U.S. Regulation of Biosimilars: Key Issues

RAPS Annual Convention 2014
Austin, Texas

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2014 RAPS
THE REGULATORY CONVERGENCE
27 September–1 October
Austin, Texas

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What We Will Cover

- The "Good" News – 351(k) BLAs Have Been Filed at FDA
- Interchangeability
- State Substitution Laws
- Naming
- Where FDA Stands on Biosimilars

Finally – Biosimilar Apps Filed at FDA

Two 351(k) Filings

- **Sandoz** – July 24 – announced FDA had accepted for filing its Biosimilar application for a version of Amgen's Neupogen® (filgrastim)
- **Celltrion** – August 11 – announced it had "completed the filing process" at FDA for its Biosimilar application for a version of Janssen's Remicade®
  - using its own trade name of Remsima®
  - first MAB biosimilar

Interchangeability

The Gospel According to Woodcock

A finding by the Agency that a follow-on protein product may be approved as safe and effective is distinct from a determination that the follow-on protein product would be substitutable for the referenced protein product. 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.

Testimony of Janet Woodcock, before the House Committee on Oversight & Government Reform. "Follow-on Protein Products." March 26, 2007.

What BPCIA Says – 351(k)(4)

"(4) SAFETY STANDARDS FOR DETERMINING INTERCHANGEABILITY.—Upon review of an application submitted under this subsection or any supplement to such application, the Secretary shall determine the biological product to be interchangeable with the reference product if the Secretary determines that the information submitted in the application (or a supplement to such application) is sufficient to show that—

"(A) the biological product—

"(i) is biosimilar to the reference product; and

"(ii) can be expected to produce the same clinical result as the reference product in any given patient; and

"(B) for a biological product that is administered more than once to an individual, 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.

Where is FDA Going?

- **Not clear;** guidance due out this year
  - I am unaware of any statements inconsistent with Woodcock's 2007 and 351(k)(4) meshes with her view
- **A few things we know:**
  - an interchangeable biologic is ***not*** a new active ingredient under PREA
  - interchangeability can only be proven with reference to the U.S. Reference Product
  - FDA reluctant to let you go straight to interchangeability
- **Interchangeability** – infuses all the other issues
- **Nomenclature** – is it time to *stop* calling biologics that are interchangeable "biosimilars"?
  - "Purple Book" – uses "I" for Interchangeable

Current Industry Approaches

- **EGALITY** (Sandoz) –
  - Randomized, Double-Blind Multi-center Study to Demonstrate Equivalent Efficacy and to Compare Safety and Immunogenicity of a Biosimilar Etanercept (GP2015) and **Enbrel®** in Patients with Moderate to Severe Plaque-type Psoriasis
  - 564 subjects @ 64 sites in 12 countries – 22-month long study
- **ADACESS** -- Humira Study (Sandoz) – similar to EGALITY
  - A Randomized, Double-blind, Multicenter Study to Demonstrate Equivalent Efficacy and to Compare Safety and Immunogenicity of a Biosimilar Adalimumab (GP2017) and **Humira®** in Patients With Moderate to Severe Chronic Plaque-type Psoriasis
  - 448 patients – 2-year study (only one location mentioned)

Current Industry Approaches

- **SB2/Remicade (Samsung Bioepis)**
  - Randomized, double-blind, parallel group, multicentre clinical study to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of SB2 compared to Remicade in subjects with moderate to severe Rheumatoid Arthritis (RA) despite Methotrexate (MTX) therapy.
  - 584 patients – year long study – 2 locations listed
- **What is not clear** – are these for U.S. applications?

