Regulatory and Scientific Issues that Impact the Development of Biotherapeutics

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NJDMDG 2009 Spring Meeting

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Presentation Outline

- Definitions
- Small vs Large Molecule Therapeutics
- Preclinical Development Strategy
- Regulatory Environment
  - Update: ICH S6 Revision
  - Biosimilars/Follow-on Biologics
- Summary

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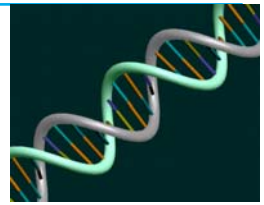
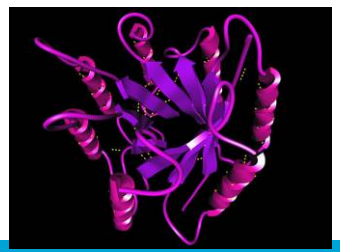
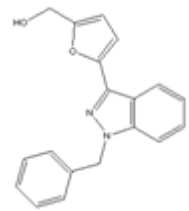
Definitions



- Interchangeable terminology: Biologicals = Biotherapeutics
- Biotherapeutics = **proteins** (monoclonal antibodies, cytokines, growth factors, enzymes, thrombolytics, etc), **nucleic acids** (siRNA, dsRNA), **peptides** and **vaccines**
- Biotherapeutics = typically produced using living production systems (cell culture, fermentation), high molecular weight
- Small molecules = typically low molecular weight molecules and chemically synthesised
- Small peptides and oligonucleotides are a grey area especially if chemically synthesised





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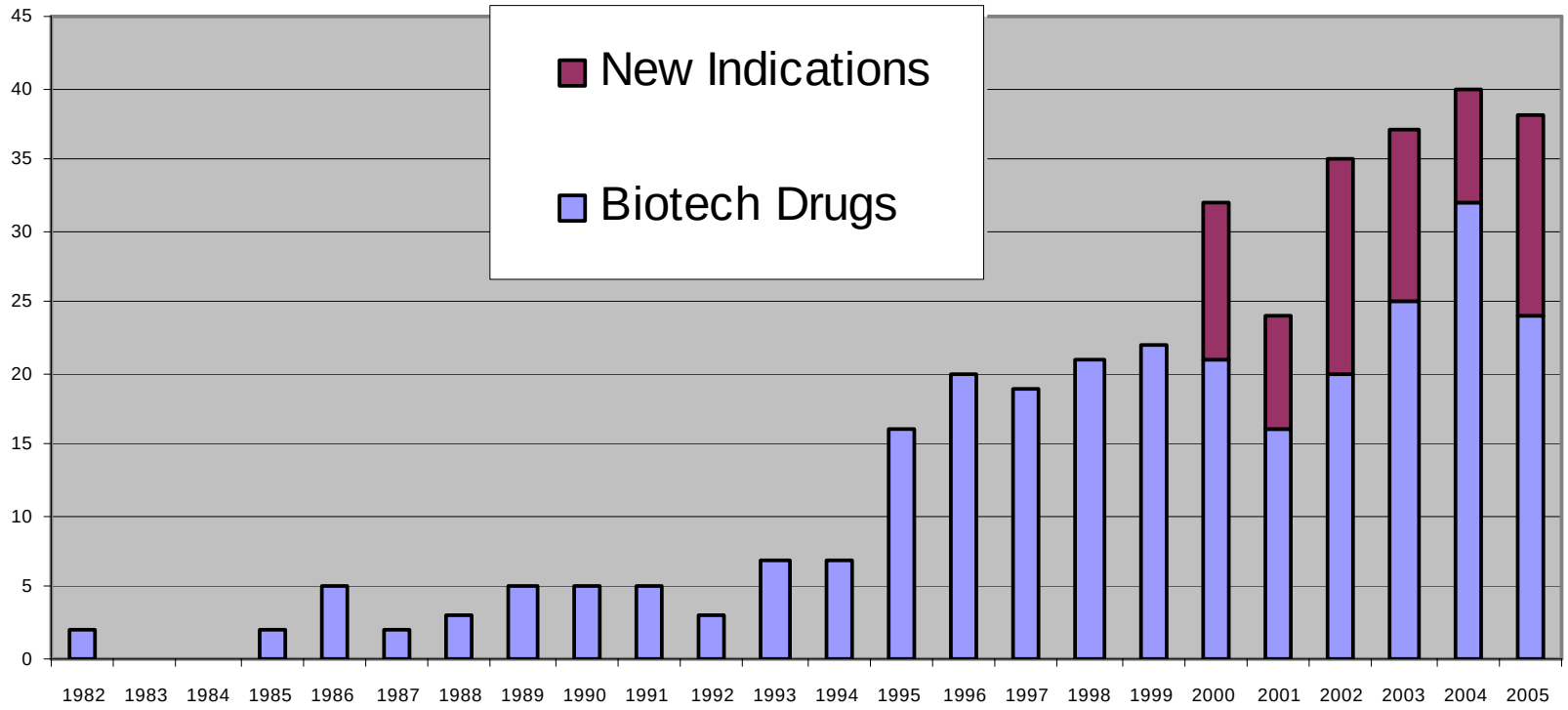
Steady Growth in New Biotech Drug Products Approved, 1980-2005



