Originally presented at the 2013 AAPS National Biotechnology Conference - BIOTEC Open Forum

Update (see slide #2) 7/14/2013

BIOSIMILARS: ON THE REALM OF REALITY

DETERMINANTS OF SUCCESS

Ajaz | Insight

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Update

Approvals & Uncertainty

06/28/2013

EMA/EC approve "Remsima and Inflectra both contain the same known active substance, infliximab."

- Shown to be similar to Remicade" and authorized in the same indications as Remicade, covering a range of autoimmune diseases such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis.

06/27/2013

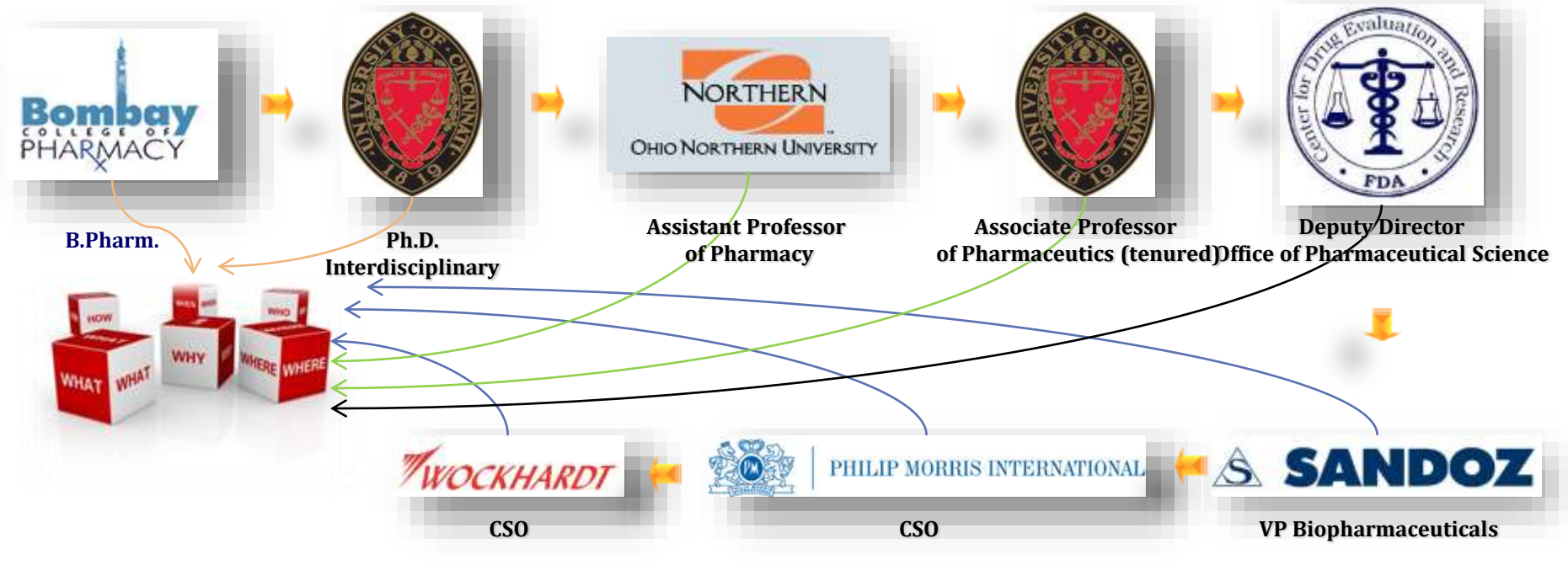
Efforts to reduce regulatory uncertainty in the US (see the video on right)

- FDA open to 'extrapolation' but the company would need to justify
- Interchangeability and naming

DIA CDER Town Hall

- Click on the photograph to see the video on YouTube; biosimilars discussion starts @ 6:27

This is my personal point of view



This presentation reflects my current interest

- *After leaving FDA my focus has been on practicing QbD by contributing to building*
  - *effective multidisciplinary teams,*
  - *business decision processes and technical infrastructure*
- *To deliver, in highly uncertain business environments, complex products and the necessary scientific evidence*