What Will Guidance Say – A Few Views

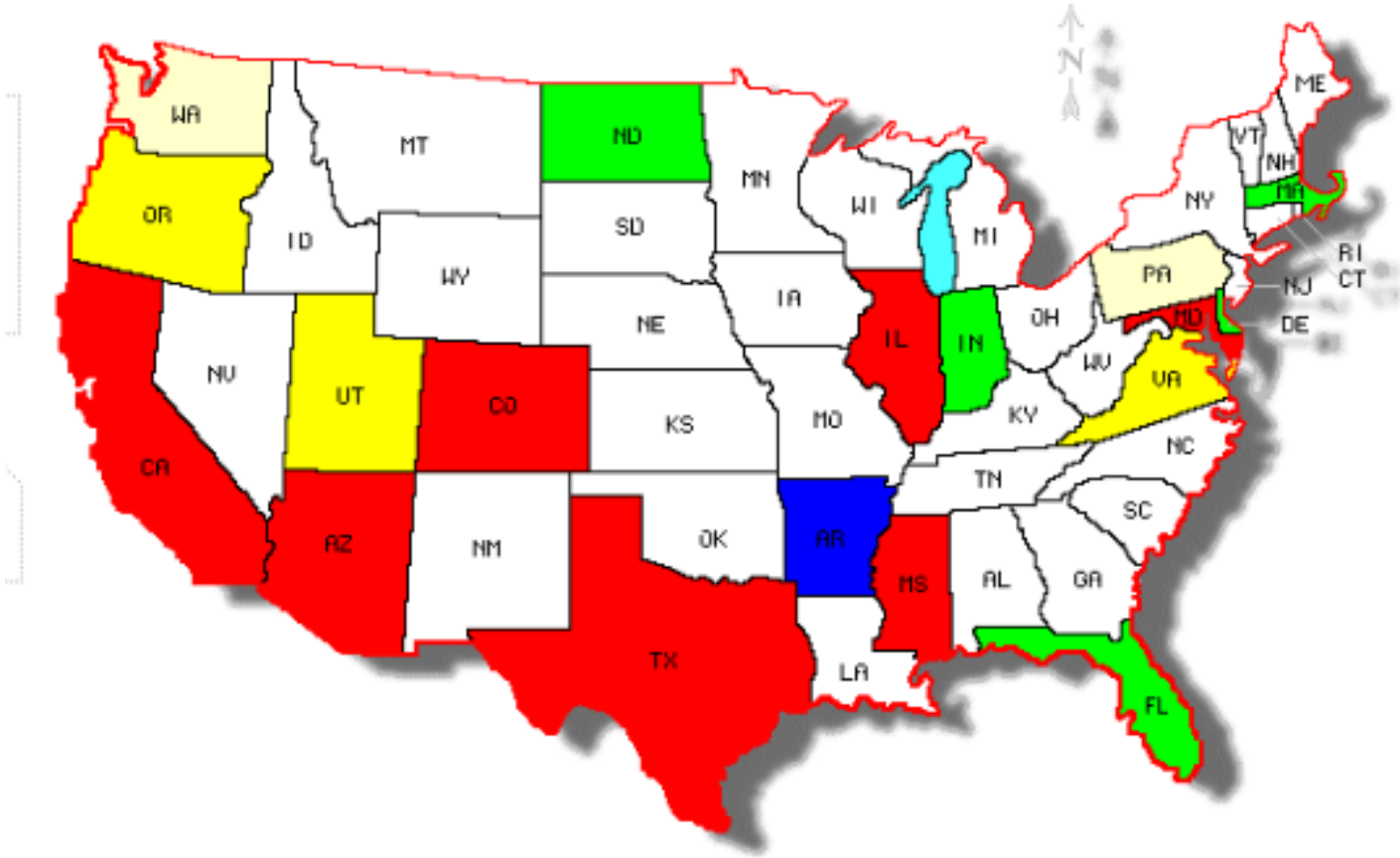
- **Key issue** – how will FDA deal with the "***any given patient***" language of 351(k)(4)?
  - studies will need to be indication specific
  - strong argument exists that interchangeability must be proven in all indications to satisfy the "any given patient" standard
  - result – more likely to be shown in biologics with just one or a few indications
- **Number of patients** – will need to high enough to tease out safety/immunogenicity/efficacy differences

State Substitution Laws

Where Do We Stand?