2004: 40 products/7 new indications

Source: FDA, Burrill & Company, 2006

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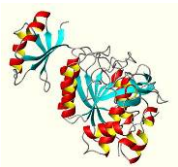
Differences Between Small Molecules And Biologicals

- **Biologicals**
  - Produced in living cells →
  - High molecular weight →
  - Target specific →
  - Relevant and non-relevant species →
  - Immunogenic potential →
  - Proteolytic degradation →
  - Exaggerated pharmacology →

- **Small Molecules**
  - Chemically synthesised
  - Low molecular weight
  - Less target specific
  - Generally active in many species
  - Generally no immunogenic potential
  - Metabolism
  - Toxicity from parent or metabolite



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Development Strategy: Drugs vs. Proteins

General testing requirements	Small MW Drug	Protein Therapeutic	
PK/TK	Yes (2 species)	Yes (1-2 species)	
Genotoxicity	Yes	No	
Tissue Cross Reactivity	No	Yes (mAb)	
Mammalian Tox/Path	Yes (2 species)	Yes (1-2 species)	
Immunotoxicology	Yes (Tier)	Immunogenic? Biomarker?	
Safety Pharmacology	Yes	Limited (in tox study)	
Developmental Tox	Yes	Yes	
Carcinogenicity	Yes	No(?)	
ADME studies	Yes	Limited	

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Regulatory Environment

- **ICH S6 – *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (1997)**
- Main focus continues to be:
  - Proteins
  - Peptides
  - Antibodies
  - Other biological products not *specifically* covered by S6 are
    - Gene therapy products
    - Stem cell products
    - Vaccines
    - Nucleic acid therapeutics

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Regulatory Environment

- **ICH S6**
  - Step 4 finalised in 1997
    - Advocates flexible “science based” approach to development
    - One program design may not look like another
  - 10 years of advances in technology and drug development experience are the drivers for revision
  - Revision expected to be finalised by June 2010

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ICH S6 Revision

5 main topics under discussion/review

- Species selection for nonclinical safety testing
- Study design
- Reproductive/Developmental toxicity
- Carcinogenicity
- Immunogenicity

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ICH S6-Species Selection

- **The ICH S6 Species Selection Issues under review:**
  - Approaches used to justify the choice of a species
  - Clarify role of tissue cross-reactivity
  - When to use a second species
  - Use of alternative models
    - Use of transgenic animals
    - Use of surrogate (homologous) proteins

