is your target, any previous examples?
- How well is your biopharm and/or its target conserved across species?
- Is the target antigen expressed in animal species?
  - Does your drug bind to the target?
  - Does the target antigen have a similar role to that in human?
  - Are the downstream effects the same?
  - Is the target expressed in similar tissues?
- Is the potency similar to that in human?

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Sounds simple enough but….

- Humanised mAb recognises 2 isoforms for antigen on cells in human
  - but only 1 isoform present in animal species
- Potency lower in animal species – how low is too low?
- Antigen expressed in disease state in patient population only – none in animals
- Target Antigen not expressed in animals
  - mAb against bacterial/viral toxin or cancer antigen
- Standard study design not practical for species

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Number of Species?

- Default is for two
  - However, for LMW products only one species is required to be pharmacologically relevant – 2 species used based on metabolism differences and off target toxicity
- Single species for chronic study already suggested by ICHS6
  - Therefore can the chronic study be carried out in rodent (not always non-rodent)
- Situations for one species from the start
  - Biology of target is well understood
  - Biology known to be more relevant in one species vs another species
  - Target poses little concern for significant toxicities
  - Parameters to assess target organ toxicity are more sensitive in one species
  - Species does not contain target but do have disease model in single species
- When no relevant species (including alternatives) – can we rely on in vitro data?

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DURATION OF STUDIES

Support for Single-dose Clinical Trial

Chronic Use Products: 6-month Sufficient

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Support for Single Dose Clinical Trial

[Addendum to ICH S6 (R1)]

"The duration and dosing regimen of toxicity studies supporting single dose clinical trials should take into account the anticipated duration of action of the biopharmaceutical in humans"

- Tox study should include minimum duration of 14 days of observation to support single dose clinical trials
- However, in addition to matching clinical exposure, should also take into account anticipated duration of effect

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Duration of Studies - General Principles

[Addendum to ICH S6 (R1)]

"For chronic use products, repeat dose toxicity studies of 6 months duration in rodents or non-rodents are sufficient"

"Studies of longer duration are not anticipated to provide useful information to change the clinical course of development"

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S6 vs M3: Why the Difference?

- Majority of toxicity of biopharmaceuticals is exaggerated pharmacology
- Pharmacology often evident in shorter term studies
- Absence of drug metabolism changes with time and absence of active/toxic metabolites
- Non-pharmacologic chronic issues recognized as established for biologics
  - e.g potential for immune complex deposition secondary to immunogenicity

Impact of 9 or 12 month study vs 6 month – Ethical and Practical Issues

- Animal Use
  - 100% more non-rodents if chronic tox needed for Phase II support i.e. 6 and 9/12 month needed so need scientific justification
- More protein needed
  - 50% increase (replace 6 with 9 month) to 300% increase (add 12 month in addition to 6 month due to clinical phase support)
- Opportunity cost
  - Dedicated additional manufacturing slots delay other new research product slots
- Absolute $ increase
  - 1.5 to 4.5M$ (study costs and material manufacture costs)

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Historical analysis

Who?

- Members of a subcommittee of the Preclinical Leadership Committee for BioSafe
  - Although opinions expressed those of the members and do not represent an official position of BIO
- What?
  - Criteria for inclusion in dataset
    - Approved products only
    - Publicly available information
    - Chronic Indications
    - Derived from living cells
- 23 Biopharmaceuticals were evaluated

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These Biopharmaceuticals Represented

- Broad Therapeutic Classes
  - Recombinant forms of endogenous proteins
  - Immune –mediated disease modifiers
  - Anti-tumour Agents
- Different Product Types
  - Endogenous proteins:7+
  - Monoclonals:8
  - Fusions: 3
- Questions?
  - Was any new information obtained in studies > 6 months in duration?
  - How did the data from 6 month studies compare with studies less than 6 months in duration?
  - How predictive was the preclinical data for patient safety?