- **Legislation adopted:**
  - Delaware, Florida, Indiana, Massachusetts, and N.D.
  - Oregon, Virginia, and Utah (sunset)
- **Legislation Rejected:**
  - Arizona, California, Colorado, Illinois, Maryland, Mississippi, Texas
  - Arkansas (but referred to committees)
- **Pending**
  - Pennsylvania, Washington

The Map



Key:

Green: Enacted

Red: Rejected

Buff: Pending

Yellow: Enacted, with sunset

Blue: Rejected and referred to committee

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Enacted Requirements

State	Patient/Prescriber Notification by Pharmacist	Sunset	Pharmacy Record Keeping on Substitution	Prescriber Record Keeping on Substitution	BOP List Requirements
Delaware	*Prescriber*—within 48 hrs. after dispensing by Pharmacist *Patient*—Pharmacist must notify of subs.	*None*	Must record on the Rx label (1) product name of interchangeable drug, (2) what drug "substituted for", and (3) mfr. of interchangeable *3-years*	Must write either "Brand Necessary" or "Brand Medically Necessary" on the prescription slip if wants to bar substitution	
Florida	*Prescriber*—none *Patient*—Pharmacist must notify of subs.	*None*	*2-years*	*None*	*Yes*—as to FDA-approved interchangeable biosimilars
Indiana	*Prescriber*—with *Patient*—Pharmacist must notify of subs. within 5 days		*5-years*	For substitution to occur, Dr. must indicate "may substitute" *5-years*	*Yes*—as to FDA-approved interchangeable biosimilars
Massachusetts	*Prescriber:*—within a "reasonable time" by pharmacist via (a) notification in patient's "interoperable electronic health record" (or) if pharmacist lacks access to EHR by fax, electronic transmission, or a note in the patient's records, which are accessible by Dr. by request *Patient*—Pharmacist must notify of subs.	*None*	*1-year minimum*	Can bar substitution	

Enacted Requirements

State	Patient/Prescriber Notification by Pharmacist	Sunset	Pharmacy Record Keeping on Substitution	Prescriber Record Keeping on Substitution	BOP List Requirements
North Dakota	*Prescriber*—Pharmacist must notify orally, in writing or electronically of the subs. w/in 24 hrs. *Patient*—Pharmacist must notify of possible subs. and that patient has right to refuse the subs.	*None*	*5-years*	*5-years*	*Yes*—list or link to FDA as to FDA-approved interchangeable biosimilars
Oregon	*Prescriber*—Pharmacist must notify of the subs. w/in 3 business days. *Patient*—Pharmacist must notify of possible subs.	*3-years*	*3-years*	*None*	*Yes*—Post and regularly update on a website maintained by BOP as to FDA-approved interchangeable biosimilars
Utah	*Prescriber*—Pharmacist must notify of the subs. w/in 3 business days. *Patient*—Pharmacist must notify of possible subs.	*2-years*—as to prescriber notification	*As per federal/state laws*	*None*	*None*
Virginia	*Prescriber*—Pharmacist must notify of the subs. w/in 5 business days. *Patient*—Pharmacist must notify of possible subs.	*2-years*—as to prescriber notification	*3-years*	*2-years*	*None*

Washington – "Compromise" Agreement -- Pending

- **Strange Bedfellows?**
  - BIO, Wash. Biotechnology & Biomedical Assn., Amgen, Genentech
  - Actavis, Hospira, and Sandoz
- **Provisions for interchangeable biologics:**
  - Physician consent required -- 2-line Rx sheets in Wash. – DAW or Substitution Permitted – doc signs on one of lines
  - Pharmacist –
    - has to note on file copy of Rx: (1) mfr.; (2) brand name or, if none, non-proprietary name
    - has 10 days to record in an "interoperable health records system" or, if none exists, communicate to prescribing doc the (1) drug name and (2) mfr.

Washington Legislation

- **Mandatory substitution** – pharmacist "shall" substitute – if he/she has a TE drug or interchangeable biologic if wholesale price is less than the prescribed drug; 60% of savings must be passed to consumer
- **Visible sign required at pharmacies:**
  - "Under Washington law, a less expensive interchangeable biological product or equivalent drug may in some cases be substituted for the drug prescribed by your doctor. Such substitution, however, may only be made with the consent of your doctor. Please consult your pharmacist or physician for more information."
  - not clear how this jibes with consent req.

