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## Follow-On Protein Products: FDA's View

Elaine H. Tseng  
King & Spalding LLP  
202.626.5576 or 415.955.2782  
etseng@kslaw.com




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## Overview

- Key FDA FOPP-related activities
- FDA position on issues relating to FOPPs
- Future regulatory steps





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## Key FDA FOPP-Related Activities


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## FDA Activity

- No regulations or guidance specific to follow-on protein products (FOPPs)
- Several approvals of peptide/protein FOPPs
  - Most complex to date is rhGH

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## Approvals

- rhGH approved as FOPP (Omnitrope)
  - \* Application approved under Federal Food, Drug, and Cosmetic Act (FDCA) sec. 505(b)(2)
  - \* Approval supported by significant original clinical data

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## Approvals

- Other peptides/proteins approved as FOPPs
  - FDCA sec. 505(b)(2) only
  - Recombinant peptide hormones shorter than rhGH
  - Safety/immunogenicity clinical data needed (unlike ANDAs)
- Second generation product changes and comparability assessments\*
  - Clinical data not necessary, but these changes were effectuated by same manufacturer or under agreement with original manufacturer to access manufacturing information

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## Petition Responses

- FDA Response to Citizen Petitions Opposing Approval of Omnitrope (May 30, 2006)

<http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn001.pdf>

- FDA Response to Citizen Petitions Challenging Agency Interpretation of Section 505(b)(2) (October 14, 2003)

<http://www.fda.gov/ohrms/dockets/dockets/04p0231/04p-0231-c000001-Exhibit-29-vol4.pdf>

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## FDA's Position on FOPP Issues

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## FDA's current views on abbreviated approval for FOPPs

- FDCA Products

### **ANDAs under section 505(j) generally not appropriate for FOPPs.**

“Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product. Therefore, the section 505 (j) generic drug approval pathway, which is predicated on a finding of the same active ingredient, will not ordinarily be available for protein products.”

Janet Woodcock, M.D., FDA Deputy Commissioner  
and Chief Medical Officer (May 2, 2007)

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## FDA's current views on abbreviated approval for FOPPs

- FDCA products

### **Section 505(b)(2) may be applicable, but determination is fact-specific.**

“The approval of Omnitrope does not signal that the Agency has concluded that...every protein product approved under section 505 of the [FDCA] is an appropriate candidate for reference by an applicant seeking approval of a follow-on protein product through an abbreviated approval pathway.”

FDA response to citizen petitions opposing  
approval of Omnitrope (May 30, 2006)

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## FDA's current views on abbreviated approval for FOPPs

- Similarly:

“The approval of Omnitrope does not establish a pathway for approval of follow-on products for biological products licensed under section 351 of the Public Health Service Act, nor does it mean that more complex and/or less well understood proteins approved as drugs under the Food, Drug, and Cosmetic Act could be approved as follow-on products.”

FDA's Omnitrope (somatotropin [rDNA origin])  
Questions and Answers (Omnitrope Qs and As)

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## FDA's current views on abbreviated approval for FOPPs

- PHSA Products

**No abbreviated approval mechanism presently exists.**

- FDA stated in its Omnitrope petitions response that “there is no abbreviated approval pathway analogous to 505(b)(2) or 505(j) [of the FDCA] for protein products licensed under section 351 of the PHSA.”
- Same statement made in Qs and As document issued in conjunction with Omnitrope approval and petitions response, with added note that, “Such a pathway for the approval or licensure of [FOPPs] under the [PHSA] would require new legislation.”

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## Omnitrope: Lessons learned for FOPP 505(b)(2) applications

- **Approval standard: “*highly similar*” to (as opposed to “same” as) reference drug**
  - But standard not clearly defined
  - Factors used to determine that Omnitrope and Genotropin are highly similar “do[] not imply that a finding that two products are highly similar with respect to any specific property or set of properties is always necessary to support reliance in the 505(b)(2) context.”

FDA response to citizen petitions opposing approval of Omnitrope (May 30, 2006)

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## Omnitrope: Lessons learned for FOPP 505(b)(2) applications

- **Factors supporting a determination of “highly similar”:**
  - Protein well-characterized and without complexities such as glycosylation
  - High degree of structural similarity can be determined
  - Mechanism of drug action is known and toxicity profile well understood
  - Clinically relevant bioassays and qualified biomarkers available
  - Long history of clinical use well documented in published literature
  - No need to refer to CMC or other trade secret data to assess similarity

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## Omnitrope: Lessons learned for FOPP 505(b)(2) applications

- **Significant clinical data are likely to be needed.**

Data supporting approval exceed those required to demonstrate bioequivalence for small molecule, chemical drugs:

- Original clinical data supporting Omnitrope “extensive.”
- Sandoz conducted 4 phase 3 studies in pediatric patients in addition to pharmacokinetic and pharmacodynamic studies.
- Immunogenicity data key.