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The Dataset

6 months or less	9 months	12 months
Etanercept	Adalimumab	Alefacept
Infliximab	Cetuximab	Epotein alpha
Bevacizumab		GCSF
Trastuzumab		Growth Hormone[1]
Omalizumab		Teriparatide
Dornase alfa		Insulin
Interferon beta-1a		Abatacept
PEG-GCSF		
Efalizumab		
Natalizumab		
Imiglucerase		
Darbepoetin alfa		

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[1]Insufficient information was available to discuss the findings of the 12 month study

Results

YES	NO
Adalimumab	Alfefacept
Insulin aspart	G-CSF
	Teriparatide
	Abatacept
	Cetuximab
	Epotein alpha

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New Findings >6 months

- Adalimumab
  - Immune complex deposition in the kidney after 9 months
  - Secondary to anti-drug antibody response
  - Not observed in one month study
  - Did the finding represent new hazard or risk formation?
- Insulin aspart
  - Mammary tumors in 12 month studies
  - Study was carcinogenicity assessment in place of a 2 year bioassay
  - Clearly new information
  - Is Carcinogenicity risk assessment a goal of chronic studies?

Predicitivity of Patient Safety

- Commonly reported clinical adverse events (AEs) generally predicted by 6 months
  - Rash, diarrhea – Cetuximab
  - Increased WBC – Natalizumab and Efalizumab
  - Hypoglycemia, injection site reactions – Insulin
  - Injection site reactions, liver enzyme elevations, elevated temperature – Interferon Beta

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Predicitivity of Patient Safety

- Rarely predictive of uncommon clinical AEs
  - Anaphylaxis
  - Malignancy
- Or certain serious AEs
  - Infection – anti-TNFs, Alefacept, Natalizumab
  - Cardiomyopathy – Trastuzumab
- Did not appear to relate to duration

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Conclusions

- Reiterates that biologics toxicities largely pharmacological and predicted by 6 months or less
- **6 Months Generally Appropriate**
- Should be scientific rationale for longer not shorter
  - Should there be a scientific rationale for 6 months?
- Publication:
  Regulatory Toxicology and Pharmacology, 50 (2008) 2-22.
  - Authors: Janet Clarke, Biogen Idec, Laura Andrews, Genzyme, Joy Cavagnaro, Access BIO, Shawn Heidel, Eli Lilly, Chris Hurst, Biogen Idec, Pauline Martin, Centocor, Barbara Mounho, Amgen, Rafael Ponce, Zymogenetics, Theresa Reynolds, Genentech, John Vahle, Eli Lilly

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DOSE SELECTION

Application of PK/PD Principles

Dose Selection

- Application of PK/PD Principles
  - Provide rationale for high dose selection
  - PK/PD relationships important
  - Dose should be corrected to account for differences in affinity/potency between species
  - Route, schedule should mimic clinical regimen and exposure

If toxicity is not seen with this approach, higher doses will not provide useful information on the risk to patients at clinically relevant doses