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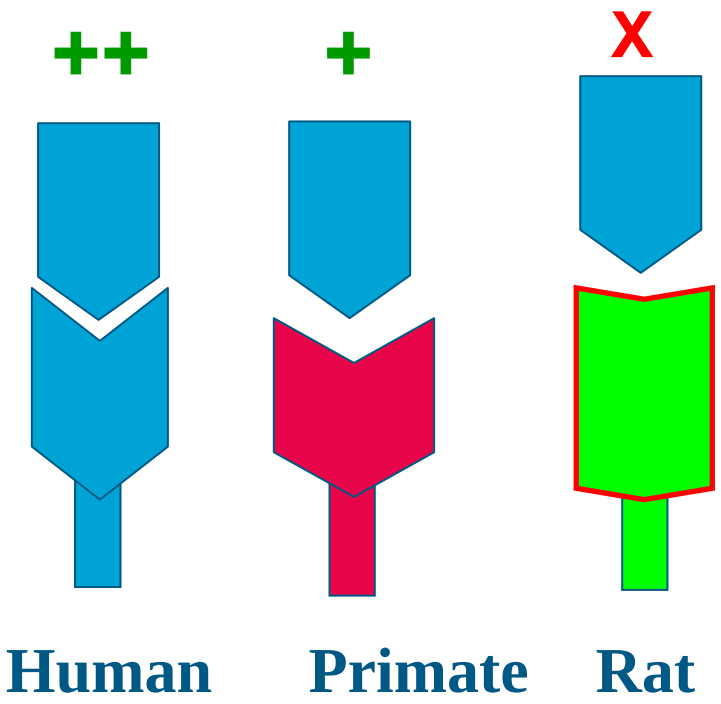
ICH S6-Species Selection

- Relevant species - product is active due to the presence of a receptor/epitope



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Number of Species: Is Two required?

- "If it can be shown…by means of kinetic, pharmacological, or toxicological data…that the species selected is a relevant model for humans, *a single species can be sufficient*" (ICH S5A)
- "Safety evaluation should *normally include two relevant species*. However, in certain justified cases, one relevant species may suffice" (ICH S6)
  - One relevant species may suffice when:
    - Biological activity well understood, pharmacologically active in only one species
    - Long term toxicity studies where tox profile is comparable in short term studies in two species
    - Immunogenicity
    - NHP can put limitations on reproductive toxicity testing

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2008 BioSafe Survey

- *"For a mAb candidate that cross reacts and is pharmacologically active in a rodent and non-rodent species, would you conduct IND-supporting toxicology studies in both?"*

- Yes- 23
- No-2

ICH S6-Species Selection

- **Justifying Appropriate Nonclinical Species**
  - BLAST
    "Basic Local Alignment Search Tool" search (DNA/protein sequence homology across species)
  - *In vitro* receptor binding studies
  - Verify pharmacological effect in animal tox species
  - Tissue Cross Reactivity screening…..

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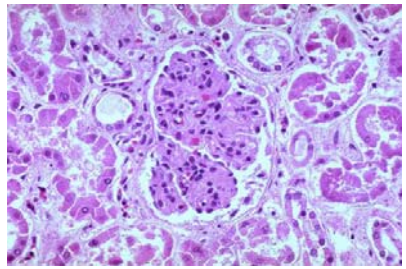
ICH S6-Species Selection



- **Tissue Cross Reactivity**
  - Useful for ligand binding molecules like antibodies, antibody fragments and non-antibody ligand binding molecules.
  - Used to assess off-target binding
  - Comparing binding patterns from different species to human assists in demonstrating relevance.
  - TCR does not show biological activity…so while binding may be similar, no biological effect seen.