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## Lessons learned for FOPP 505(b)(2) applications

- **In general, clinical data needed for complex proteins because of technology limitations.**

“It is the combination of the protein’s amino acid sequence and its structural modifications that give a protein its unique functional characteristics. Therefore, the ability to predict the clinical comparability of two products depends on our understanding of the relationship between the structural characteristics of the protein and its function, as well as on our ability to demonstrate structural similarity between the follow-on protein and the reference product. Although this currently may be possible for some relatively simple protein products, technology is not yet sufficiently advanced to allow this type of comparison for more complex protein products.”

Janet Woodcock, M.D., FDA Deputy Commissioner  
and Chief Medical Officer (May 2, 2007)

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## Lessons learned for FOPP 505(b)(2) applications

### - Clinical data generally needed to assess immunogenicity.

“Neutralizing antibody” responses can decrease the clinical effect of a protein. ...Immune responses to administered protein products can be extremely serious or life-threatening; therefore, this issue requires significant attention. The ability to predict immunogenicity of a protein product, particularly the more complex proteins, is extremely limited. Therefore, some degree of clinical assessment of a new product’s immunogenic potential will ordinarily be needed. The extent of independent testing needed will again depend on a variety of scientific factors such as the indication, whether the product is to be administered chronically, the overall assessment of the product’s immunogenic potential, and whether there is the possibility of generating a cross-reaction with an important endogenous molecule.”

Janet Woodcock, M.D., FDA Deputy Commissioner  
and Chief Medical Officer (May 2, 2007)

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## Omnitrope: Lessons learned for FOPP 505(b)(2) applications

### • Interchangeability for FOPPS is uncertain.

- Decision does not address whether standards for therapeutic equivalence of FOPPs can be established
- June 2007: “[L]egislation should not allow for determinations of interchangeability at this time.” (June 26, 2007 letter from HHS Secretary Leavitt to Sen. Edward Kennedy)
- Lack of ‘sameness’ of active ingredients presents issues for meeting existing TE standard
  - \* Will FOPP legislation establish a new TE standard or preclude interchangeability?

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## Lessons learned for FOPP 505(b)(2) applications

### - Scientific challenges to establishing TE exist.

“To establish that two protein products would be substitutable, the sponsor of a follow-on product would need to demonstrate through additional clinical data that repeated switches from the follow-on product to the referenced product (and vice versa) would have no negative effect on the safety and/or effectiveness of the products as a result of immunogenicity. For many follow-on protein products -- and in particular, the more complex proteins – there is a significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited.”

Janet Woodcock, M.D., FDA Deputy Commissioner  
and Chief Medical Officer (May 2, 2007)

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## Future Regulatory Steps

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## FDA and New Legislation

- In February, the Bush Administration published its FY 2009 budget proposal, which includes a provision regarding FOPPs:

“For FY 2009, the Administration will seek new statutory authority to allow FDA to approve abbreviated applications for certain biologic products licensed under the Public Health Service Act (PHS Act). . . .”

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## FDA and New Legislation

- **Elements of anticipated legislative proposal:**

“The legislative proposal will...

- [I]nclude necessary provisions to ensure the safety and effectiveness of [FOPPs]....
- [I]nclude a predictable and public guidance process for licensing follow-on protein products under the Public Health Service Act.....
- [P]rescribe the type of data required for FDA to review applications for follow-on protein products....

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## FDA and New Legislation

- **Elements of anticipated legislative proposal (cont'd):**

“The legislative proposal will...

- [R]equire labeling for the safety concerns related to the interchangeability of these products....
- [I]nclude adequate intellectual property protections to preserve continued robust research into new and innovative life-saving medications....
- [I]ncludes a financing structure to cover the cost of this activity through user fees....”

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**Thank you.**

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## Fine Print

This presentation and the accompanying discussion provide general information on recent legal and regulatory developments. They are not intended to be, and should not be relied upon, as legal advice.



