A FDA Product Reviewer's Perspective on Building A Quality Dossier

CASSS Bay Area Discussion Group
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South San Francisco Conference Center

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Disclaimer

The opinions expressed in this presentation are based on my professional experience and may not necessarily reflect FDA policy.

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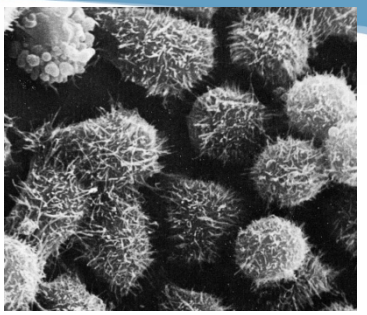
Presentation Overview

1. OBP Products
2. preIND Meeting and the IND Submission
3. IND Amendments
4. The BLA and BLA Supplements (sBLA)

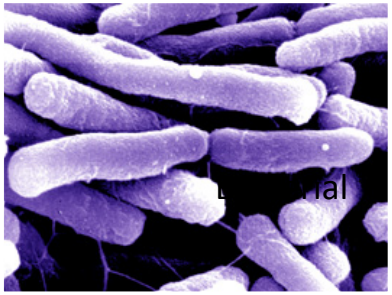
Please Ask Questions if Something is Not Clear

CDER/Office of Biotechnology (OBP) Products

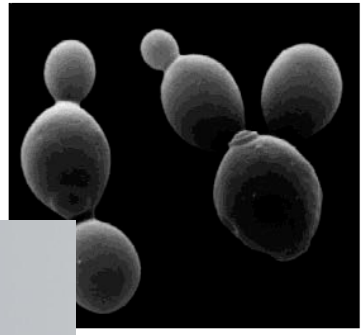
- Monoclonal Antibodies
- Enzyme Replacement Therapies
- Growth Factors
- Cytokines
- Toxins
- Fc and Fab Fusion Proteins
- Antibody Drug Conjugates



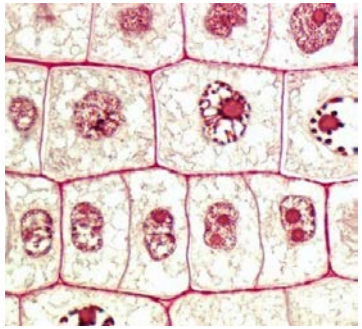
Mammalian



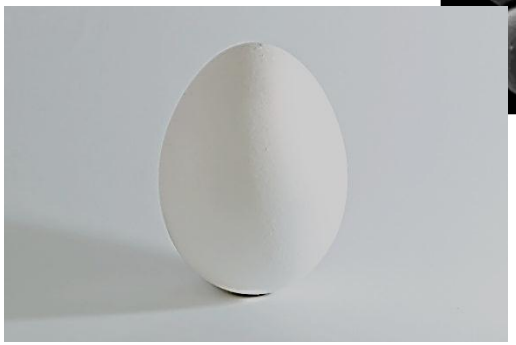
Bacteria



Yeast



Plant



Office of Biotechnology Regulatory Review Work

IND

•157 new product IND reviewed in 2015
•165 pIND Meeting in 2015
•2000 + active INDs

BLA

•16 BLAs filed in 2015
• 300 BLA Supplement s Reviewed in 2015
•140 Approved BLAs and NDAs

Biosimilar

•57 Biosimilar programs (pIND and IND)
•4 Companies Publicly Announced Biosimilar BLAs
•First Approved Biosimilar BLA (filgrastim-sndz) in 2015

The AAPS Journal (© 2015)
DOI: 10.1208/s12248-015-9833-6

Meeting Report

Pharma Success in Product Development—Does Biotechnology Change the Paradigm in Product Development and Attrition

Ronald P. Evens[1,2,3,4]