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Dose Selection

Low Dose ~ Clinical therapeutic dose

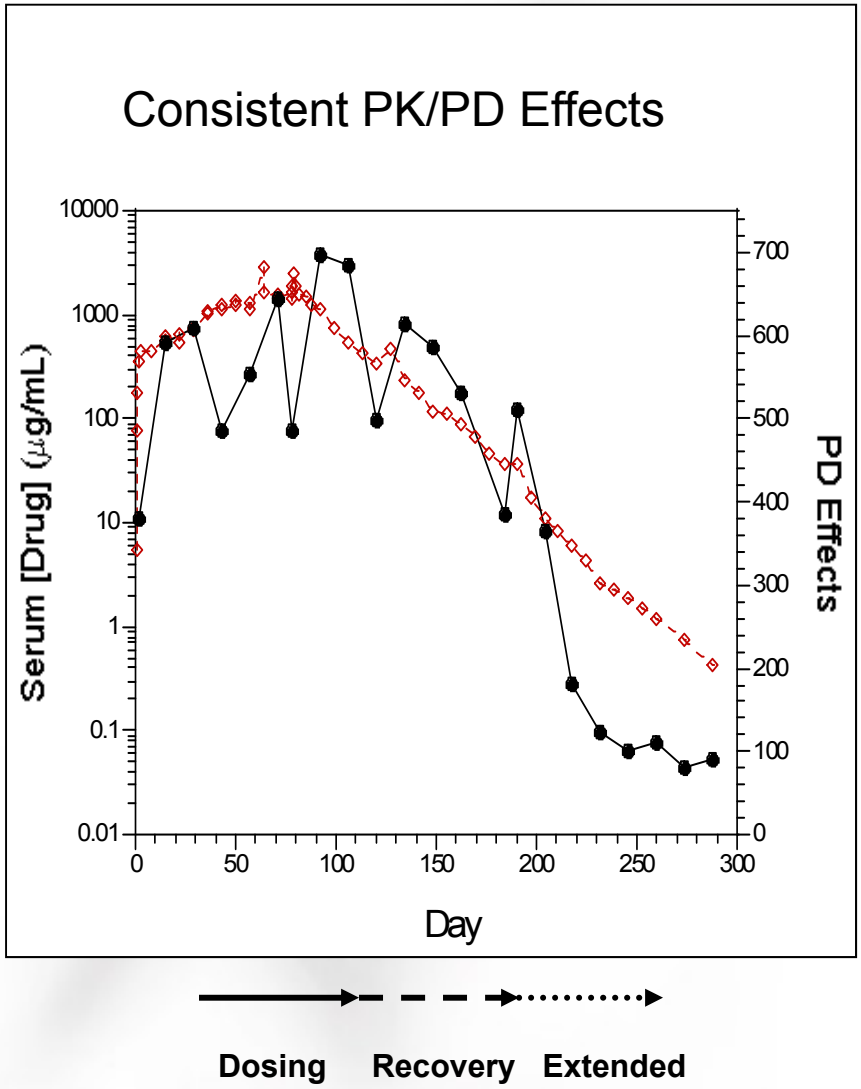
High Dose *(choose the higher option, unless you can justify use of a lower dose)*

- Maximum intended pharmacological effect dose in preclinical studies
- Dose that is up to 10-fold exposure multiple to expected clinical dose

Using the same route, regimen results in clinically meaningful pharmacology and toxicology

When adding more drug won't change PD, no clinical relevance in excessively high circulating durg

Consistent PK/PD relationship provides predictive power for clinical projections



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Dose Selection

- For biopharmaceuticals, toxicity is most often due to exaggerated pharmacology
  - Bevacizumab (Avastin, anti-VEGF)
    - Effects on bone growth plates and female reproductive tissues
  - Cetuxmab (Erbitux, anti-EGFr)
    - Skin rash
  - Darbepoetin alpha (Aranesp, erythropoietin)
    - Increased erythroid parameters, increased kidney, spleen weights
- Dose at which maximal biological response is achieved is most relevant to potential clinical safety events
  - Clinical route of administration
  - PK should guide dosing frequency
  - Goal is to achieve clinically relevant exposure

Dose Selection

- Low Dose ~ Clinical therapeutic dose
- High Dose: Provide rationale for dose selection
  - Maximum intended pharmacological effect in preclinical studies OR
  - Dose that is up to 10-fold exposure over highest anticipated clinical exposure

- Example:
  - Projected efficacious dose = 5 mg/kg
  - Maximum pharmacologic effect = 10 mg/kg
  - Maximum projected clinical exposure = 10 mg/kg

Doses to be tested in toxicology study:
Low: 5 mg/kg High: 100 mg/kg Mid: 25 mg/kg

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Dose Selection

Summary

- Toxicities from biopharmaceuticals are commonly due to exaggerated pharmacology
- Using same route, regimen results in clinically meaningful pharmacology and toxicology
- When pharmacodynamic (PD) effects have been maximized, adding more drug won't change PD, so there is no clinical relevance in excessively high circulating drug
- Dose selection should take PK/PD into account when possible along with species differences in potency, binding affinity
- Consistent PK/PD relationship provides predictive power for clinical projections