Pennsylvania – SB 405 and HB 476

- **Provisions – just reported this past week out of committee**
  - substitution only for interchangeable biologics
  - if prescriber bars verbally or in writing, no substitution
  - Patient notice -- pharmacist must notify consumer of planned substitution
  - Prescriber notice – within 72 hours
  - Record retention – 2 years
  - Sign in pharmacy about substitution
  - State – can determine that a drug is not interchangeable (notwithstanding what FDA says) – no standard articulated

Pros and Cons

- **Pros**
  - Transparency -- "right to know"
- **Cons**
  - Veiled attempts to being anti-competitive – especially notification mandates, which favor biologics with large sales forces – pushes uptake in brand use (TN-epilepsy drugs)
  - Undermines FDA interchangeability decision – contrary to BPCIA – ***Preemption????***
  - Disincentive to biosimilar development
  - Doctors don't want to know from a liability perspective
  - The law in most states already provides for physician notice when a pharmacy wants to substitute non-TE drugs for what was prescribed (whether on a brand/brand basis or gen.)

Naming

The Naming Process

- **U.S. Adopted Name (USAN) Council** – AMA, American Pharmacists Assn., USP
  - Independent of WHO and INN process
  - Drug substances only
  - Biologics –
    - primary sequence – characteristics of the biopolymer
    - if different glycosylation pattern – Greek suffix
    - further elements – numbers (Interferon Alfa – 2a)
- **USP** – monographs for drug products as well
  - if official, name must be used by approved drug/biologic
- **If no official USP name,** FDA picks

Naming Process

- **INN**
  - April 2013 – consensus to develop a naming convention
  - Oct. 2013 – suggested a naming system to be done separate from INN – nothing resolved yet
    - did comment that, for PV, reimbursement and substitution, an INN itself is insufficient
    - focus on drug ***substance,*** not ***product*** non-proprietary names
    - would mull using a worldwide "Biological Qualifier" – BQ
  - July 2014 – ***INN issues Biological Qualifier (BQ) Proposal*** – comments were due by Sept. 19

    http://www.who.int/medicines/services/inn/bq_innproposal201407.pdf?ua=1
    - non-glycosylated protein – always same NN as innovator

Naming Process …

- **INN – July 2014 "Biological Qualifier" (BQ)**
  - **BQ =** an alphabetic code assigned at random to a biological active substance made at a specified site
  - **"voluntary" –** person can make application for a BQ
  - technically, not part of the INN, but, where "use of a BQ is considered by an authority to be desirable, availability of a single global scheme will avoid proliferation of separate and distinct national qualifier systems."
  - **prospective and retrospective –**
  - **four letters (no vowels) –** 160,000 combinations
- **EMA** – was comfortable with its current approach – same for NN for RP and biosimilar

Arguments -- Con

- **Five key ways drugs are tracked in U.S.** – the generic name is only one aspect of this
  - NDC # -- Bar code
  - Trade name -- Generic name
  - Manufacturer
- **Express Scripts to the FTC** – we can track every drug we paid for without reference to INN
- **FDA to WHO in 2006**
  - rejects relying on non-proprietary names relative to interchangeability
  - not needed for AE/PV handling

Arguments -- Con …

- **FDA –**
  - allows a branded biologic to keep same INN after mfg. change via a comparability protocol –
    - both this and biosimilarity rely on the same premise – that there are "no meaningful clinical differences" between either:
      - RP1 and RP2 (in mfg. change situation)
      - RP and Biosimilar
  - already assigns same INN to biologics from different makers (e.g., Avonex v. Rebif – both Interferon Beta-1A)
  - ***Pro*** -- lacks current authority to insist on a brand name
- Confusion created by multiple INNs?