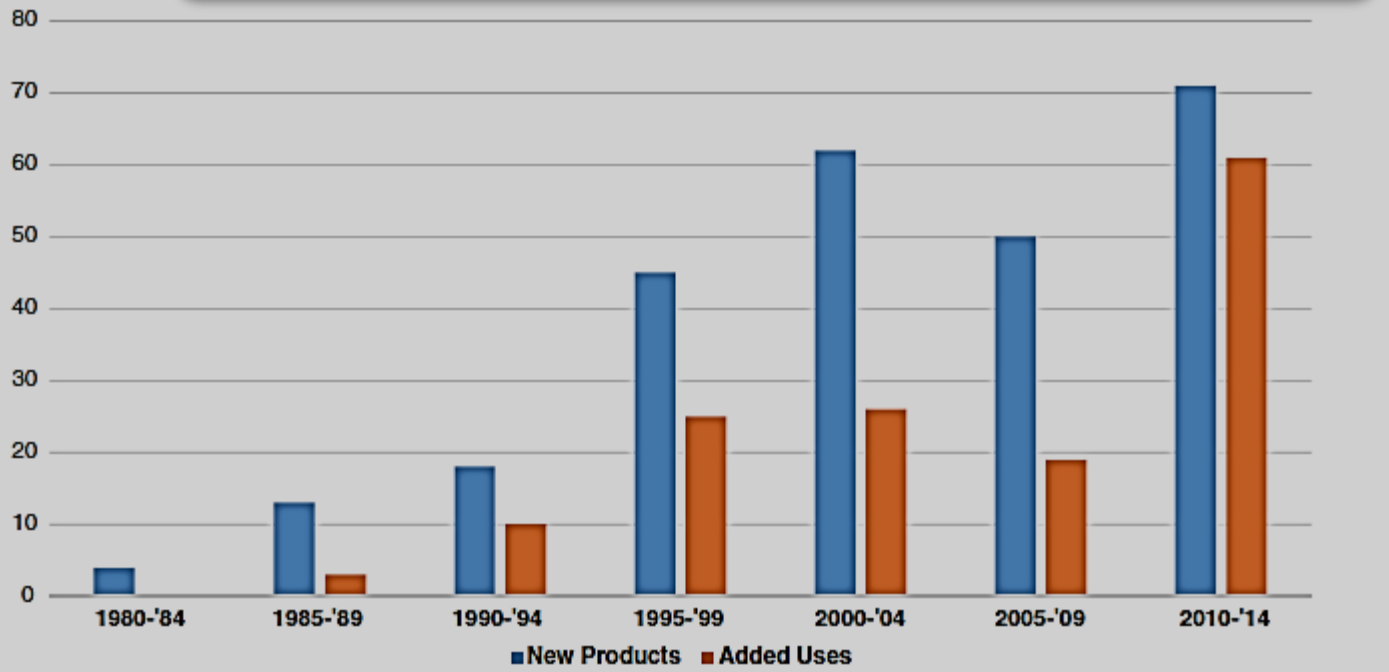
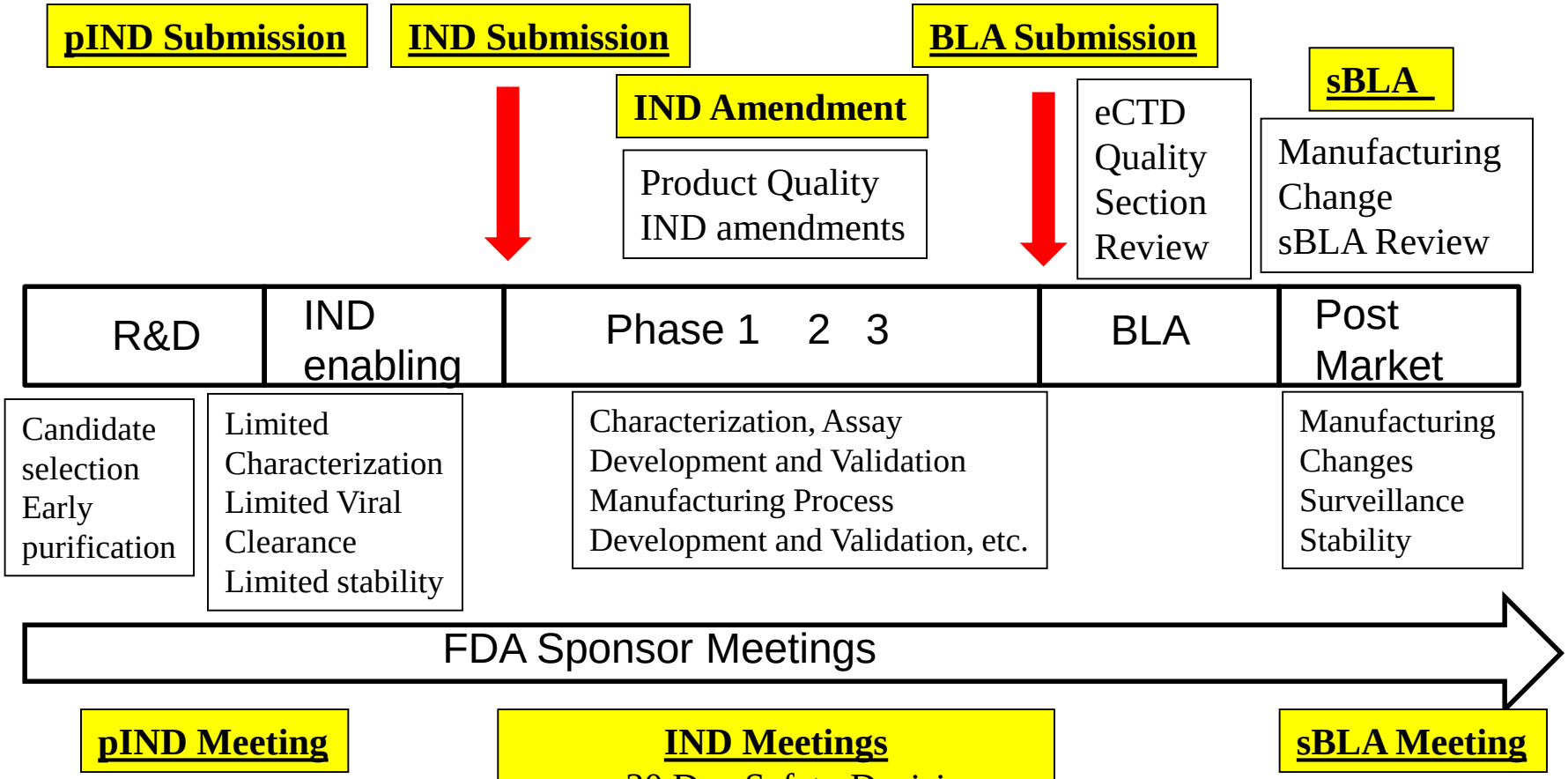