- *Sandoz*
  - *Biosimilars and complex generics (e.g., enoxaparin) – within a German/Swiss org. environment*
- *Philip Morris International*
  - *Plant based vaccines and MRTP's – QbD systems in a "non-pharma" sector (Swiss org. environment)*
- *Wockhardt*
  - *Biosimilars and NCE's – Indian org. environment*

An information-theoretic definition: Similarity

Similarity between A and B may be measured by the ratio between the amount of information needed to state the commonality of A and B and the information needed to describe what A and B are

$$Sim\ (A, B) = \frac{Log\ I\ (Common\ A, B)}{Log\ I\ (Describe\ A, B)}$$

A way to think about the challenges in developing, and communicating about, biosimilars.

D. Lin (1998). *http://webdocs.cs.ualberta.ca/~lindek/papers/sim.pdf*

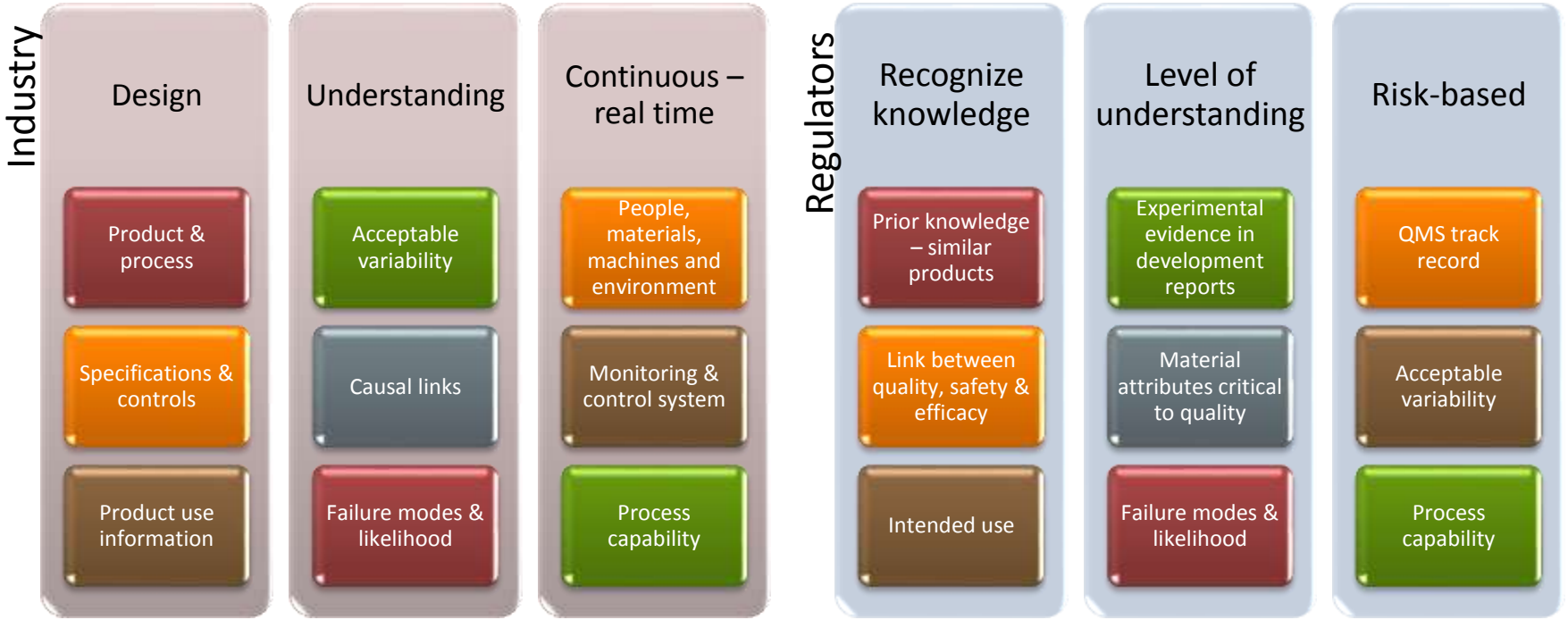
Success (for this presentation)