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RECOVERY PERIOD

Reversibility and Dose Response

Value of Recovery Data

Immunogenicity

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Recovery - General Principles

[Addendum to ICH S6 (R1)]

"Recovery from pharmacological and toxicological effects with potential adverse clinical impact should be understood when they occur at clinically relevant exposures"

- Understanding the nature of the toxicity is essential to assessing reversibility
  - Can be done by evaluating at least 1 dose level in at least 1 study
  - If no toxicities are present at the end of dosing, no need for recovery data

- Purpose of the recovery phase is to assess reversal of findings
  - NOT to assess delayed toxicity or immunogenicity
  - Demonstration of complete recovery not essential

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Recovery

Example: bevacizumab (Avastin, anti-VEGF)

Effects on female reproductive tissues

- Decreased ovarian and uterine weights (*up* to 50%)
- Absence of corpora lutea
- Changes were **dose-dependent**
- Observed in the 3- and 6-month studies

	↓ Ovarian/Uterine Weights			Corpora Lutea Absent		
	2 mg/kg	**10 mg/kg**	**50 mg/kg**	**2mg/kg**	**10 mg/kg**	**50 mg/kg**
1-Month	-	+	+	-	-	-
3-Month	+	+	+	-	+	+
6-Month	+	+	+	-	+	+

Doses administered 2x/week in 1- and 3-month studies; 1x/week in 6-month study

Recovery

How might the guidance be applied?

Good PD marker

- ↑↓ circulating cell population
  - *Neutrophils, lymphocytes, RBCs, platelets*

- Characterization of systemic toxicity and recovery
  - Are toxicities exaggerated pharmacologic activity?
  - Dose-response or threshold effect?
  - Predictable PK/PD relationship?

Using a weight-of-evidence approach, what data are expected from additional systemic toxicology studies that will inform clinical development?

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Recovery

Example: B-cell depleting Antibody

- Good PD marker
  - ↓ circulating cell population
    - *B-lymphocytes*
  - Characterization of systemic toxicity and recovery
    - Toxicities ARE exaggerated pharmacologic activity
      - B-cell depletion can be associated with increased infection risk
      - Depletion of germinal centers in lymphoid tissues
    - Strong threshold effect with dose-proportional recovery
    - Predictable PK/PD relationship

