The Challenge of Biosimilars:
Is the Juice Worth the Squeeze?
Who am I?

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Immunologist
Founder, CSO, CEO, Director - Immunex Corporation
Founder, CEO, Chairman – Corixa Corporation
Why Immunology?

- Very young science
- Not a lot was known about the immune system when I was in college
- I’m not a dinosaur - just a fossil
- Most fundamental discoveries have been made in the past 30 years by people I know.
- Luckily I made a few as well.
Brief History

- Potted IVY BA - Williams College
- Ph.D. Dartmouth College
- Original recruit - FHCRC
- Wrote grants to get $$$ from NIH, charities
- Hired technicians, post-doctoral students, graduate students
- 1980 - Pharmaceutical companies start knocking - offering to pay our research expenses for rights to things we might invent
- Instead of saying yes, WE (Chris Henney and I) left FHCRC to start a company
Brief History

- Company is Immunex – now owned by Amgen
- Created a number of immune system hormone based products that are now used by doctors and patients around the world including one with about $5 billion in annual sales (Enbrel) which should come under biosimilar competition in 2013
- 14 years later, left Immunex
- Started another company, focused on vaccines
- Company was Corixa – now owned by GSK
Relevant Experience

- Taken 14 recombinant proteins into trials
  - Both antibodies and growth factors
- Oversaw Process Development and Manufacturing Operations including:
  - Fermentation
  - Purification
  - Formulation
  - Fill/Finish
- Defended CMC sections of IND(s), BLA(s), ELA(s) with FDA
Recombinant Protein Therapeutics

- Biotechnology’s Biggest Success Story
  - Growth Factors
  - Cytokines
  - Therapeutic Antibodies
- Over $25 Billion in annual sales could face competition from biosimilars by 2013
A Few Major Examples

- Enbrel®
- Neulasta®
- Aranesp®
- Rituxan®

Tuck School of Business at Dartmouth
Biosimilars – Follow on Biologics

- Generic Recombinant Proteins
- A Brave New World

As we look forward in time to the introduction of such products in the United States we need to realize that these are not simply generics, in the same sense of the word.
Let’s understand Generic Drugs (small molecules) first

- Usually MW of less than 600
- Produced by chemical synthesis
- Available in 100% purity
- Single molecule species
- Stable
- Not subject to degradation by enzymes
- Can be manufactured at enormous scale (tanker car loads) at pennies to low dollars per dose
Recombinant Protein Therapeutics

- Large complicated molecules up to 200,000 mw
- Many are coated with sugar (glycosylated)
- Produced by genetically modified living cells
- Easily degraded
- Complex production and purification systems (more later)
- Never 100% pure
- Difficult to accurately guarantee relative potency from lot to lot
- Costs dollars to low hundreds of dollars per dose to manufacture
Recombinant Protein Manufacturing

- Complex and Highly Regulated
  - Master Cell Bank
  - Working Cell Bank
  - Fermentation
    - In process controls monitored according to GMP
    - Batch records reviewed by FDA
  - Purification
    - Can introduce impurities
  - Formulation
    - Can allow for degradation
Potency Assays

- Biologics use biological assays to determine potency
  - Cell line assays - even tests in animals
- FDA reviews all lot release data
- At approval FDA conducts its own potency assays using your protocol to make sure they get the same data on material you produced
- Lot to Lot variation can be high
- FDA very concerned in having an assay that can distinguish between hypo and hyper-potent lots
Small Molecule Generics

- Proving that you make the same chemical structure in 100% purity is enough
- Easily accomplished by following manufacturer’s recipe
- Mass Spectroscopy proves identity
- Bing Bang ... You’re done
Differences can be significant

“Even if the biosimilar product has the same gene sequence, vector, host cell line, culture conditions and purification methods as the innovative protein, it can still differ in its biological and clinical properties”

-Huub Schellekens, Utrecht Central Animal Laboratory, Utrecht Netherlands
How can this be?: Glycosylation

- Innovator proteins produced in yeast and mammalian cells are glycosylated.
- Small differences in terminal sugars added to proteins can make huge differences in terms of what parts of the protein are “seen” by the immune system.
- Different glycosylation translates into different immunogenicity.
- More immunogenicity, more injection site reactions, lack of efficacy and threat of anaphylaxis.
How can this be? - Glycosylation

- Subtle differences in glycosylation can also alter the activity of molecules with both binding domains and effector function domains.
- Antibodies are such molecules.
- Changes in glycosylation can dramatically change the ability of immune system cells to recognize antibody coated targets and destroy them.
- Take Rituxan, anti lymphoma antibody, different glycosylation pattern could result in lower tumor cell kill, lower efficacy.
How can this be? – Off target binding

- Minor changes in protein shape and aggregation can greatly affect the affinity of the protein therapeutic for its target. Weaker affinity usually translates into weaker biological activity and decreased efficacy.
- Even worse...changes in shape and aggregation can dramatically change off target binding...the ability of the protein to interact with other targets in other cells.
- Such interactions can lead to new biological effects many of which are unwanted and could result in increased toxicity.
How can this be?: Protease sensitivity

- Proteins produced in bacterial expression systems are extremely sensitive to proteases (molecule clipping enzymes) that are also present in bacteria.
- Minor differences in fermentation (temperature, nutrient feed rate, pH, agitation, etc.) can enhance protease activity yielding final product containing protein species that are truncated.
- Such clipped protein molecules may not fold appropriately giving rise to product of compromised potency and enhanced immunogenicity.
Foreign proteins produced in bacteria are tightly packed by the organism in dense granules called inclusion bodies.