>>Primary consideration should be receptor mediated activity

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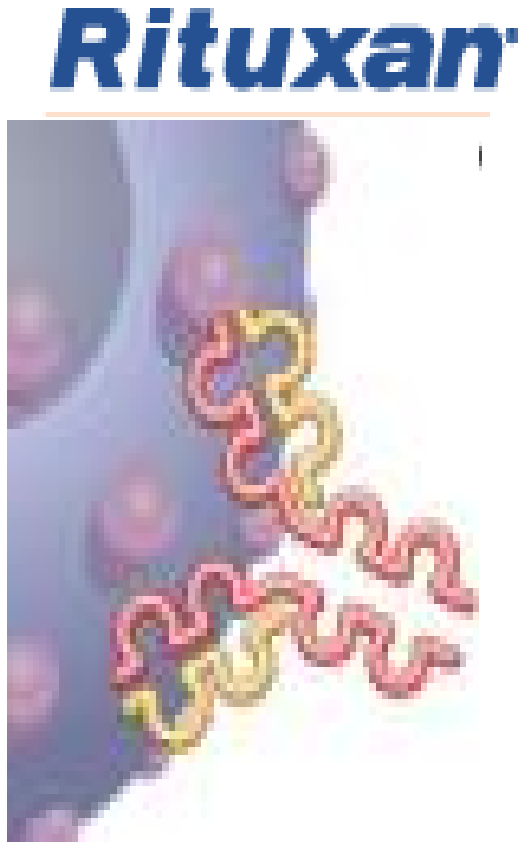
Tissue Cross Reactivity: Genentech's Rituxan®

- IgG1 chimeric human/murine monoclonal Ab
- Produced by mammalian cell culture (CHO cells)
- Binds to CD20 antigen on B-lymphocytes
- Non-Hodgskin's Lymphoma
- Tissue cross reactivity expected tissue binding:
  - Thymic lymphoid tissue
  - Splenic white pulp
  - Peripheral and lymph node B-cells
  - **Minimal binding in non target tissues**



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What if there is no relevant species?

- Use of homologous (surrogate) proteins
  - May be specific instances where use in toxicology studies is warranted
  - Not always predictive (pk, feedback control, immunogenic)
  - May differ from clinical product (impurities/contaminants of production process)
  - Development timeline/cost of goods
- Use of transgenic animals expressing human receptor
  - May be useful to understanding pharmacological properties of the human drug, particularly if target is not well understood
  - Historical controls? Response comparable to “normals”?

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ICH S6-Study Design

- **Exposure Duration and Recovery**
  - "Standard" pharmaceutical short-term preclinical study designs frequently not applicable to biologicals due to long half-lives.
    - Intact IgG molecule (MW 150 Kda) may have a plasma half-life of 21 days thus standard 14 or 28 day studies are not suitable.
  - Complicates TK collection, duration of recovery
  - What should the duration be of chronic studies?

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Duration of Chronic Toxicity Studies

- Chronic toxicity studies: Is 6 months duration sufficient?
  - Database of 23 approved drugs evaluated
    - Were 6 month studies predictive?
    - Was there new data suggesting 6 months was not long enough?
    - Were toxicity findings identified only after 6 months?
    - What were the similarity of findings at 6 months or less?
    - Predictivity of chronic studies to known clinical adverse events?
  - Only 2/23 cases "new" tox findings observed after 6 months
    - Insulin aspart (tumors), adalimumab (immune complexes)
  - "Although specific circumstances may require a longer study…no new data to *refute* utility of 6 month studies to support chronic clinical dosing of biologics"

Clarke, J. et al., Reg Pharm Tox, 50 (1): 2-22, 2008

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ICH S6-Study Design

- **Dose Selection**
  - Dosing regimen guided by PK/PD and clinical plan.
    - To ensure target saturation/max pharmacol effect with excess built in to address off-target effects
    - Often 10x higher than anticipated human therapeutic dose
  - If no information is available then PK study should be considered first or samples taken during the tox dose range finder.
  - High Dose – Maximum feasible dose or multiple of intended clinical dose.
    - Based on dose volume limitations for proteins at <20 mg/ml.
  - Determining MTD may not add value
    - Dose response, NOAEL most important