Fig. 1. Biotech approvals with FDA—new products and added uses, 1980 to 2014

Product Lifecycle



The pIND Package and Meeting

- Type B Meeting (21.CFR 312.82)
- Submission 4 Weeks Prior to the Meeting
- Key Product Quality Aspects
    1. Brief Summary of Product History and Development Program
    2. CMC Specific Questions
- "Face to Face", Teleconference, or Written Responses
- FDA Guidance For Industry Formal Meeting Between the FDA and Sponsors or Applicants 2009

The pIND – General Comments

1. The quality of the pIND submission varies widely.

2. Provide well written questions and focus background information on each question.

3. Typical Questions Include
   - **Is the proposed release testing strategy appropriate for the phase I trial?**
   - **Will the proposed drug substance release testing strategy support the future phase 3 clinical trial and BLA?**

     The focus of the meeting should be on getting the original US FDA IND started. Schedule a meeting latter in product development for this type of questions.

The pIND – General Comments

3. Typical Questions Include (Continued)

The non-clinical lots were manufactured by X and the clinical lots will be Manufactured by Y. Does the FDA have any concerns regarding the manufacturing process and are the lots comparable?

The IND should contain the primary results of the physico chemical comparability studies and provide a summary of all differences between the manufacturing process at the two facilities.

IND CMC Information

- Description of the Product – Mechanism of Action
- Expression system and cell bank
- Name of the Manufacturer
- Brief Description of the Manufacturing Process and In-Process Controls
- List and Grade of Raw Materials
- Results of Viral Clearance Studies
- Results of Characterization Studies
- Release Specifications, Release Results for the non-Clinical and Clinical Lot
- Stability Results, Stability Protocol, and In-Use Stability Results
- Description of the Container Closure System
- Summary of Plans to Monitor Anti-Drug Antibodies (ADA)
- Description of the Placebo (if applicable)
- Investigational labeling

IND – General Comments

1. Specifications should adequately control the critical product attributes for the lot(s) to be used in the initial phase I clinical trial and future clinical trials.