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## Follow-On Biologics: Current Legislative Models

Erika Lietzan  
Covington & Burling LLP




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## Background

- Two statutes (FDCA & PHSA)
- Agency decisions about handling recombinant versions of naturally derived proteins
- Enactment of Hatch-Waxman provisions of FDCA & application to FDCA proteins
- EU legislation, guidelines, and approvals



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## Key Issues for US Legislation

- Premarket (science) issues
  - Characterization requirements
  - Data/study requirements
  - Data for all indications
- Postmarket (science) issues
  - Post-approval requirements
  - Interchangeability
  - Naming & Labeling
- Exclusivity (innovation) issues
- Patent provisions

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## Current Models

- Biologics Price Competition and Innovation Act (S. 1695): Kennedy, Clinton, Hatch, Enzi
- Patient Protection and Innovator Biologic Medicines Act (H.R. 1956): Inslee
- Access to Life-Saving Medicine Act (H.R. 1038): Waxman; (S. 623): Schumer & Clinton
- Affordable Biologics for Consumers Act of 2007 (S. 1505): Gregg
- Pathway for Biosimilars Act (H.R.5629): Eshoo & Barton

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## Required Characterization

- Omnitrope (floor): “highly similar”
- Comparative
- Waiver?
- Highlights
  - Kennedy & Eshoo: “highly similar” but waiver
  - Gregg: full comparative characterization
  - Waxman: “highly similar principle molecular features,” but . . .

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## Non-clinical and Clinical Data

- Comparative?
  - Clinical endpoints?
- Waiver?
- Standard?
  - Every indication?
- Highlights
  - Kennedy: waiver
  - Eshoo: waiver, but immunogenicity requires guidance
  - Gregg & Inslee: comparative
  - Waxman: “any necessary” study + waiver

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## Post-Market Surveillance and Studies

- Backdrop: FDA Amendments Act of 2007
  - Postmarket studies/trials
  - REMS
- Highlights
  - Kennedy & Eshoo: no provision other than REMS
  - Waxman: postmarket studies but . . .
  - Inslee: every FOB application needs a postmarket safety plan
  - Gregg: similar to Inslee

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## Naming

- Background
  - Not a federal governmental function (USAN, WHO)
  - Section 508 of the FDCA
- Two issues for FOBs
  - tracking adverse events
  - physician knows about substitution
- Waxman: official name of an FOB must be the same as that of the reference product
- Gregg & Inslee
  - distinct name one way or another
  - labeling warning
- Kennedy: No provision
- Eshoo: distinct name

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## Labeling

- Gregg:
  - accurately characterize the FOB & account for differences
  - describe new data submitted
  - disclose any special safety issues specific to the FOB
- Inslee:
  - old biologics: warning that change between products should be made cautiously & only if authorized and supervised by prescriber
  - new biologics: warning against substitution unless authorized and supervised by prescriber
- Kennedy: silent

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## Interchangeability

- Inslee & Gregg
  - FDA may not designate FOBs as interchangeable
  - labeling
  - reassess every two years
- Kennedy & Eshoo & Waxman
  - FOB applicant may submit information
  - interchangeability standards
  - Eshoo requires final guidance first

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## Data Exclusivity (1/3)

- Issues
  - TRIPS & international benchmarks
  - Core period
  - Incremental innovation
  - Pediatric research
- Waxman
  - No data exclusivity, no incentives for incremental innovation, no pediatric research incentives
- Kennedy:
  - FOB application may not be submitted until 4 years after innovator approval
  - FOB approval may not be effective until 12 years after innovator approval
  - No incentives for incremental innovation, no pediatric research incentives

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## Data Exclusivity, continued (2/3)

- Gregg
  - FOB application may not be submitted until 12 years after innovator approval
  - FOB approval may not be effective until 14 years after innovator approval
  - plus 2 on base for one important new indication
  - plus 3 (like Hatch Waxman) for other incremental research
  - no pediatric incentives
- Inslee
  - FOB application may not be submitted until 12 years after innovator approval
  - FOB approval may not be effective until 14 years after innovator approval
  - plus 1 on base for one important new indication
  - no pediatric incentives

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## Data Exclusivity, continued (3/3)

- Eshoo
  - FOB application may not be submitted until 4 years after innovator approval (or beginning guidance process, if later).
  - FOB may not be approved until 12 years after innovator approval (or completion of guidance process, if later).
  - plus 2 on base for one important new indication
  - six months of pediatric exclusivity

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## Patent Provisions

- Over-arching issues
  - Notice to patent owners & identification of relevant patents [third parties?]
  - Litigation prior to FDA approval (act of infringement, incentive/penalty) [how early?]
  - Linkage (stay? no FOB approval if unexpired valid infringed patents?) [FTAs]
- Highlights
  - Inslee: silent
  - Waxman: generic controls; penalties
  - Kennedy: too complex
  - Eshoo: fairly straightforward


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**Consensus?**

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**Questions?**

**Erika Lietzan**  
**Covington & Burling LLP**  
**elietzan@cov.com**  
**+1 202 662 5165**

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