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ICH S6-Reproductive Toxicology

- Need is dependent on the product, clinical indication, and intended patient population (inclusion of WOCBP)
- Designs can be modified based on species specificity, immunogenicity, biologic activity, and half-life
- FcRn transporter allows IgG across placenta (important for transferring maternal immunity)
- Complete prior to enrollment of WOCBP in Phase 3

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2008 BioSafe Survey: "For monoclonal antibody candidates which are pharmacologically active in rodents and NHP, describe your general strategy for evaluation of reproductive toxicity for non-oncology indications"

Strategy	# Companies	Comments
Evaluate all aspects of Repro Tox in rodents	15	"Providing there is no significant anti-test article responses that would impact exposure" "All assessments in rodents if biology is conserved across species"
Evaluate some aspects of repro tox in rodents and some in NHP: •Rodents: fertility and early embryonic development, pre, postnatal development •NHP: embryo-fetal development	2	"General approach in our company is to perform all repro studies in rodents. To deviate from this approach would be case-by-case"

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ICH S6-Carcinogenicity

"Standard Carcinogenicity Studies are *Generally* Inappropriate for Biotechnology-Derived Therapeutics"

- Understanding the pharmacological pathway is critical
  - Growth promotion by hormones, growth factors
  - Immunosuppressives
- Traditional 2 year bioassay is not feasible for many biologics
  - Immunogenicity and study feasibility (neutralizing Ab's)
  - Relevance of surrogate?
  - Approach to dose selection vs small molecule
- May require an alternative approach or novel assessment
  - Cell proliferation measures in chronic tox studies
  - 6 month study with surrogate
  - Promotion of tumor cell lines in vitro
  - Promotion of tumor xenographs in SCID animals

Biopharmaceutical ≠ Don't worry about carcinogenicity
Carcinogenicity assessment of a biologic ≠ 2 year study

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ICH S6-Immunogenicity

- Immunogenicity is an immune reaction against antigen (drug product, foreign protein), resulting in production of anti-antigen antibodies

- Anti-drug antibodies can affect toxicology studies by:
  - Cross-reacting with endogenous proteins
  - Causing adverse effects not directly related to the product (e.g., immune complex deposition)
  - Decreasing activity by neutralizing the product's activity or increasing clearance
  - Sustaining activity by decreasing clearance
  - Complicating NOAEL interpretation