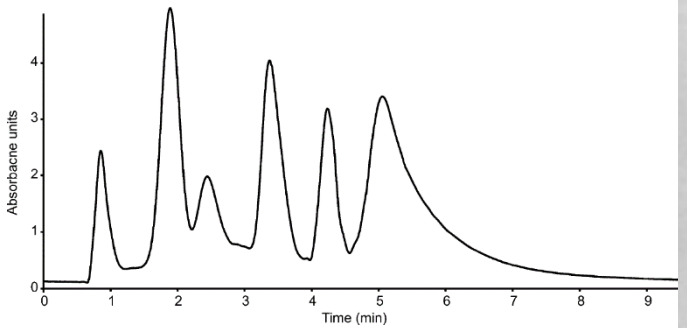
2. "Report Results" for a method acceptance criteria may not be appropriate if the product attribute is not controlled by the testing strategy.

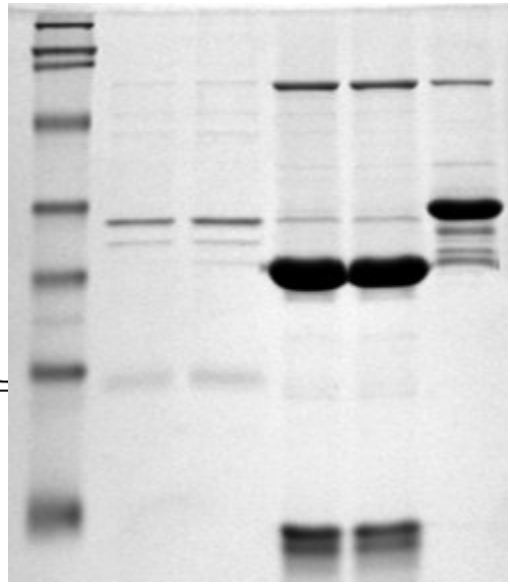
Release Specifications

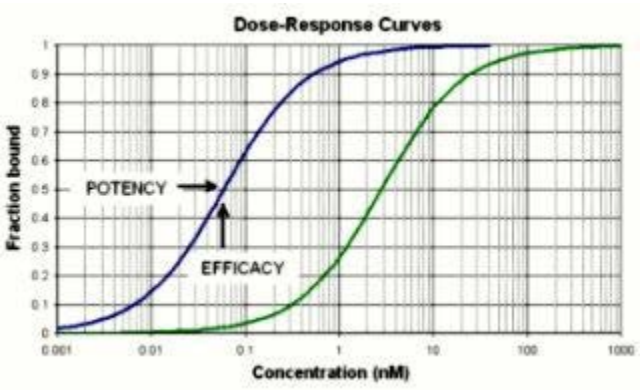
Method	Attribute	Accpt. Crit.
Appearance	Quality	Clear
pH	Quality	6 - 7
Osmolality	Quality	245 - 370
Western Blot	Identity	Pass
UV_{280}	Strength	1.8 – 2.2 mg/ml
Bioassay	Potency	70 – 130 % of RS
RP-HPLC	Purity	Repot Results
IEX-HPLC	Purity	Report Results
SEC-HPLC	Purity	> 90%
Host Cell Protein	Purity	< 100 ppm
Host Cell DNA	Purity	< 100 pg/mg
Bioburden	Purity	< 1 CFU/ml
Endotoxin	Purity	< 3 EU/mg

IND – General Comments

3. Primary results for important release methods should be included in the review.
   - RP-HPLC Chromatograms
   - Picture of SDS-PAGE Gels
   - Dose Response Cure For Potency Method







Courtois J et at. 2006 Polymer 47:2603
https://upload.wikimedia.org/wikipedia/commons/b/bf/SDS-PAGE.jpg
https://upload.wikimedia.org/wikipedia/commons/7/70/DoseResponse000.svg

IND – General Comments

4. QC method reports may be included in the IND. FDA often will request the reports to evaluate and verify the results. There are issues when QC Methods results do not match the methods in release summary tables.

5. A plan should be provided in the IND to develop methods to monitor for anti-drug binding and neutralizing antibodies. Patient serum should be banked and tested with ADA assays are available.

IND 30 Day Decision Date

The FDA does not approve an IND. If there are deficiencies that are a risk to patient safety the IND will be placed on clinical hold.

