Testimony of

Dr. William Hancock

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Introduction

Thank you for the opportunity to testify today on the issues around the production of follow-on biologicals (recombinant DNA or rDNA derived protein pharmaceuticals). My name is William S. Hancock, and I am Professor and Bradstreet Chair in Bioanalytical Chemistry at Northeastern University in Boston, Massachusetts. I am familiar with the significant scientific hurdles associated with manufacturing biological products from more than thirty years working in the area in academia, industry and government. Though my government service was brief, I served as a Visiting Scientist at the Food and Drug Administration's Bureau of Drugs in 1983. From 1985 to 1994, I worked on biological drug products at Genentech, one of the pioneers in this area, first as a staff scientist and later as Acting Director of Pharmacology. I have also held scientific positions at Hewlett Packard Laboratories and ThermoFinnigan Corporation, a maker of mass spectrometry instuments, where I served as Vice President of Proteomics from 2000 to 2002 before accepting my current position on the faculty of Northeastern University. I have authored or co-authored over 150 peer-reviewed books and articles, many dealing with issues regarding the characterization and manufacture of biologics. I thus appreciate the opportunity to share my thoughts with the Committee on this difficult but important subject.

Summary

I believe that there is a substantial scientific challenge (both analytical and non-analytical) to achieve the adequate characterization of any biotechnology product. Furthermore, I believe that the production of safe and effective follow-on biologicals is very difficult, if not impossible, in the near future. The following discussion will highlight the major differences between small molecule drug products and biologics which present the greatest scientific challenges for approval of follow-on biologics.

Outline of Testimony

1. Overview: Comparing scientific aspects of small molecule drugs and biologics

? Physical properties
? Structure and mechanism of action
? Manufacturing and product quality
o Process, quality assurance
? Product safety aspects

2. Physical Characteristics

? Composition: drugs may be composed of dozens of atoms; biologics may be composed of millions of atoms
? Molecular Weight (Size): drugs may be measured in 100s of Daltons; biologics in 100's of KiloDaltons
? Structure: drugs can be described by a chemical formula that is fixed; biologics typically cannot be described by a single chemical formula
? Production: drugs are chemically synthesized by scientists according to a "cookbook"; biologics are synthesized by "organisms" (e.g., bacteria, mammalian cell culture)
? Mechanism: for drugs, the mechanism of action is usually understood; for biologics it is not always understood

3. Manufacturing and Product Quality

a. Making a small molecule drug vs making a biologic

? Starting Material: for drugs, it is chemicals; for biologics, it is DNA plasmid vector & cells or a whole animal
? Initial Process: for drugs, it is chemical reactions and synthesis; for biologics, it is transfection or insertion of DNA into a host organism
? Vessel for synthesis: for drugs, it is specialized glass and/or metal containers; for biologics, it is bacterial, insect, mammalian cells or whole animal
? Initial Product: for drugs, it is a highly purified chemical compound; for biologics, it is a cell lysate or cell culture medium
? Components: for drugs, the components of the product are defined; for biologics, the components typically are complex and undefined

b. Quality and GMP

? "Process controls" are a key element in defining product quality
o Such controls are quite different for chemical and biologic manufacture
? Product vs process knowledge
o For small molecule drugs, process knowledge is less important than product knowledge
o For biologics, experience with process is essential for biologic manufacture - 'the process is the product'
? Contamination during manufacturing
o Easily avoided for small molecule drugs; detectable; often removable
o For biologics, possibility of contamination with viruses & other adventitious agents; detection may be harder; removal impossible

c. Process "know how" for biologics

? Familiarity with production process essential for understanding of which changes affect final product and which do not
? Apparently small changes, such as a new batch of cells, can dramatically--and unpredictably--alter function of final product
? This experience can only be obtained over years of manufacturing

d. Analytical Testing

? Small Molecule Drugs
o Simple physical & chemical methods
o Precise composition & structure

? Biologics
o Complex physical & chemical methods
o Primary protein structure (sequence)
o 3-dimensional structure - only sometimes
o Protein modifications
? Glycosylation
? Phosphorlation
o Prohibitively resource intensive to determine precisely
o Biological products often a heterogeneous mix

4. Product Safety Aspects

Immunogenicity
? Small molecule drugs rarely elicit immune response
? Macromolecules (proteins) of biologic drugs are capable of triggering immune response with varying consequences
o Antibodies may neutralize the molecule making it therapeutically ineffective
o Rare but serious autoimmune responses can be life-threatening
o Immunogenicity of biologic drugs is unpredictable, unforeseeable
o Small changes in a macromolecule can completely shift its immunogenicity profile

5. Scientific and medical challenges with biologics

? Limits of Analytical Testing
o For small molecule drugs, full characterization readily undertaken
o For biologics, full characterization technically impossible today

? Quality, GMP considerations different than for small molecules

? Process changes and access to innovator data
o For small molecule drugs, the process does not define the product
o For biologics, the process uniquely defines the product

? Immunogenicity and Safety: An issue for biologics that is not present for small molecule drugs

6. Final Thoughts

? Biologic drugs are orders of magnitude more complex than small molecule drugs
? Safety & efficacy of final product are exquisitely sensitive to small changes in process

? It is difficult to impossible to predict the effect of these small changes--experience counts
? Potential for dramatic negative health consequences