Follow on Biologics – Understanding the Changing Regulatory and Patent Landscape

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Greetings from the Nation's Capitol

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FDA Commissioner

- Commissioner of Food and Drugs
  - New Commissioner: **Dr. Andrew C. von Eschenbach M.D.** from Director National Cancer Institute (sworn in Dec. 2006).
    - Oncologist from MD Anderson Cancer Center (Houston)
    - Goal to make cancer a chronic disease that people can live with instead of die from

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Follow-on Biologics (“FOBs”)

- What’s in a name – still trying to reach general agreement
  - Generic Biologics
  - Biosimilars
  - Follow on Biologics
  - Follow on Protein Products (FDA term)
- Market growth driving “generic” approval pathway
- Biologics are growing at almost twice the rate of total pharmaceuticals
- Current sales of marketed biologics = $30+ Billion
  - Projected to double by 2010

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Follow-on Biologics (“FOBs”) (cont.)

- Current regulatory framework
  - Food, Drug, And Cosmetic Act (“FDCA”) applies to **Drugs**
  - § 505(b)(1) New Drug Application (“NDA”) – requires full reports of safety and efficacy for innovator drugs
  - § 505(j) Abbreviated New Drug Application (“ANDA”) – used for generic drugs shown to be “the same as” and bioequivalent to an NDA-approved drug
  - §505(b)(2) – companies can rely on FDA findings of safety and efficacy, and/or scientific literature for some NDA data requirements

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Follow-on Biologics (“FOBs”) (cont.)

- Statutory framework balances availability of less-expensive generic drugs w/continued new product R&D – provides patent term extensions and periods of market exclusivity

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Follow-on Biologics ("FOBs") (cont.)

- Public Health Services Act ("PHS Act") applies to **Biologics**
  - Most complex biotech products
    - "a virus, therapeutic serum, toxin, antitoxin, blook, or blood component or derivative . . . or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." PHSA § 351(i)
  - With few exceptions, approved under a "biologics licensing application" ("BLA") with data requirements at least as stringent as an NDA
- No statutory pathway for generic biologics comparable to generic drug framework under either the PHSA or the FDCA

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Follow-on Biologics ("FOBs") (cont.)

- Key Regulatory Issues
  - For products regulated as **biologics**
    - No statutory authority for abbreviated generic approval
  - For products regulated as **new drugs**
    - Ability to demonstrate **sameness** and **bioequivalence** of complex biological products derived from unique manufacturing methods
    - FDA can rely on prior safety/efficacy findings of innovator products w/o disclosing or relying on trade secrets and/or unconstitutionally taking IP

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Follow-on Biologics ("FOBs") (cont.)

- Key Scientific/Technical Issues
  - Biological medicines typically large, complex protein molecules
    - Derived or manufactured from living cells
    - Highly product-specific processes
    - Complex mixtures of proteins and impurities, only partly characterized and understood
  - Differences in manufacturing processes make product unique
  - Potential unpredictable/uncontrollable differences in immunogenicity profiles are a key safety concern
  - Criteria to establish therapeutic equivalence? Are products interchangeable?

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Follow-on Biologics ("FOBs") (cont.)

- Past Activity on FOPPs
  - FDA held 2 public workshops (Sept 2004 and Feb 2005)
    - "White Paper" never published.
  - Congress – Senate Committee Hearings – Summer, 2004
    - No consensus on or schedule for likely legislative action
  - Companies are eyeing potential targets for FOPPs applications. Beginning to move ahead on a case x case basis
    - Data requirements likely determined by negotiation w/FDA
    - Submissions LIKELY require considerable data than traditional ANDAs for conventional small-molecule drugs

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Sandoz Omnitrope Situation

- Sandoz Omnitrope Application
  - Application submitted July 30, 2003
  - Sandoz filed suit against FDA Sept. 13, 2005.
- Requested declaration that 505(b)(2) approval pathway can be used for protein based biologic drugs regulated under Section 505(b) of the FD&C Act
- Alleged FDA violated the FD&C Act and the Administrative procedures Act by failing to act on the NDA for recombinant human growth factor in a timely fashion
  - NDA contained results of preclinical, clinical, comparability tests, literature references and reliance on FDA's determination that the reference listed drug, Pfizer's Genotropin

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Sandoz Omnitrope Law Suit Against FDA (cont.)