Examples of Product Quality Clinical Hold Deficiencies

- Differences in the non clinical and clinical lots (e.g. new peak in RP-HPLC)
- Inadequate product characterization with regards to purity, identity, potency, safety
- No specification for product impurities or product variants
- High Level of Impurities (e.g. host cell proteins)
- Release Method Acceptance Criteria Too Wide
  Bioassay for potency acceptance criteria 50% - 200% of Ref. Std

Immunogenicity Risk for IND Protein Products

Anaphylaxis – Extreme and Severe Allergic Reaction

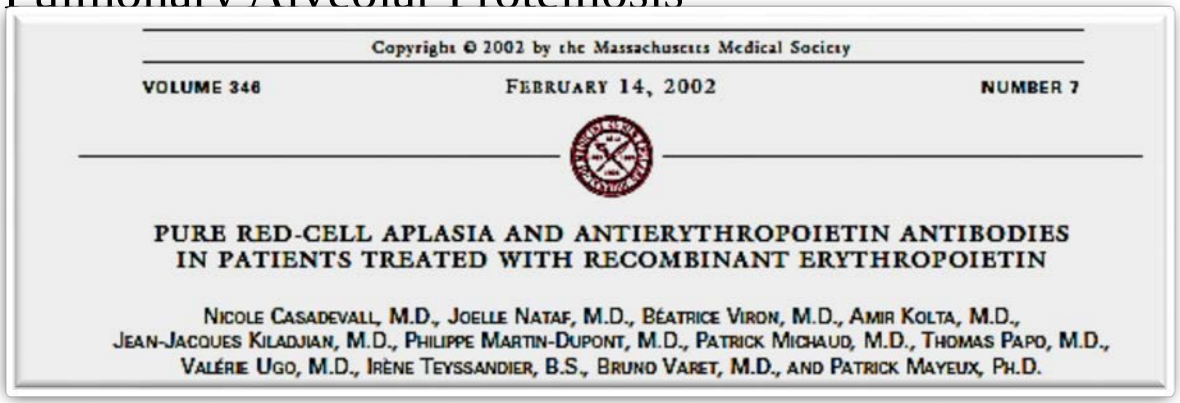
- Non-Human Proteins (e.g. aprotinin, asparagine)
- Replacement Human Proteins (e.g. Factor IX for Hemophilia B)

Immune Complex Mediated Disease – Deposition of Antigen Antibody Complexes

- Serum Sickness: Nephropathy

Anti-Drug Neutralizing Antibodies – Neutralization of Endogenous Protein

- Erythropoietin (EPO) – Pure Red cell Aplasia
- Thrombopoietin (TPO) – Thrombocytopenia
- GM-CSF – Acquired Pulmonary Alveolar Proteinosis

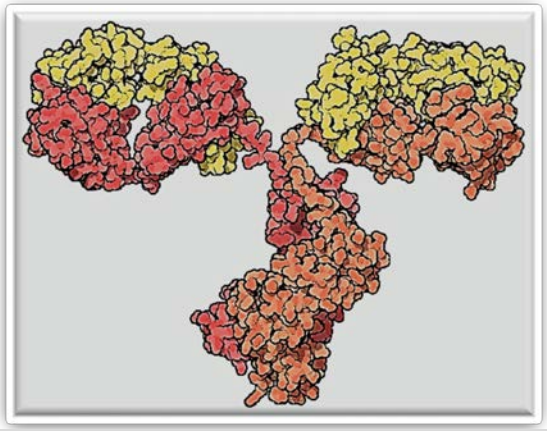


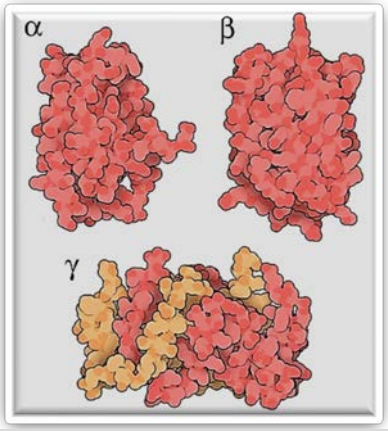
VOLUME 346 FEBRUARY 14, 2002 NUMBER 7

PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

NICOLE CASADEVALL, M.D., JOELLE NATAF, M.D., BÉATRICE VIRON, M.D., AMIR KOLTA, M.D., JEAN-JACQUES KILADJIAN, M.D., PHILIPPE MARTIN-DUPONT, M.D., PATRICK MICHAUD, M.D., THOMAS PAPO, M.D., VALÉRIE UGO, M.D., IRÈNE TEYSSANDIER, B.S., BRUNO VARET, M.D., AND PATRICK MAYEUX, PH.D.