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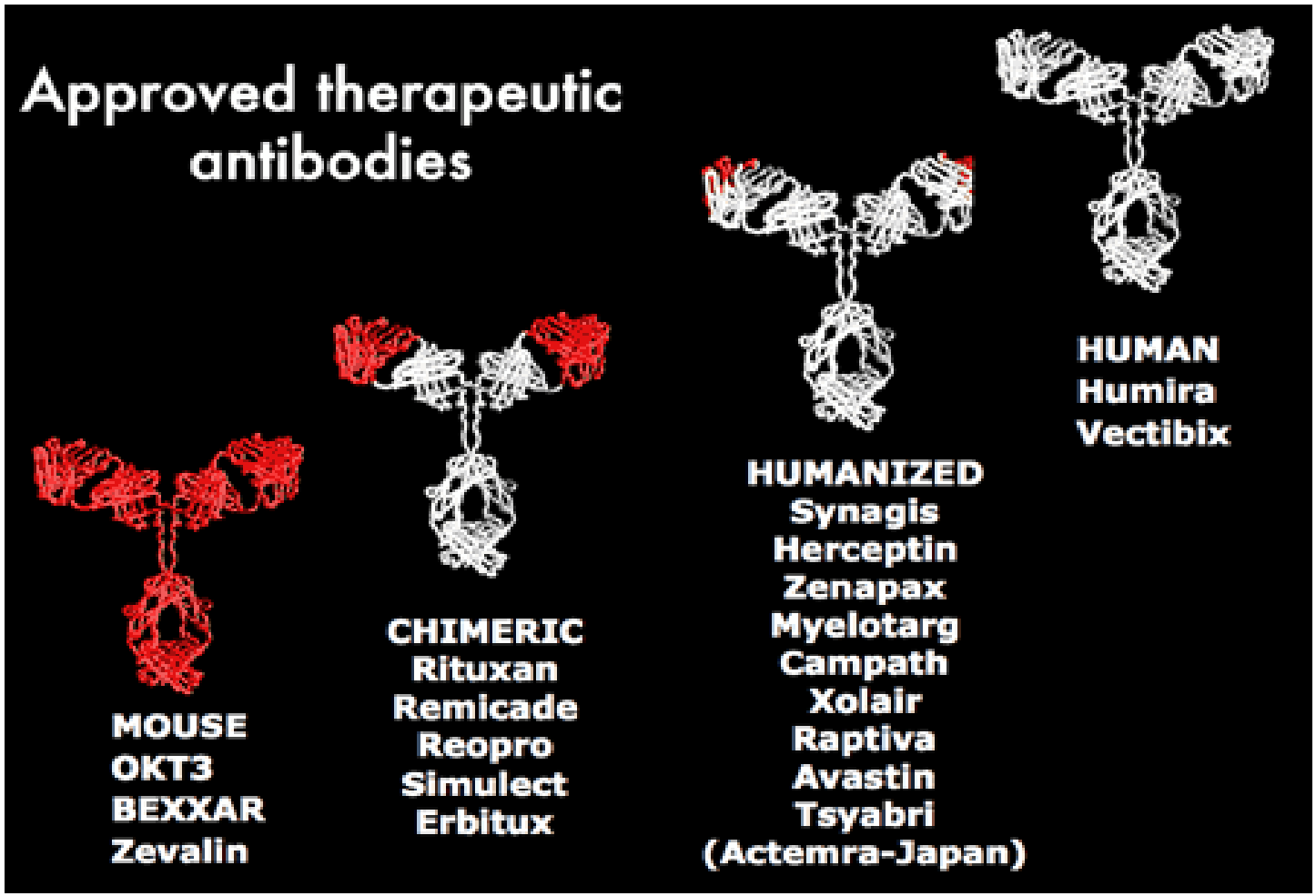
Evolution of mAb Technology



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Immunogenicity

- Included as an endpoint in toxicology studies
  - Aid in the interpretation of toxicokinetics and toxicity findings

- 2009 BioSafe Working Group white paper discusses approaches for generating and interpreting immunogenicity data to support progression into clinical trials.

>>Immunogenicity in animals not necessarily predictive of response in humans

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Agenda

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Regulatory Environment

- **Biosimilars/Follow-on Biologics**
  - Total Biologicals market in 2007 approx. $75 Billion*.
  - Biosimilar/Follow-on biologics market expected to exceed $10 billion by end 2015.
  - Regulatory guidelines exist in Europe.

* IMS Health

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BioSimilars/Follow-on Biologics

- **USA position**
  - Currently no Regulatory pathway for the development of follow-on biologic
  - New Waxman follow-on biologics Bill introduced into Congress 3/11/09 (H.R. 1427 - Promoting Innovation and Access to Life-Saving Medicine Act)

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Regulatory Environment

- **Biosimilars/Follow-on Biologicals in Europe**

  - **Main guideline EMEA Directive 2004/27/EC (CHMP/437/04)**

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Regulatory Environment

- **Biosimilars/Follow-on Biologicals**

  - **Some Important quotes from guideline CHMP/437/04**

> "Due to the complexity of biological/biotechnology-derived products the generic approach is scientifically not appropriate for these products. The "similar biological medicinal products" approach, based on a comparability exercise, will then have to be followed."

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Regulatory Environment

- **Biosimilars/Follow-on Biologicals**

  – **Some Important quotes from guideline CHMP/437/04**

    "similar biological medicinal product is applicable to any biological medicinal product."