- FDA unable to reach a decision on Omnitrope due to unresolved scientific and legal issues (9/04)
- FDA failed to act over 1 year later
- April 10, 2006 – DC District Court rules in Sandoz favor.
- On May 30th, 2006 FDA approved Omnitrope and issued a response to the Citizen Petitions submitted by Pfizer and BIO.
- Why is this important?
  - Shows how difficult it is for FDA to make these types of decisions.

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Woodcock House Testimony

- 3/26/07 - Dr. Woodcock testified on FOPPs.
  - "Sameness not appropriate terms for FOPPs"
  - Protein comparisons are "scientifically challenging"
  - "unlikely that for most proteins ... could demonstrate" product is identical.
  - "technology is not yet sufficiently advanced to allow for [structural comparisons of] more complex protein products"
  - Where mechanism of action not well understood, "even very extensive structural and functional comparisons between [products] may not be sufficient to allow broad reliance on conclusions regarding a prior product."
  - Some degree of clinical assessment of a new product's immunogenic potential will ordinarily be needed."

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What Does This Mean?

- Woodcock testimony and Omnitrope example demonstrate that even with FDA authority to approval "generic biologics", the pathway to approval will remain difficult as FDA believes that many challenges still remain.

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Pending Legislation

- Biologics Price Competition and Innovation Act of 2007 (BPCIA)
  - Sponsored by Sen. Kennedy (D-Ma).
  - Co-Sponsors include: Sens. Clinton, Hatch, Enzi and Schumer.
  - Kennedy had attempted to attach to the pending PDUFA bill but objections forced him to keep them separate.

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What would the bill do?

- BPCIA would amend Sec. 351 of the Public Health Service Act
  - Licensure of Biological Products as Biosimilar or Interchangeable.
    - Application demonstrating:
      - Biosimilar to a reference product
      - Analytical studies demonstrating "highly similar" to reference "notwithstanding minor differences in clinically inactive components"
      - Animal studies
      - A clinical study(ies) "sufficient to demonstrate safety, purity, and potency".

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BPCIA – Biosimilar

- FOPP and reference must:
  - Utilize the same mechanism of action
  - Same conditions of use
  - Route of administration, dosage form, strength
- FOPP must be manufactured in facility which meets GMP standards.
- FDA has discretion as to type of data that must be required for approval.

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BPCIA – Interchangeable

- To demonstrate interchangeability, must meet biosimilar requirements;
- And show "can be expected to produce the same clinical result and the reference product in any given patient."
- And for a biological product that is administered more than once, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

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Balancing Act…

- "Generics" get:
  - Biosimilar pathway
  - First "interchangeable" approval gets 1 year exclusivity.
- "Innovators" get:
  - 12 year exclusivity after approval
  - FOBB cannot be "filed" for first 4 years.

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Biological User Fees?

- Suggested that user fees may be appropriate beginning in 2012.
- Required FDA to have open meetings and public review of user fees.
- Must submit recommendations to Congress.