MAB and Therapeutic Protein Anti-Drug Antibodies Product Risks





Binding ADA		
No Clinical Effect	Yes	Yes
PK Parameters	Yes	Yes
Tissue Distribution	Yes	Yes
Immune Complex Disease	Yes	Yes
Neutralizing Antibodies		
Loss of Product Efficacy	Yes	Yes
Neutralization of Endogenous Protein	No	Yes

Images from http://www.rcsb.org/pdb/education_discussion/molecule_of_the_month/images/1igt.gif

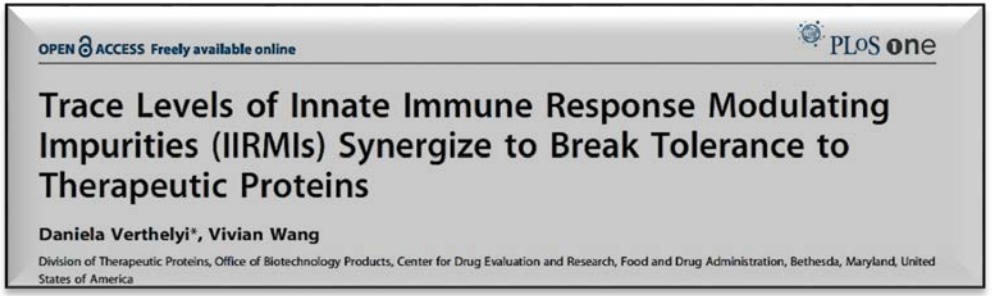
Product Quality Can Impact Immunogenicity Risk

Product Variants or Product Impurities

- Aggregates
- Protein Subvisible Particles
- Oxidation/Aldehyde Modifications
- Deamidation
- Citrullination

Process Impurities/Leachable Impurities ("Adjuvant")

- Host Cell Protein
- Endotoxin
- Leachables

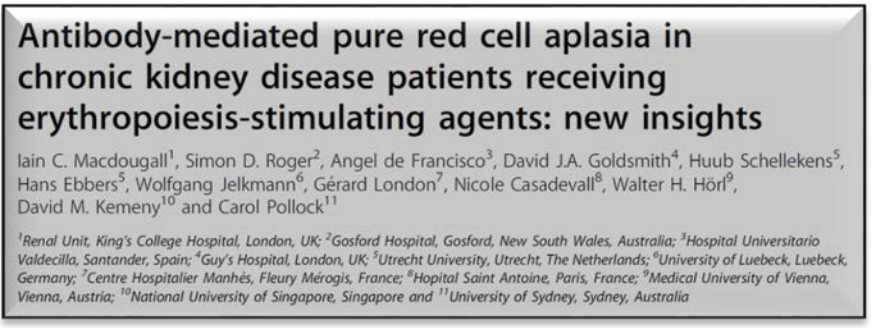


OPEN ACCESS Freely available online PLoS one

Trace Levels of Innate Immune Response Modulating Impurities (IIRMIs) Synergize to Break Tolerance to Therapeutic Proteins

Daniela Verthelyi*, Vivian Wang

Division of Therapeutic Proteins, Office of Biotechnology Products, Center for Drug Evaluation and Research, Food and Drug Administration, Bethesda, Maryland, United States of America



Antibody-mediated pure red cell aplasia in chronic kidney disease patients receiving erythropoiesis-stimulating agents: new insights

Iain C. Macdougall[1], Simon D. Roger[2], Angel de Francisco[3], David J.A. Goldsmith[4], Huub Schellekens[5], Hans Ebbers[5], Wolfgang Jelkmann[6], Gérard London[7], Nicole Casadevall[8], Walter H. Hörl[9], David M. Kemeny[10] and Carol Pollock[11]

[1]Renal Unit, King's College Hospital, London, UK; [2]Gosford Hospital, Gosford, New South Wales, Australia; [3]Hospital Universitario Valdecilla, Santander, Spain; [4]Guy's Hospital, London, UK; [5]Utrecht University, Utrecht, The Netherlands; [6]University of Luebeck, Luebeck, Germany; [7]Centre Hospitalier Manhès, Fleury Mérogis, France; [8]Hopital Saint Antoine, Paris, France; [9]Medical University of Vienna, Vienna, Austria; [10]National University of Singapore, Singapore and [11]University of Sydney, Sydney, Australia