Arguments -- Con …

- **Europe –**
  - does not rely on INN for adverse event reporting
  - INN is (usually) same for brand and biosimilar
  - much greater penetration
- **Negative Penetration** – data shows using different INNs markedly reduces use of the biosimilar
  - Australia
  - Japan
  - Europe – in cases where there are different INNs (e.g., Hospira's EPO zeta) – excluded from tenders
- **Prefixes or suffixes** – will confuse docs

Pro -- Branded Views …

- **Amgen**
  - Different naming is essential to traceability
  - Claims naming does not impact market uptake
  - Physicians favor "similar name" to brand, with "additional nomenclature" to make clear it is a biosimilar
- **Pfizer**
  - Study – AE's for small molecule drug with generic competition
    - 14% of AE's not traceable to actual manufacturer
    - only 10% had NDC #'s; 30% of those were inaccurate
  - 99% traceable to brand name of biologic
  - But, not all global jurisdictions – including FDA -- can require a trade name; thus, need a ***second*** identifier – a distinct INN

Solution?

- **Require brand names for biosimilars globally?**
  - Pfizer – need two identifiers -- both INN and brand names to be different (Japan has this approach)
- **But, can you satisfy with:**
  - batch #
  - better use of NDC numbers?
  - brand name?
  - Track and Trace requirements under the Drug Quality & Safety Act – are they the solution relative to alleged AE issues?
    - too long a lead time?
    - info in "wrong" hands – e.g., distributors and wholesalers?

Other Naming Issues

- **What if a product is first approved as a non-interchangeable biosimilar and later gets FDA nod as interchangeable?**
  - What happens with the INN?
- **Does FDA have the legal authority to mandate brand names?**
  - pro – yes under "efficient enforcement of law" provisions
  - con – not authorized under BPCIA or FDCA

Other Naming Issues …

- INNs as a basis for AE tracking does not address problems with batch/batch variations
  - Eprex problem – would not have been addressed by INN and brand name – needs NDC # in mix to tease out that type of situation
  - but – NDC numbers are hard to access and input (10 digits) and are solely used in U.S.

Where Does FDA Stand?

Current Guidances

Category	Title	Type	Date
Biosimilarity; Procedural	Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (PDF - 272KB)	**Draft Guidance**	03/29/13
Biosimilarity	Guidance for Industry on Biosimilars: Q & As Regarding Implementation of the BPCI Act of 2009	**Draft Guidance Updated for 508 compliance.**	02/09/12
Biosimilarity	Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (PDF - 576KB)	**Draft Guidance**	02/09/12
Biosimilarity	Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (PDF - 432KB)	**Draft Guidance**	02/09/12
Biosimilarity	Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (PDF - 142KB)	**Draft Guidance**	05/13/14
Procedural; Biosimilarity	Reference Product Exclusivity for Biological Products Filed Under (PDF - 99KB)	**Draft Guidance**	08/04/14

Future Guidances

- 2014

CATEGORY – Biosimilarity

- Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
- Considerations in Demonstrating Interchangeability to a Reference Product
- Labeling for Biosimilar Biological Products
- Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act

Questions?

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About Your Speaker

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Before joining Duane Morris in March 2012, Swit served for seven years as a vice president at The Weinberg Group Inc., a preeminent scientific and regulatory consulting firm in the Life Sciences. His expertise includes product development, compliance and enforcement, recalls and crisis management, submissions and related traditional FDA regulatory activities, labeling and advertising, and clinical research efforts for all types of life sciences companies, with a particular emphasis on drugs, biologics and therapeutic biotech products.

Mr. Swit has been addressing vital FDA legal and regulatory issues since 1984, both in private practice with McKenna & Cuneo and Heller Ehrman, and as vice president, general counsel and secretary of Par Pharmaceutical, a top public generic and specialty drug firm. He also was, from 1994 to 1998, CEO of *FDANews.com,* a premier publisher of regulatory newsletters and other specialty information products for FDA-regulated firms. He has taught and written on many topics relating to FDA regulation and associated commercial activities and is a past member of the *Food & Drug Law Journal* Editorial Board.

He earned his A.B., *magna cum laude*, with high honors in history, at Bowdoin College, and his law degree at Emory University, and is a member of the California Bar and previously was admitted in both Virginia and D.C., but is inactive in those jurisdictions.