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IP Issues Related to Follow On Biologics (FOBs)

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At the moment …

- Drugs/small molecule non-biologics
  - Statutory pathway exists for abbreviated approval of generic drugs
  - Hatch-Waxman Act balances availability of less-expensive generic drugs with incentives for new R&D via patent term extensions and periods of market exclusivity
- Biologics
  - No statutory pathway for abbreviated approval of generic biologics (FOBs)
  - Pending legislation

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Hatch-Waxman Act

- §271(e)(1) "safe harbor"
  - No infringement if research is "reasonably related to the development and submission of information" to FDA
- §271(e)(2) "infringement" by submitting ANDA or 505(b)(2) application

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Implications of *Merck v Integra* for FOBs

- *Merck v. Integra*
  - In 2005, Supreme Court broadly interpreted §271(e)(1) regarding "safe harbor" for patent infringement
    - free use of patented pharmaceutical inventions, if use is "reasonably related" to an FDA submission
  - Does not exclude biologics submissions

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Merck v Integra (S. Ct. 2005)

- Preclinical studies are not exempt from safe harbor
- Research is "reasonably related" to FDA submission, if one has:
  - (1) "a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect," and
  - (2) "uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA"

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Merck v Integra (S. Ct. 2005)

- Not necessarily excluded from safe harbor:
  - (1) experimentation on drugs that are not ultimately the subject of an FDA submission or
  - (2) use of patented compounds in experiments that are not ultimately submitted to the FDA."
- To fall w/in safe harbor, experiments need not:
  - be included in IND application
  - be directed to establishing safety in humans
  - meet FDA "good laboratory practices"

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Integra v. Merck (Fed. Cir.)

- Federal Circuit (July 27, 2007) on remand:
  - Safe harbor does not depend on distinction between "discovery" and "routine" experiments, but on whether threshold biological property and physiological effect has already been identified
  - Safe harbor applies to all uses "reasonably related" to development and submission of info to FDA
    - Applies to contested preclinical studies
    - All experiments were relevant to FDA submission as to candidate that would be selected as optimal for clinical trials

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§271(e)(2)

- Submitting ANDA or 505(b)(2) application = infringement
  - with respect to patents listed in Orange Book
- §271(e)(2) "infringement" does not benefit BLA holders because no "ANDA-like" application currently exists for biologics

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Current ANDA/505(b)(2)

- NDA holder lists patents in Orange Book
- ANDA must include a certification of:
  - (I) patent not listed in Orange Book;
  - (II) patent has expired;
  - (III) date patent will expire; or
  - **(IV) patent is invalid or will not be infringed**
- If ANDA includes a Para IV certification:
  - Within 20 days after FDA provides notice that ANDA is filed, generic must provide notice to patentee/NDA holder with statement of factual and legal basis of opinion that patent is invalid or not infringed

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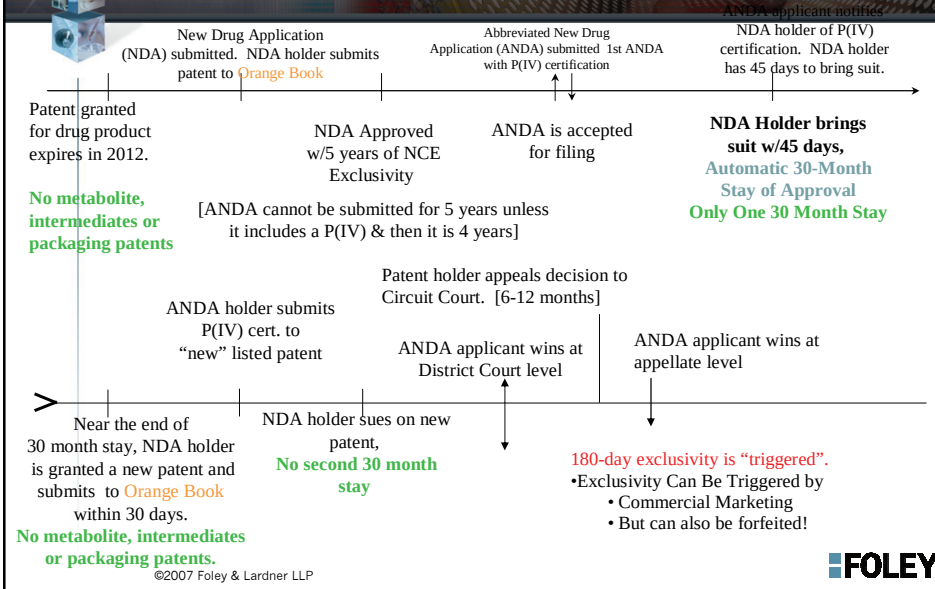
Current law and FDA regulations