The Immunogenicity Risk and IND product Development

If there is a significant safety concern (i.e. health subjects receiving a new cytokine) sensitive methods should be validated and subjects serum evaluated during the Phase I trial. The method validation reports should be provided in the original IND

For most protein products the FDA requests that the IND contain a plan for monitoring ADA. If validated methods are not available for the phase I trial, patient's serum should be frozen. Serum should be tested when the ADA methods are validated and the results provided in an IND amendment.

OBP often will review ADA method validation reports and provided feedback to sponsors.

ADA Methods should be validated for the phase III clinical trial.

Product Quality IND Amendments

- A IND amendment should be submitted to the FDA for manufacturing changes that have a significant potential to affect the safety of the product

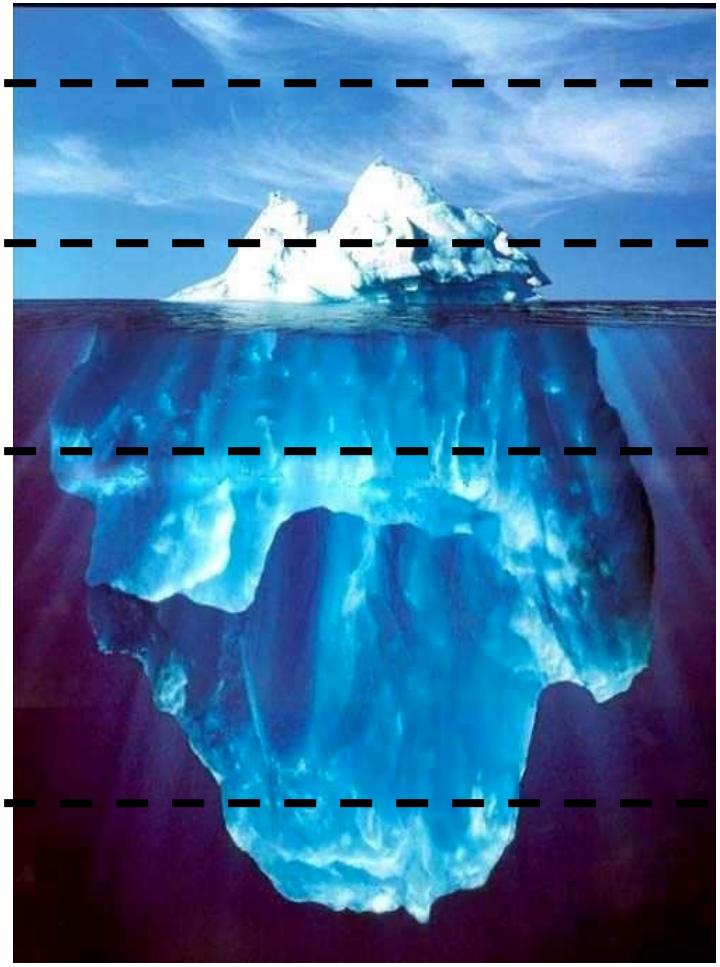
- Guidance for Industry: INDs for Phase 2 & Phase 3 Studies, CMC Information

Examples of Significant Changes to be Submitted in an IND Amendment

- Manufacturing Process Scale Up
- Transfer of the Manufacturing Process to a New Facility
- Change of a Critical Raw Material
  (i.e. pegylation reagent, new cell bank)
- Major Changes in the Purification Process
- Container Closure System Change Affecting Product Stability

The BLA

Extensive Knowledge, Characterization, and Control of The Product



- QC Release tests
- Process & Product Characterization
- Process Control
  - Procedures
  - Validation
  - Training

Quality Control Strategy

Process → Product

- Facilities and Equipment
- Control of Raw Materials
- In-Process Testing
- In-Process Controls
- Process Validation
- cGMPs (QC/QA)

