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Conundrums in Biotechnology: How Does Quality Impact Safety?

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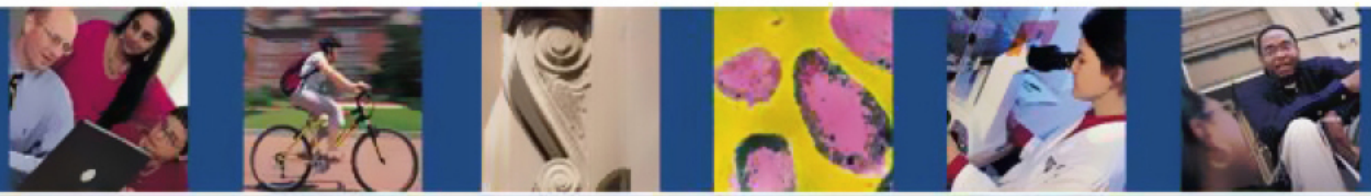

Protecting Health, Saving Lives—*Millions at a Time*

Disclosures

- Chair, FDA Peripheral and Central Nervous System Advisory Committee
- Consultant: IQVIA, MesaRx Innovations
- Equity Holder: Monument Analytics
- Member: OptumRx National P&T Committee
- Funding: FDA, CDC, AHRQ, NHLBI, NIDA, DHHS/ASPE, AstraZeneca, Arnold Foundation, Robert Wood Johnson Foundation…

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Center of Excellence in Regulatory Science and Innovation

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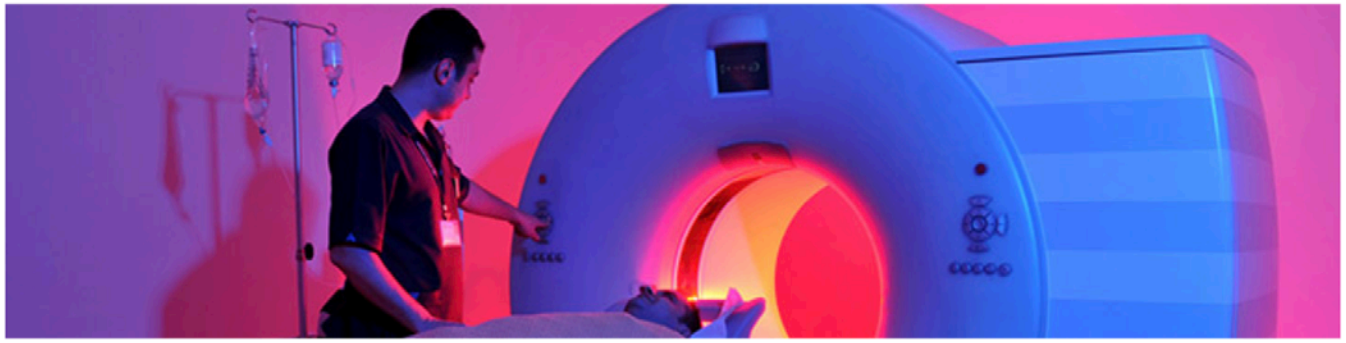

In our rapidly evolving scientific landscape, the complexity of the Food and Drug Administration's primary charge – to safeguard the health and well-being of the public through the application of scientifically sound regulatory activities – is constantly being challenged.

Active Investigations

1. Evaluating Development Strategies and Regulatory Outcomes for FDA-Approved Biologics
2. Assessing Drug Development in Pediatrics
3. Use of Existing Drugs as Novel Treatment Strategies in Low Resource Settings
4. Comparing Qualitative and Quantitative Approaches to Eliciting Patient Preferences: A Case Study on Innovative Upper Limb Prostheses
5. Incorporating the Patients' Perspective in Selecting Outcomes for Glaucoma
6. Increasing Compliance with Reporting Requirements at Academic Medical Centers
7. Synthesizing Real-World Data For Regulatory Decision Making In Single-Group Medical Device Clinical Studies
8. Understanding Flavors in Electronic Nicotine Delivery Systems

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9. **Conundrums in Biotechnology: How Does Quality Impact Safety?**

Biologics and biosimilars

- **Xultophy** (insulin degludec/liraglutide)
- **Xermelo** (telotristat ethyl)
- **Dupixent** (dupilumab)
- **Ocrevus** (ocrelizumab)
- **Bavencio** (avelumab)
- **Trulance** (plecanatide)
- **Siliq** (brodalumab)