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Intellectual Property – Small Molecules

- IP for biologics differs from that for drugs/small molecules
- IP for drugs/small molecules often relate to :
  - product per se – drug substance (API) or drug product (formulations)
  - new uses for product
  - methods of making product

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Intellectual Property – Biologics

- IP for Biologics
  - Naturally occurring biologics and their activity (i.e., uses) may be known
  - For some biologics, may only obtain "method of making" claims
  - Patentable inventions often correspond to manufacturing process for commercial scale up

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Limits to Orange Book Listed Patents

- Patents having only "method of making" claims cannot be listed in Orange Book
- Innovators of biologics unable to list patents in the Orange Book may not want a pathway allowing FOB approval, based on data they generated

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Current Remedies Available to Biologic Patent Holder

- Patent holder may still sue a generic biologic in district court if they infringe via marketing
- But "method of making" patents are easier to design around
- Much of the value in a biologic may be cost and effort invested in the FDA approval process

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Options for the Future

- May want to reexamine how "method of making" process patents are treated under Hatch-Waxman Act
- Ask whether current law (and/or pending legislation) adequately meets challenges facing biologics

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Legislation Pending

- Pending bills for abbreviated approval pathway for generic biologic (FOB):
  - **H.R. 1038** (Waxman et al.) (Feb. 14, 2007) – favors generics
  - **S. 1695** (Kennedy et al.) (June 26, 2007) – more likely to move forward

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Current versus proposed

- **FD&C Act**
  - ANDA or 505(b)(2) application ("ANDA")
  - NDA must list patents in Orange Book to allow for possible ANDA litigation
  - NDA holder may only list patents relating to drug or methods of use—not methods of making drug
- **S. 1695**
  - Application for Licensure of Biological Product ("ALBP")
  - No Orange Book equivalent
  - Relevant patents often relate to methods of making product

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Current versus Proposed for FOB

- **ANDA**
  - Within 20 days, generic must provide to patentee/NDA holder:
    - Notice that ANDA has been accepted for filing
    - Statement of factual and legal basis of opinion that patent is invalid or not infringed
- **ALBP (FOB)**
  - Upon filing, generic must provide legal counsel for BLA holder (not other BLA holder employees) confidential access to:
    - (1) copy of application; and
    - (2) other information describing process(es) used to manufacture product

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Proposed for FOB

- Within 20 days after ALBP is accepted, generic must provide BLA holder:
  - (1) copy of application; and
  - (2) other information describing process(es) used to manufacture product

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Proposed for FOB

- Within 60 days after receipt, BLA holder must provide generic:
  - (a) list of patents that "could be reasonably asserted" in infringement claim; and
  - (b) identify which patents BLA holder would license

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Proposed for FOB

- Within 60 days after receipt of list:
  - generic *may* provide BLA holder patent list
  - generic *must* provide BLA holder regarding each listed patent (by either party):
    - (I) statement of factual and legal basis of opinion that patent is invalid, unenforceable or not infringed; or
    - (II) statement that generic will not market before patent expiration

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Proposed for FOB

- Within 60 days after receipt of list/statement, BLA holder must provide statement as to why patents are infringed, valid and/or enforceable
- *Q: Will BLA holders need to obtain infringement opinions?*

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Proposed for FOB

Patent resolution negotiations:

- After receipt of statement by BLA holder, generic must engage in good faith negotiations regarding which patents are to be subject of infringement action

** No time limit requirement for generic initiate negotiations?*

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Proposed for FOB

- If parties agree regarding patents, BLA holder must sue within 30 days of agreement (or limited to reasonable royalties via §271(e)(6))

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Current versus Proposed for FOB