A firm's ability to successfully develop and introduce into markets

Biosimilar products per

EMA regulatory requirements	Several approvals and few failures (interferon, insulin and EPO)
US FDA regulatory requirements	351k evolving (note – Omnitrope® , generic enoxaparin & Tevagrastin®) Biosimilarity & Interchangeability

Quality of development and regulatory communication



Common pitfalls and symptoms

- Inadequate focus on TPP, QTPP (analytics) & market research
- Functional check-box
- Rush to clinical
- Cut-paste approach to clinical trials

Determinants of success

Practicing 'quality by design'	Design of products, manufacturing processes, clinical trials to deliver a 'Target Product Profile'
Execution excellence	Business processes for developing the target products and evidence needed; and effectively communicating the scientific rigor achieved to diverse stakeholders
Break-away from past practices	Certain past business practices and processes often not compatible with 'Design Thinking'; unless actively addressed pose a risk to success

Practicing 'quality by design'

US FDA	Championed the need for 'quality by design'	Introduced the notion of 'design space'
Creating effective business processes requires overcoming several hurdles	Internal hurdles	'typical generic mind-set', 'functional divide', optimistic business projections
	External hurdles	divergent understanding of 'quality by design' within regulatory agencies

US FDA QbD Efforts and in the background….

AAPS Annual Meeting 2003

Challenging Opportunities

- Identifying and addressing industry's varied needs
- Identification of *Best Practices*
- Maintaining effective communication with industry
- Guidance and decision making on product comparability issues
- Clarifying product jurisdiction between CDER and CBER
- Follow-on biotech products

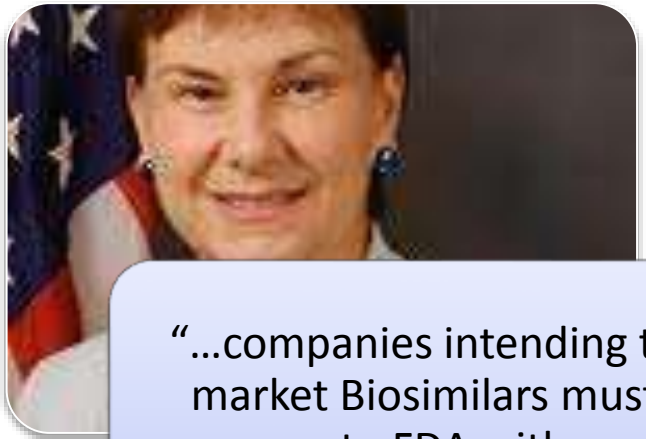
Closing remarks on Follow-on Proteins

14-16 Feb 2005

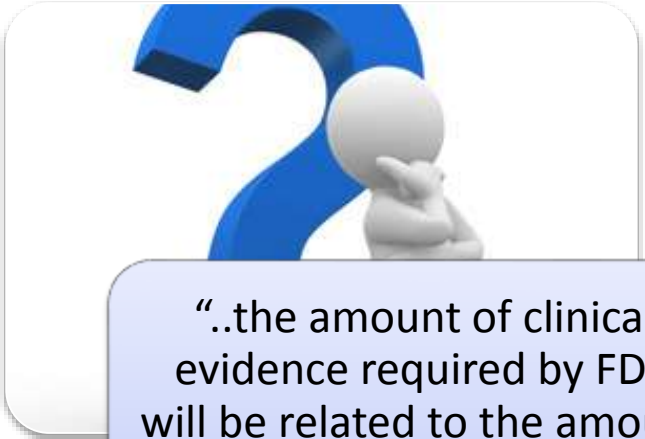
Previous Discussions of Relevance to this Workshop

- A Critical Path Initiative Proposal by the Office of Pharmaceutical Science, CDER, FDA
  - Presented to the FDA's Advisory Committee for Pharmaceutical Science (19 October 2004)
- Goal: To develop a common scientific decision framework for addressing uncertainty in the context of complexity of products and manufacturing processes in Offices of New Drug Chemistry, Biotechnology Products, and Generic Drugs
  - Motivation: A common scientific decision framework, irrespective of the regulatory path or process for these products, will provide a basis for efficient and effective policy development and regulatory assessment to ensure timely availability of these products.