    - **Importantly from this – no product class is excluded so includes everything from Insulin to mAbs**

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Biosimilars/Follow-on Biologicals

- **Currently registered Biosimilars in Europe**
  - Erythropoietin (5 products)
  - Growth Hormone (2 products)

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Biosimilars/Follow-on Biologicals

- **3 Key Issues:**
  - Must have a chosen “Reference Product”
  - Must be given by same dose route as reference product
  - Characterisation critical

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Regulatory Environment

- **Biosimilars/Follow-on Biologicals**
  - **Comparative Preclinical Studies**
    - **Pharmacodynamic studies**
    - **Toxicology**
      - **Single relevant species**
      - **28 days duration**
      - **Local tolerance study (possibly as part of the repeat dose toxicology study if feasible)**
      - **Safety Pharmacology, reprotox, gene tox and carcinogenicity on a case-by-case basis**

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Regulatory Environment

- **Biosimilars/Follow-on Biologicals**
  - **Studies Performed to support registration:**
    - **PK/PD**
    - **Safety Studies**
    - **Efficacy studies (single Phase 3 in most cases)**

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Regulatory Environment

- **Biosimilars/Follow-on Biologicals**
  - **Is the comparative approach ideal?**
    - Perhaps not always
    - Technology advances mean that follow-on products could be an improvement over the original
    - May be more suitable to perform a standard development package

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Regulatory Environment

- **Biosimilars/Follow-on Biologicals**
  - **Challenges**
    - Method of manufacture of biosimilar will not be the same as for reference product.
      - Microheterogeneity especially for complex biologicals like monoclonal antibodies

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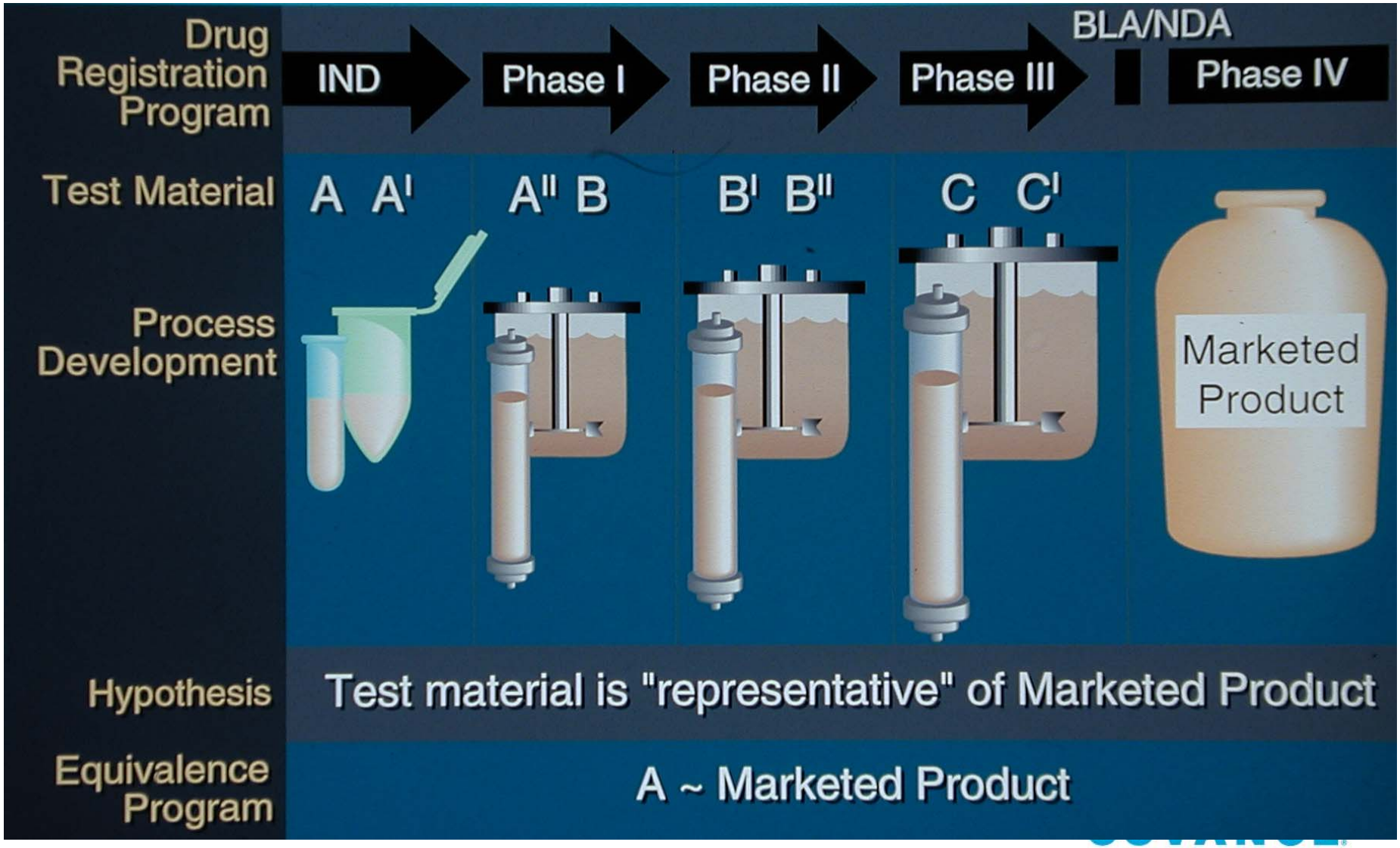
The Product is the Process