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Recovery

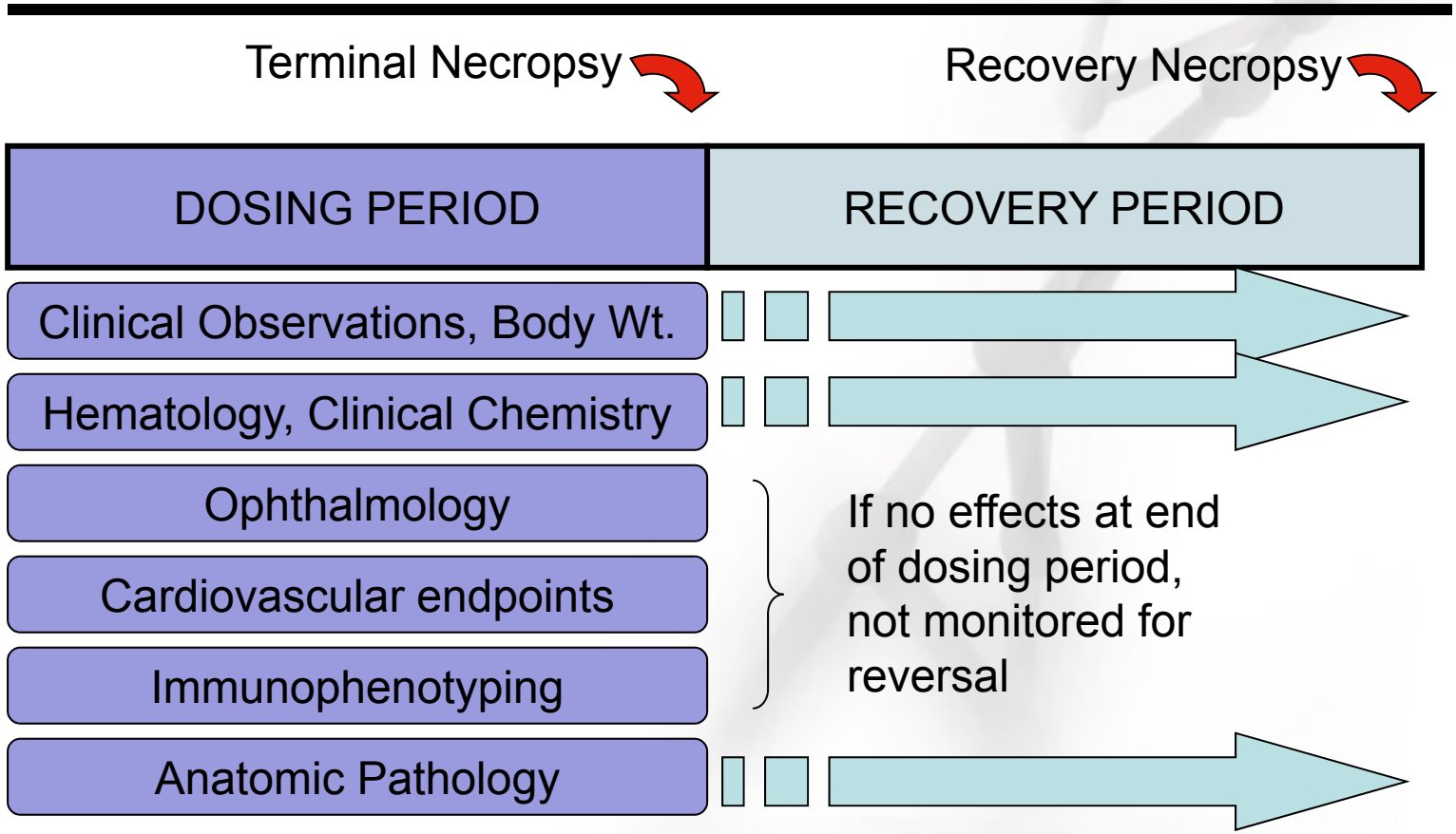
Example: B-cell depleting antibody

Weight of evidence and impact on clinical development

- Now that the relationships have been characterized….
  - Peripheral B-cell counts can be followed in comparability studies or for comparison to 2nd generation molecules

Recovery

When characterizing toxicity for the first time, e.g. IND-enabling studies, it's not possible to know what the toxicities are, or whether they will be reversible



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Recovery Period Summary

- A thorough understanding of the
  - Mechanism of action of your molecule and
  - It's role in normal and disease processes

  can guide study design decision making
- The role of recovery data are to
  - Inform clinicians and patients of reversibility of findings
  - At clinically relevant exposures
- Full recovery from effects is not essential, use
  - Dose response
  - PK/PD relationships → predictive power

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Recovery Period & Immunogenicity

"Immunogenicity assessments are conducted to assist in the interpretation of the study results and design of subsequent studies" [Addendum to ICH S6 (R1)]

- Immunogenicity is NOT relevant as a recovery endpoint
- Anti-Drug Antibody response (ADA) in animals is a response to a foreign (human) protein therapeutic
- Only useful to interpret toxicity data
  - Did ADA affect drug exposure in animals?
  - If there were no toxicities, is it because there was no exposure?
  - Can toxicities be attributed to drug/antibody complexes?

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Impact on the 3R's

The 3R's of Animal Testing - Reduce, Refine, Replace

- All systemic toxicity studies
  - Recovery groups not required, determine need/value on case by case basis
- Chronic toxicity studies
  - Include fertility endpoints
  - Single species acceptable (even when 2 species are relevant)