Woodcock: 'Paradigm Shift' in Reviews



"…companies intending to market Biosimilars must come to FDA with an extensive characterization package, comparing theirs with the reference product."

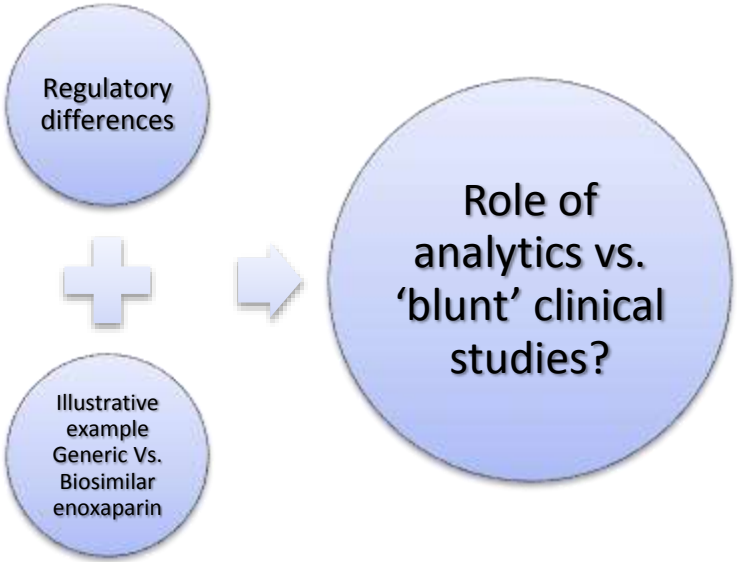


"..the amount of clinical evidence required by FDA will be related to the amount and the quality of analytical and functional information that is available on any biosimilar product…"

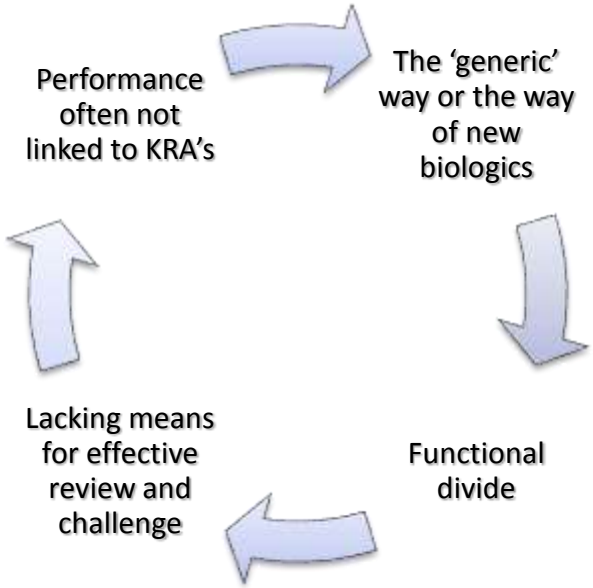
DIA/FDA Biosimilars Conference 12 September 2012

Hurdles in practicing 'quality by design'

- External



- Internal



Enoxaparin in EU 2007 and currently

Ajaz Hussain: 5th EGA Symposium on Biosimilars, London, 3-4 May 2007

Organizing for success

Common pitfalls and symptoms

- Inadequate focus on TPP, QTPP (analytics) & market research
- Functional check-box
- Cut-paste approach to clinical trials
- Rush to clinical