ANDA

- Within 45 days after notice, NDA holder may sue with respect to patents cited in ANDA having (IV) certification
- NDA holder may sue regarding any patents listed in Orange Book, where ANDA designates a (IV) certification
- If ANDA has (IV) certifications, FDA will approve immediately (if meet other requirements) unless patentee sues within 45 days

ALBP (FOB)

- If parties fail to agree w/in 15 days, generic must notify BLA holder of number of patents that will be in list
- Within 5 days, both parties must exchange list of patents
- **BLA holder may not list more patents than number provide by generic—if generic lists none, BLA holder may list one (1)**
- Within 30 days of exchange of patent lists, BLA holder must sue (or is limited to reasonable royalties via §271(e)(6))

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Proposed for FOB

- Within 30 days after complaint is served, generic must provide notice to FDA and a copy of complaint
- FDA will publish notice of complaint in Federal Register

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Proposed for FOB – new patents

- If any relevant patent newly issues or is exclusively licensed to BLA holder, BLA holder has 30 days to provide supplement patent list to generic
- Within 30 days, generic applicant must provide statement regarding newly listed patents

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Current versus Proposed for FOB

ANDA

- If suit is brought within 45 days, FDA will approve:
  - after 30-month stay (starting from date of receipt of notice) or
  - when Dist. Ct. decides patent is invalid or not infringed (or date of settlement stating similar), or
  - when Ct. of Appeals decides patent is invalid or not infringed (or date of settlement stating similar)

ALBP (FOB)

- No 30-month stay

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Proposed for FOB

- At least 180-days before first commercial marketing, generic must provide notice of date of marketing to BLA holder
- Upon notice and before generic marketing, BLA holder may seek preliminary injunction lasting until court decision regarding initially listed patent(s), but not regarding patent(s) already listed during negotiation or resolution stage *[?]*

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Current versus Proposed for FOB

ANDA

- Generic may file DJ action if ANDA has (IV) certification, and 45-day period has expired and patentee/NDA holder has not filed infringement suit
- Patentee cannot file DJ action except as normally available after generic commercially markets

ALBP (FOB)

- If generic provides BLA holder copy of application and mfgr info, neither party may file a DJ action until generic provides 180-day notice of first marketing
- BLA holder may file DJ action if:
  - Generic fails to provide copy of application and mfgr info within 20 days, action
  - Generic fails to do later actions, BLA holder may file DJ action

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35 U.S.C. §271(e)(2)

ANDA

- §271(e)(2)(A), (B)
- Submitting ANDA = infringement
  - with respect to patents listed in Orange Book

ALBP (FOB)

- §271(e)(2)(C)
- Submitting ALBP = infringement
  - with respected to patents identified on provided lists, OR
  - if generic fails to provide application and mfgr info, with respect to patents that could be included in patentee's list

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35 U.S.C. §271(e)(4)

Possible relief for patentee/NDA holder

- (A) FDA approval only upon expiration of patents;
- (B) Injunction to prevent commercial manufacture, use, sale, offer to sell or importation; and
- (C) Damages or monetary relief if commercial manufacture, use, sale, offer to sell or importation

Possible relief for patentee/BLA holder

- (B)
- (C)
- (D) Permanent injunction prohibiting infringement until expiration of patent if patent is subject of a final court decision, and product has not yet been approved due to 12-year exclusivity period *[?]*

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Proposed for FOB

§271(e)(6)

- Exclusive remedy = reasonably royalties if:
  - Action is brought after 30-day period (after agreement on patents, or if no agreement, after exchange of patent lists) or brought within 30 days but case dismissed without prejudice or in good faith not pursued

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Impetus for Change - $$

- Why do we need FOBs?
  - More than 400 biologics are currently in clinical trials, targeting more than 100 diseases
  - Biologics demand is expected to reach $90 billion by 2009
  - Cost of biologics to patients is significant ($10K–100K per year)
  - For traditional drugs, generic drugs save consumers $8–10 billion/year

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