- Method Validation
- Release Testing
- Characterization
- Stability Testing

Product Heterogeneity

- Amino Acid Substitution
- Truncation
- Mismatched S-S bonds
- N- and C-terminal difference
- Aggregation
- Multimer Dissociation
- Denaturation
- Acetylation
- Acylation
- Addition of lipid
- Amidation/Deamidation
- Carbamylation
- Carboxylation
- Formylation
- Gamma Carboxyglutamic acid
- O-linked Glycosylation
- N-linked Glycosylation
- Methylation
- Oxidation
- Phosphorylation
- Sulphation

sBLA - Changes to an Approved Application

601.12 (2) Before distributing a product made using a change, an applicant must assess the effects of the change and demonstrate through appropriate validation and/or other clinical and/or nonclinical laboratory studies the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product

<u>Prior-Approval supplement</u>

- For changes with high risk to impact quality, purity, safety or potency
- Sponsor cannot implement the change and release product until the supplement is approved

Reporting changes

Changes Being Effected in 30 days (CBE30)

- Moderate risk to product quality
- Sponsor can implement the change and release product 30 days after submission

Changes Being Effected (CBE)

- Minimal risk to product quality
- Sponsor can implement the change immediately

Annual Report

Changes that have very little if no impact on product quality

If the FDA does not agree with the reporting category the reporting category can be upgraded.

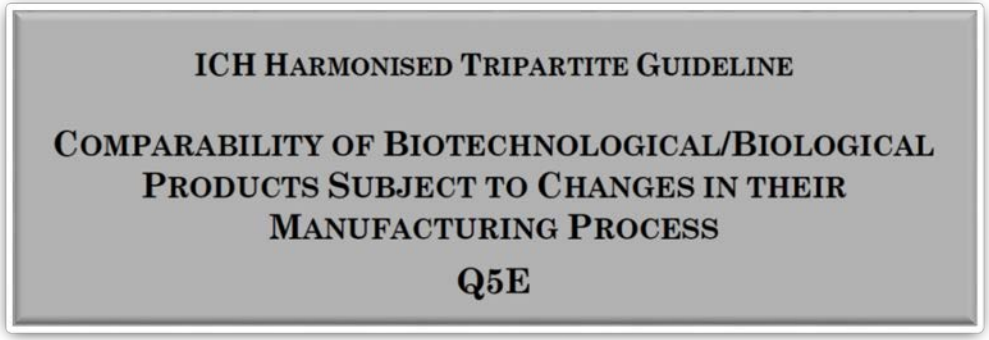
Examples of sBLA submitted to OBP in 2015

- Addition of a New Drug Substance or Drug Product Manufacturing Facility

  A "comparability exercise": the activities including study design, conduct of studies, and evaluation of data that are designed to investigate whether a change in the manufacturing process will have an adverse effect on the quality, safety and efficacy of the drug product

  For simple changes little or no comparability is required (e.g. replacement of same equipment)

  For complex changes (e.g. new master cell bank, new DS facility) the sponsor will need perform a full comparability exercise (release, characterization, stress and stability studies) that may include non-clinical and clinical studies



Examples of sBLA submitted to OBP in 2015

- Transfer of an Analytical Release Method to a New Facility
- Addition of a New Product Configuration (e.g. Auto-Injector)
- Replacement of an Analytical Method
- Change in Critical Raw Material

sBLA Comments – General Comments

1. 21 CFR 601.12(a)(5) A supplement or annual report must include a list of all changes contained in the supplement or annual report. For supplements, this list must be provided in the cover letter.

   sBLA submitted for a new manufacturing facility.
   Some analytical methods were transferred to the new facility.
   Analytical method transfer not stated in the cover letter and not indicated in the correct section of the eCTD document.

2. sBLA submitted under the wrong reporting category.
   Replaced a method related to safety testing

FDA Guidance for Industry – Changes to an approved Application: Biological Products

sBLA FDA & Sponsor Meeting

- Prior to Submitting a Major Supplement Sponsors Often Request a FDA Meeting
- Meeting Package Submitted 30 Days Prior to the Meeting.
- FDA Provides Responses to Specific Questions
- FDA Usually Provides a Written Response. A Teleconference (or Formal Meeting) Occurs if Further Clarification is Requested.

sBLA FDA & Sponsor Meeting – General Comments

- Provide Sufficient Background and Summary Information For Each Question.

- FDA Will Provided Advice. The Final Determination Will be Made When the sBLA is Reviewed. Method Validation, Physico-chemical Comparability Results, etc. Require a Formal FDA Review

Acknowledgements

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Juhong Liu
Daniela Verthelyi

Thanks

Questions?