Early investment in analytics and understanding variability in RLD

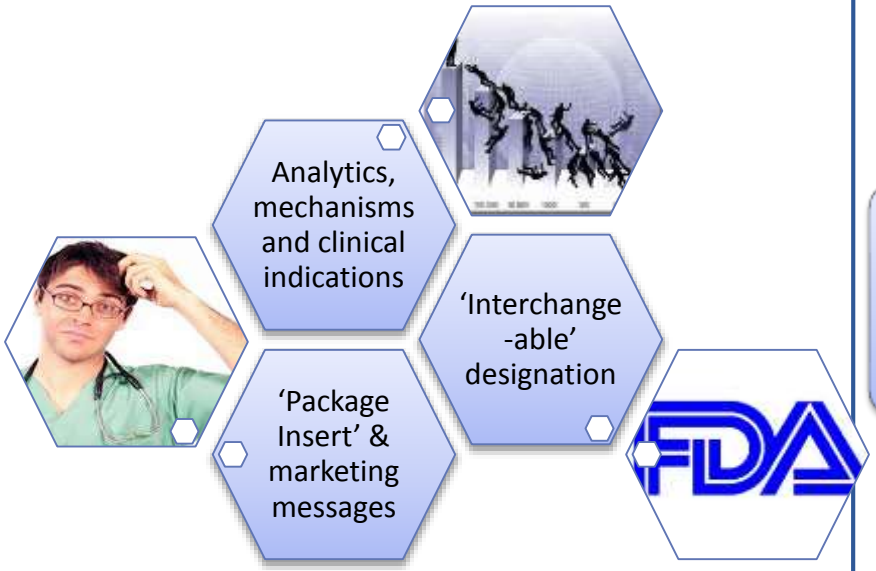
TPP & QTPP in the context of residual uncertainty

Review/challenge culture and decision ‘gates’

Design of clinical trials to address scientific and clinical (market) uncertainty

Often overlooked success factors

- Transdiciplianry



- Design Thinking

‘Quality by Design’ → Target Product Profile and QTPP → Ability to measure and explain → Multi-functional review and challenge → Not a *Thing*, But a *Way* (MIT Sloan Management Review, July 2, 2009)

Determinants of success

Practicing 'quality by design'	Design of products, manufacturing processes, clinical trials to deliver a 'Target Product Profile'
Execution excellence	Business processes for developing the target products and the evidence needed; and effectively communicating the scientific rigor achieved to diverse stakeholders
Break-away from past practices	Certain past business practices and processes often not compatible with 'Design Thinking'; unless actively addressed pose a risk to success

Implications for 'global development'

EU to US or ROW to EU & US

- Quality by Design* approach offers a significant advantage
  - Minimize additional development costs (e.g., estimated to be additional $ 25-70 million)
  - Note that in the US; interchangeability designation expected to weigh heavily on high (analytical) similarity