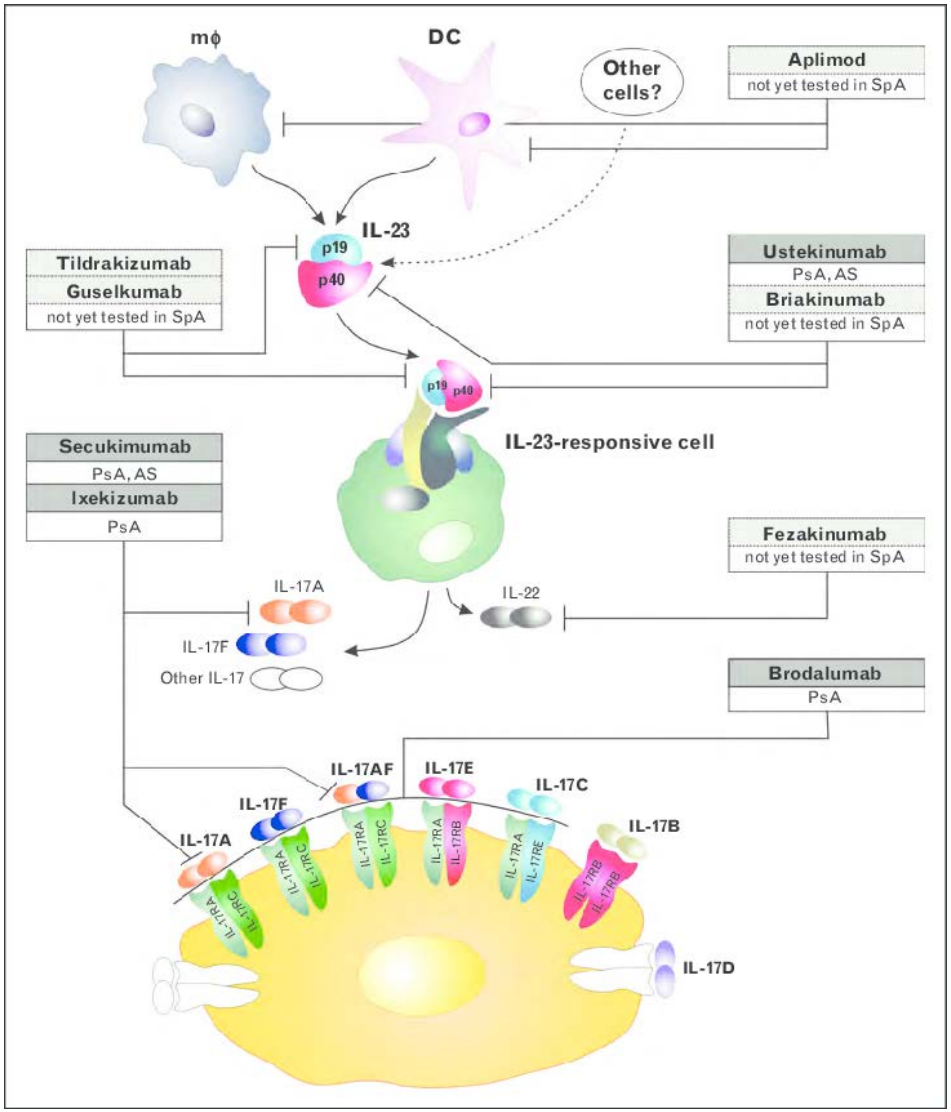
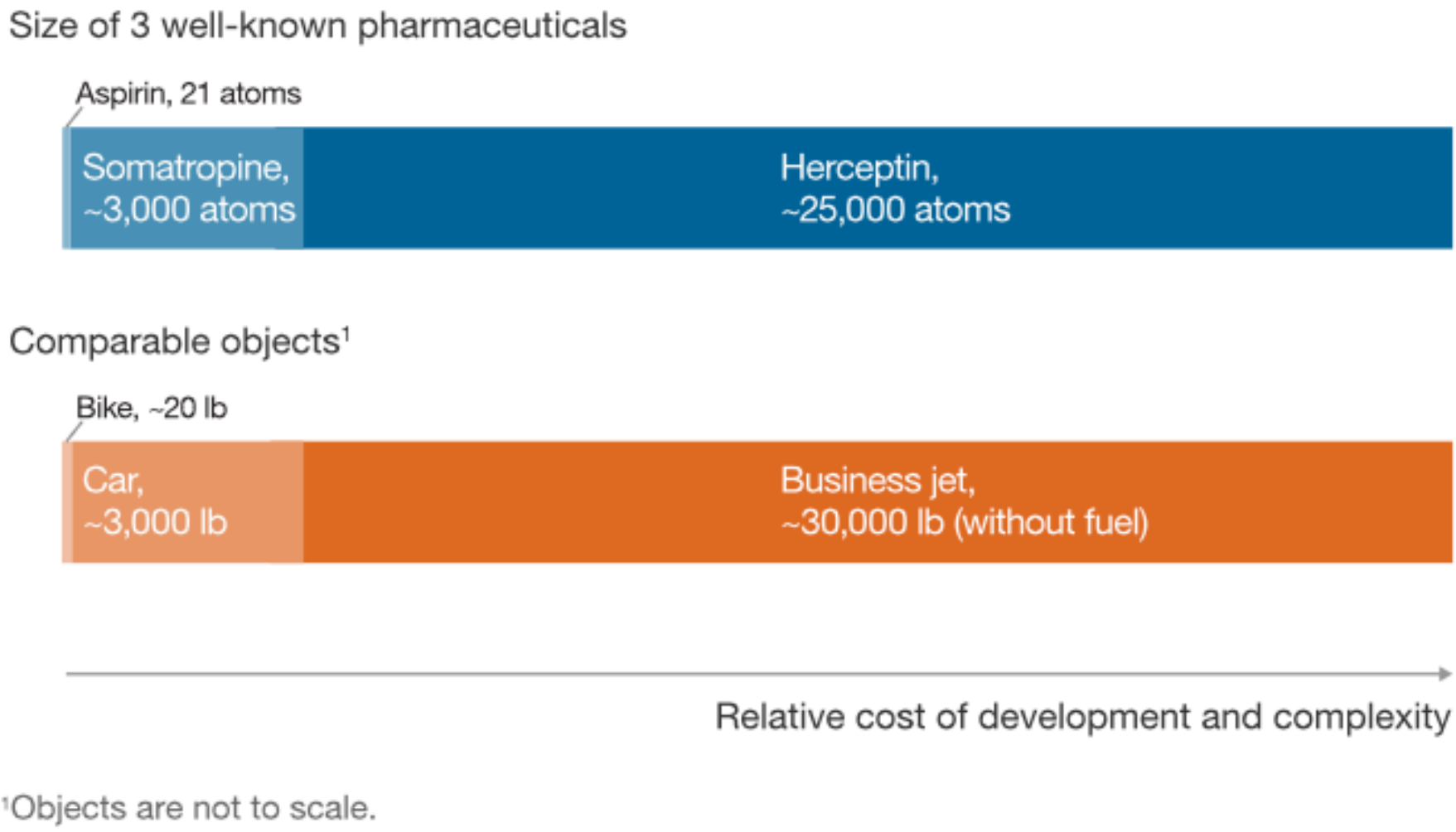


