



Biologics Preclinical Development: Translating Data to FIH Clinical Trials

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Introduce

- FDA and biologics
- INDs - First-in-Human trials
 - FDA preclinical team and initial review process
- Pharmacology review process
 - Integrate and assess data
 - “Translate” preclinical data to guide trials
 - Logic and experience - no written standards
- Biologics preclinical development
 - Key points of translation

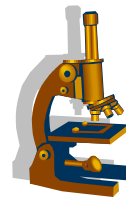
FDA Reviews Human Therapies in 3 “Centers”

- Drugs – CDER
 - Drugs, hormones, synthetic peptides
 - Recombinant proteins (since 2004)
- Biologics - CBER
 - Offices of Vaccines, Blood, Cell/Gene Rx
- Devices - CDRH
 - Medical Devices, “Structural” therapeutics, Diagnostic Kits


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Biologics are Reviewed in 2 Centers

- CBER
 - Cells, tissues, and gene therapy
 - Cancer vaccines
 - Preventative vaccines
 - Blood-derived products
 - Allergens, toxoids, antivenoms
- CDER
 - Recombinant technology
 - Therapeutic proteins
 - i.e. Monoclonals




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What is a “Typical” Monoclonals?

- Antibody (Immunoglobulin IgG1 or IgG4)
 - Recombinant production
 - Legally “drugs”, developed under INDs
- Large molecular weight “natural” proteins
 - Long half lives (weeks to months)
 - CDRs are highly selective for human target proteins
 - Sensitive to slight sequence changes
 - Toxicities arise from pharmacologic action
- Delivered i.v.
- Phase 1 in patients w/ safety, PK and efficacy endpoints


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Initial INDs Contain (21 CFR 312)...

- Investigator’s Brochure
- Clinical protocol
- Past human experience
- Preclinical pharmacology and toxicology
- Chemistry and manufacturing (CMC)
 - Quality controls
 - Pharmaceuticals / formulation
- Literature
- (Informed Consent Form)


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Initial IND Review Process

- Drug sponsor sends the IND to FDA
- Copied to ≥ 3 core reviewers
 - Medical officer, pharmacologist, chemist
 - Once assigned the IND, they stay with it
- Others?
 - Cross-divisional consultant, clinical pharmacologist, statistician, or microbiologist



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FDA's Response

- Each FDA reviewer drafts an assessment
 - 30-days to place a clinical hold
- Project Manager collects reviews ~ day 23
 - Ensures coherent team decision
 - Managerial buy-in
- Relays comments ~ day 29
 - OK? verbal "tips"
 - Clinical hold? written comments



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Pharmacology Review: Impact on Initial Clinical Trials




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Pharmacology Review of Biologics: Broadest Scope

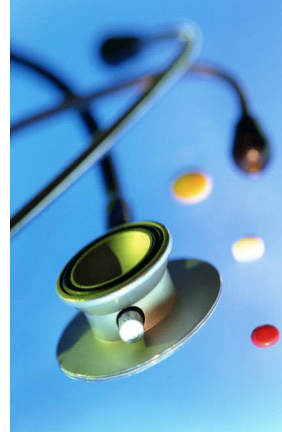
- Drug substance chemistry
- Clinical product formulation / excipients
- Molecular mechanism
- *Normal target physiology
- *Clinical pathophysiology
 - *Patient population / treatment alternatives
- *Published human experience
 - *Any product with related action*
- Animal models - *activity and toxicity
 - *Drug substance or *pharmacologic homologs


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Goal of the Pharmacology Review:

How does this “chemical” affect the “structure and function of the body?”

- Molecular pharmacology
 - Humans and animals
 - Target selectivity, density
 - Affinity and distribution
- In vitro activity
 - Agonist or antagonist?
 - Cytokine secretion
 - Intracellular signals
 - Proliferation
- In vivo pharmacology



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Monoclonal Toxicology “Program” :

ICH guidelines--- ICH S6 and M3; Production of MoAbs

- Tissue cross reactivity and cross species screening
- Pilot studies – GLP or non-GLP
 - Monkey and rodent (if relevant)
 - SD pilots, dose-ranging - tolerability, TK
 - RD pilots
 - Maximum Tolerated Dose (MTD) or
 - Maximum Feasible Dose (MFD)
- SD pharmacokinetics
 - Confirm animal RD regimen
 - Develop PK/PD models
 - V_d = blood compartment



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Pilot Data

- Improve the quality of “pivotal” GLP studies
- Improve clinical translation
- Spare both animals and overall program cost

“Quality is cheap – it’s the mistakes that cost”


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GLP MoAb Pivotal Toxicology

- 28-day RD study
 - 2 relevant species
 - Track recovery (6-7 half lives)
- Mimic human regimen / PK
 - Clinical exposures to ~20X higher
- In-life endpoints
 - Clinical observations, food, weight
 - ECGs, BPs, biomarkers, and ophths
- Gross and microscopic pathology
- Clinical pathology and immunogenicity


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Immunogenicity?

- Good for vaccines
- **Problematic for toxicologists**
- Since the drugs are “human” protein
 - Foreign to animals
 - Anti-drug-antibodies (ADAs)
- Complicates toxicology interpretation
 - (sometimes) neutralize drug
 - (rarely) cause toxicities
 - Anaphylactoid
 - Autoimmune


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Since ADAs occur in Animals and Humans...

- Critical to monitor
- Require robust assays (often ELISAs)
- Are ADAs causing issues?
 - Look at first and last dose data
 - More infusion rxns late in study?
 - Faster clearance of later doses?
- Sponsors may need “neutralizing” Ab (nAb) assays or evidence of sustained PD activity
 - throughout RD studies


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*Alternative Toxicology Models...