*Includes Clinical Quality by Design

Clinical QbD

University at Buffalo The State University of New York

UB REPORTER

LAST UPDATED: Thursday, August 2, 2012

ARCHIVES

Pharmacy receives $1 million gift

Grant to fund protein therapeutics research

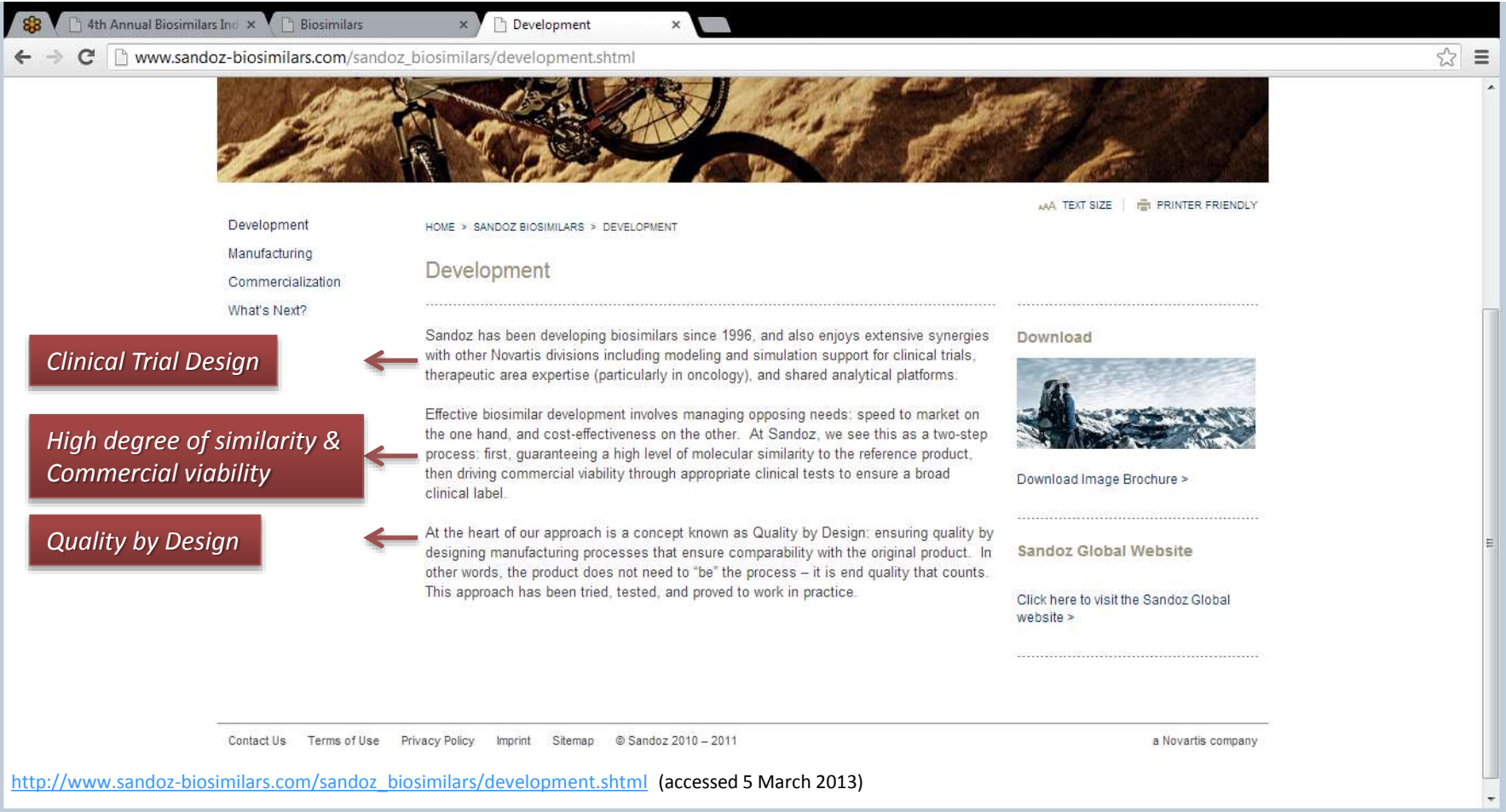
Published: September 6, 2007

By MARY COCHRANE
Contributing Editor

Donald R. Stanski, global head of modeling and simulation at Novartis, identified the opportunity to combine the modeling needs of the rich biological development pipelines at Novartis for innovative medicines and at the Sandoz generics division for the development of follow-on biological drugs with the academic expertise at UB.

Ajaz Hussain, global head of biopharmaceutical development at Sandoz, enthusiastically supports this collaboration because it will "greatly contribute to development of novel methods for understanding mechanisms of actions and for establishing comparability of biosimilar products."

http://www.buffalo.edu/ubreporter/archives/vol39/vol39n2/articles/NovartisGift.html



http://www.sandoz-biosimilars.com/sandoz_biosimilars/development.shtml (accessed 5 March 2013)

'Biosimilar rituximab development a rocky road'

Roche does not see a threat from biosimilar (rituximab) until 2015	One reason for the delay – clinical considerations; challenge of extrapolation across indications	*"Sandoz and Boehringer are both already running Phase III trials, placing them ahead of Celltrion in the race, but Samsung and Teva both suspended their Phase III programmes in October 2012 within months of starting them"* (FT, April 2013)
Clinical trial design opportunity	Bayesian hierarchical modeling (BHM) approach to clinical trial design. J Clin Oncol 29: 2011 ***(Illustrative Example)***	*"With a 35% reduction in sample size, the BHM approach enables borrowing across oncology and autoimmune indications with equal power and confidence."* ***(Illustrative Example)***

http://www.biosimilarnews.com/roche-doesnt-see-a-threat-from-biosimilars-till-2015

http://www.ft.com/cms/s/2/dcad130c-a8fb-11e2-a096-00144feabdc0.html#axzz2TqDBcYlB

Next two presentations…..

Global Biosimilar Development in a "Shifting" Regulatory Environment	Mark McCamish, Ph.D., M.D. Sandoz International GmbH
Strategies for Global Clinical Development for Biosimilars	Partha Roy, Ph.D. Parexel Consulting