In order to recover the protein, bacteria are lysed and inclusion bodies treated with harsh substances (acid/alkali) to release the protein from the inclusion body.

At this point the product is denatured and needs to be refolded.
How can this be?: Refolding

- Small changes in refolding conditions can cause drastic differences in renaturation.
- These changes can lead to mis-shaped inactive protein, dimers, trimers and aggregates...all of which can cause decreased potency and increased immunogenicity.
How can this be?: Contaminants

- All biologicals are impure – they contain traces of mis-shaped protein, traces of compounds used in purification and traces of host cell protein.
- Technology to characterize and quantify the level of trace contaminants has improved greatly making it possible to monitor the level of contaminants in every lot of biological that is released.
- Small changes in manufacturing can lead to different levels of contaminants, which can have disastrous effects on product efficacy and toxicity.
Biosimilars will need clinical verification

- Since the molecule produced by a “generic” supplier will not be identical to the innovator product, its efficacy and safety must be verified in a clinical study and such results compared to those obtained with the innovator product in the same indication.
- Labeling of the biosimilar must be limited to the indication and dosage form used by the innovator product in that same indication.
- No proof of clinical comparability – no approval for sale.
Significant Clinical Trial Investment

- Equivalent efficacy must be demonstrated
  - May require large numbers of patients – perhaps even larger numbers than were used by the Innovator
- Will also need some safety data in animals
- Moderate to extensive analysis of immunogenicity
Expensive to Produce and Test

The need for clinical data plus the high cost of manufacture means production of biosimilars in dosage forms that can get regulatory approval in the US and EU translates into significant investment.

- Investment
  - Property, plant and equipment
  - Experienced development staff
  - Clinical trial infrastructure or outside CRO costs
  - Regulatory affairs expertise
Due to technical expertise required and the large investment required to seek approval – bringing a biosimilar to market is not for the faint of heart

Not surprising that current approvals in the EU or those pending are produced by companies that have produced innovator biological products

Likely to continue this way

With the “big boys” attempting to eat each other’s lunch
What about the situation in the US?

- Biologics Price Competition and Innovation Act
- Pending Legislation
- Bill with the greatest chance of getting through Congress
  - 12 years of data exclusivity as compared to 5 years for Waxman Hatch
  - BIO and VC investors would prefer longer but this provision is probably acceptable
  - Multiple additional provisions of the bill are troubling
Limited Pre Market Litigation of Patents

- Biosimilar producer can dictate which patents of the innovator are to be litigated
- Innovator may be forced therefore to bring suits on patents it might not otherwise wish to defend or to defer suit on patents it wishes to assert.
Short Notice Time to the Innovator

- 180 day notice to Innovator by Biosimilar producer prior to launch
- Launch will therefore occur prior to results of litigation
- If Innovator wins suit – market may be damaged
Limited Time for Innovator to Bring Suit

- After Biosimilar producer provides list of patents it wishes to litigate, Innovator has only 30 days to bring suit
- 45 days under Waxman Hatch
- Puts too much pressure on Innovator as core patents may technically reside with Universities who licensed their rights to the Innovator company
- Universities can rarely do anything within 30 days, let alone retain counsel and bring suit.
Biosimilar Introduction – Litigation Minefield?

- Biologics covered by multiple patent fences
- Composition of matter
- Method of use
- Formulation patents
- Methods of manufacture
- Greater opportunity for litigation between Innovator and Biosimilar producer
Recent Generics (Small Molecule) History

- 8,259 Generic Applications to FDA between 1984 and 2000
- Only 6% raised patent challenges
- Hard to predict what the number will be for biosimilars
Why worry about litigation provisions of BPCIA?

- Because Congress continues to meddle with patent reform
- Infringement
  - Damages are currently set by the court as lost profits or a reasonable royalty
  - Pending legislation weakens “reasonable royalty provisions of the current by instructing the court to calculate forced royalty taking into account value of all “prior art”
Pending Patent Reform

- Post Grant Review
  - Allows after a patent is granted for an infringer to challenge a patent’s validity if it will cause the infringer “significant economic harm”
  - Challenges can rely on defenses other than prior art
- Broadening of inequitable conduct claims for invalidity
  - If culpable conduct or misrepresentation is found with respect to only a single claim the entire patent will be invalidated
What will the impact of Biosimilars be?

- Initially, not that much
- Road to approval in Europe is more certain than in US
- In EU, biosimilars will not make huge inroads initially
- France and Spain have passed legislation outlawing automatic substitution of biosimilars for the original product
The EU Experience

- “To compete we will have to show efficacy, safety and lower cost and we will have to do this country by country”
  - Sandoz spokesperson

- Discount is not that much (15%-25%)

- No financial incentive for the patient, the physician or the pharmacist to write script for biosimilars

- Patients don’t pay directly for drugs in the EU

- Only people interested in biosimilars are the third party payers
Biosimilar Impact in the United States

- May be similar to that seen in Europe
- Innovators have established multiple follow on products with improved characteristics
  - Longer half life – don’t have to inject as frequently
  - Liquid formulations vs. lyophilized cakes
- Lots of $$$ will be spent on marketing campaigns for Innovators touting:
  - Years of experience
  - Thousands of patients treated/studied
Biosimilar Impact in the United States

- Will Third Party payers require mandatory substitution?
- That promises to be the big battlefield
Let’s get personal

- Would I elect to take a biosimilar?
- Doubtful – Why?
  - Is it because I am a pawn of the pharma industry?
  - No... It is because having been through the ringer of FDA inspections, site visits, diligence reviews etc., I prefer having medication produced by those who have had to go through the same hurdles
  - I’m not a personal fan of generic medicine
  - I still buy Tylenol, Advil and Aleve