- *Animal models of disease*
 - Might be the only “relevant” toxicology model
 - Goal? translatable toxicology
 - Examples...
 - Xenograft implants
 - Infect animals
 - Wound models
- *Pharmacologic homologs*
 - “Surrogate drugs” designed to bind rodent targets


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Review Goal: Identify Potential Clinical Hold Issues

- Are data **adequate** to assess clinical risks?
- Or...
- Do data reveal **likely harm**?




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Sources of MoAb Review Concerns

- Weak product specs
- Binding in non-target tissues esp. heart, brain
- Evidence of disease exacerbation
- Binding in unexpected tissues
- Baggage – related to drug class or target effects
- Low risk clinical population
 - pediatric patients, healthy volunteers


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“Scary Factors” in Preclinical Data (CDER/CBER Human Start Dose Guidance)

- Steep dose-response curves
- Highly variable responses
- Delayed toxicity
- Unmonitorable or irreversible pathology
- Mortalities / absence of premonitory signs
- Erratic PK / PD / toxicity relationships
- ...may spell the need for
 - larger safety margins or clinical hold.....


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Red Flags - Elevate Clinical Concern

- Chronicity issues
 - Long half live or action
 - Intended for chronic clinical use
 - Schedule - dependent effects (IL-12)
- *Immunomodulation
 - Suppressed host defense
 - Infection related deaths
 - Autoimmunity or immunostimulants
 - TEPO, lupus-like syndrome, Grave's
 - Cytokine release

*EMA "High Risk" biologics guidance

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Red Flags....

- Reproductive risks
 - Drugs for pregnant women
 - Preeclampsia, pre-term labor
 - Class-related hormonal alterations
 - Interferons
 - GLP reproductive toxicity findings
- Intended polypharmacy in trial or
- Trials in very ill patients
 - Hard to establish link to trial drug

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Hold Flags

- Inadequate data to assess risks
 - Quixotic dose-response
 - No pharmacologic response
 - Toxicities at all doses, no NOAEL
- Evidence of harm
 - Animal disease model exacerbation
 - Inhibition of bone marrow engraftment
 - Unmonitorable or irreversible pathology
 - Tumors or deaths


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Factors Which Reduce Concerns

- Limited exposure time or site of application
- Dose-proportional drug levels and effects
- Single dose clinical trials
 - when toxicities followed multiple doses
- Non-novel drugs
 - preclinical data show typical class effects
- Only toxicities seen are clinically monitorable
- Clinical pharmacodynamic biomarkers
 - can clarify dose response by titrating to effect


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Clinical Risks Versus Benefits...



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Interpret / Weight the Toxicology Findings

- Are toxicology findings translatable?
 - To humans volunteers or to patients?
 - Physiology, pharmacology, disease/target issues
 - Correct for cross-species binding differences
 - Receptor density and tissue distribution
- Choose the best model
 - Employ for setting human doses

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Consider MoAb Clinical Trials in Light of Animal Data and Best Practices

- Nature of toxicity
 - Characterized well by non-invasive monitoring?
 - Predictable and dose-reponsive?
- Chronicity
 - Were toxicities slow in onset and reversible?
 - Over what duration?
- Dose one patient per day – monitor 24 h
- Space cohorts by ~two weeks apart for safety analysis
- Monitor two months for immunogenicity

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Risk Mitigation: IND Phase 1 Studies in Patients

- A strategic choice
 - study volunteers or patients?
 - sponsors may choose to...
- Target patients
 - Serious diseases, no treatments available
- Target a disease subpopulation
 - failed other therapies
 - intolerant to known therapies

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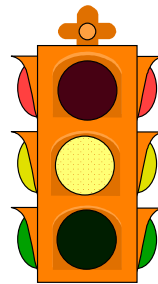
Risk Mitigation: Trial Design and Conduct

- Increased monitoring
 - nature of techniques, intensity
 - reduce cohort size - increase time between cohorts
 - tighten stopping rules
 - increase reporting to FDA clinical reviewer
 - Increase stringency of informed consent
- Dose modifications
 - narrow dose escalations, slow infusions
 - introduce larger safety margin for starting dose


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Safety Concerns can:

- Reduce FDA confidence – slow development
 - slow phase 1-2 recruitment
 - intensify competition for patients
 - intensify reporting requirements to FDA
 - require a change in trial venue
 - > sophisticated staff / services / equipment
 - > intense monitoring
 - >costs
 - limit the eventual labeling indication / market




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Real Life Mistakes

- Toxicology used non-relevant clinical route
- Cancer-style clinical trials for normals
- “No time” for pre – IND meeting
- Skipped pilot dose-ranging studies
- No pathology data in the initial IND
- Treat ped diabetes w/ novel immunomodulator
 - Based on activity model data
- Unmonitorable lesions
 - Unknown significance and no NOAEL

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Avoiding Pitfalls?

- Conduct preclinical pilot studies
- Adjust the preclinical program rigor to
 - address foreseeable problems
 - correlate dose/plasma levels with all in vivo effects
- Carefully consider the clinical options
 - Consult a varied panel of clinicians first
 - Then design the preclinical program
- Provide reviewers / consultants with thorough briefing materials
- Ask detailed questions in FDA communications

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Match Initial IND Plans to FDA Motives:

- Apply consistent standards across studies
- Risk mitigate in clinical trials
 - Assess all issues flagged in the preclinical data
- Identify a safe starting dose / regimen
- Select an appropriate clinical population
- Bring new treatment options forward
 - Grounded in translatable preclinical programs
- Provide FDA with optimal preclinical data
- Result? accelerated and safe clinical trials