Living Cell Production

- Microheterogeneity
  - Glycosylation, deamidation, oxidation, disulfide bonds, free thiols, clipping, aggregates
- Method of manufacture and process can change during development

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The Product is the Process: Biogen Idec

- **Alefacept ®**
  - **LFA3-Fc fusion protein to treat mod/sev psoriasis**
  - **Cell line change in Phase II**
  - **Change in pharmacodynamics (reduced potency)**
  - **Only detected in toxicology and clinical trials**

- **Avonex ®**
  - **Protein cytokine, interferon beta 1a to treat MS**
  - **Cell line change post Phase III**
  - **Change in immunogenicity profile (25% NAB decreased to <5%)**
  - **Only detected in clinical trials**

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Living Cell Production

- Changes in manufacturing process = changes in microheterogeneity
- Comparability assessments
  - Comparability assessment ensures that the manufacturing changes have not affected the safety, identity, purity or efficacy (including immunogenicity) of the product

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Living Cell Production

- Drug product used in preclinical studies not required to be “identical” to that going into the clinic, but does have to be “comparable” in order to extrapolate the preclinical safety data to the clinical scenario

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Living Cell Production

- If product comparability cannot be established with robust characterization, full preclinical studies will be required:
  - Pharmacokinetic assessments
  - Pharmacodynamic assessments
  - Toxicology studies

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Summary Of Critical Points

- ICH S6 review underway
  - 12 years since adopted
  - Species selection, study design, carcinogenicity, reproductive toxicity and immunogenicity are critical focus areas
- Biosimilars
  - Development regulated in Europe
  - Comparability assessment to reference product is key
  - Characterisation of product must be robust

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And in Closing…

With reference to Biologicals…

"There is no place for detailed programs of rigidly pre-defined tests to be applied automatically to all products…..

…Toxicity testing in this area is most like a series of pharmacological explorations and should not be expected to follow conventional rigid guidelines."

Dayan AD. Rationality and regulatory requirements – A view from Britain. In CE Grahm (ed) *Preclinical Safety of Biotechnology Products Intended for Human Use: Clinical and Biological Research, Vol 235. Alan R. Liss, New York, 1987, pp 89 – 106.*

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Questions

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