Exhibit 1

Copying biopharmaceuticals is not a simple task.



[1]Objects are not to scale.

McKinsey&Company, Dec 2014.

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Conclusion: Preliminary evidence supports the biosimilarity and interchangeability of biosimilar and reference TNF-α inhibitors.

Johns Hopkins
Biologic Quality and Safety Consortium (BQSC)

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Consortium Rationale

- Goal: To assess association between monoclonal antibody product quality and clinical safety
- Focus: Monoclonal antibodies (IgG1, IgG2, or IgG4 isotypes) evaluated in Phase 2 and Phase 3 trials
- Diverse portfolio of scientific questions using rigorous epidemiologic methods to maximize causal inference

Quality and Safety Measures

- Quality Measures
  - Aggregates
  - mAb Fragments
  - Charge isoforms
  - Glycoforms
  - Impurities (e.g., host cell protein)

- Safety Measures
  - Immunogenicity
  - Immunogenicity
  - Immunogenicity

Scientific Questions

1. What is the association between monoclonal antibody dimer levels and clinically-significant immunogenic reactions?
2. To what degree does this association vary across different patient populations, clinical indications, or Ig subtypes?
3. What range of batch variation in other quality attributes is associated with meaningful differences in safety?
4. How can manufacturing processes be improved to reduce batch variation that impacts clinical safety?
5. Are there other tools that can be developed to better understand correlates between product quality and safety?

Proposed Consortium: Logistics

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- Steering Committee comprised of consortium members
- Johns Hopkins to house, aggregate and curate data
- Primary analyses performed by Johns Hopkins scientists
- Potential for others (e.g., participating consortium members) to access blinded data based on terms and conditions established by Steering Committee

NIMBL

The National Institute for Innovation in Manufacturing Biopharmaceuticals

Quick Start Project Request for Proposals

Closing Thoughts

- No greater challenge than improving manufacturing efficiency and flexibility while maximizing safety
- Consortium will generate fundamental new knowledge of high relevance to manufacturers and regulators
- Delivers on the challenge presented by regulators to analyze and correlate quality and safety data
- Consortium will help to provide the most rigorous evidence to date evaluating the appropriateness of many critical quality attributes (CQAs) with respect to important safety outcomes

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