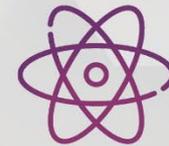
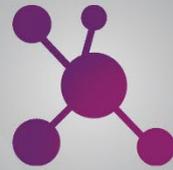
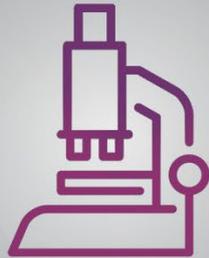


THE PRACTICAL IP FOR NATURAL SCIENCES WEBINAR SERIES



BIOSIMILARS: **PATENTABLE APPROACHES AND SURVEILLANCE**



THE PRACTICAL IP FOR NATURAL SCIENCES WEBINAR SERIES

MEET THE PRESENTER



Jim Nelson *B.S., Ph.D., J.D.*

- Registered patent attorney with 40+ years experience with Intellectual Property matters
- Practice in chemical, polymer, pharmaceutical, biotechnology, cosmetics and medical device fields.

Disclaimer

This presentation represents the personal views of Albin J. Nelson, and should not be construed as representing in any way the views of the firm or any of its members, and should not be considered as legal advice regarding any particular matter.

Patents, Profits, Drug Development

Are You a Branded, Sponsor, Generic or Biosimilar?

Will you be content to continue to copy or do you want to make something more of your expertise?

Details – Road Map

- Why did you choose this path – Copying
- Who likes this path?
- What is a COPY?
- What expertise have your scientists gained?
- Will you continue to COPY?
- Risks and Benefits of another path.
- Supergenerics and BioBettors

Why do you Copy?

- **BENEFIT**

- Great for consumers and govt cost
- Low or No Risk
- Almost Guaranteed Regulatory approval
- Reduced Development Cost

What did you do to Copy?

- **WHAT DID YOU DO?**
 - Spent years developing expertise to copy
 - Developed and copied physical and chemical features
 - Developed and copied biological and clinical features
 - Tried to copy process
 - Duplicated or came close to impurities and side products

Look Again at Copying

- Why Copy?
 - COPYING IS LEGAL – HW AND BPCIA – WITHIN CERTAIN CONSTRAINTS
 - Minimal or no risk of reg agency rejection
 - Sure thing for safety and efficacy
 - Lower clinical cost
 - Fewer preclinical proofs
 - Still need to show same chemical and physical parameters

- Easier route to earn \$\$\$



Successful Copying

- You have won the race
- What will you do now that you have a success?
- Make additional Generics and BioSimilarars?
- Continue Copying
- You think it is profitable, yes?

The Big Risk of Copying

- Years to develop
- Competition
- Brutal
- Race to lowest cost product

Price Squeeze

- Atorvastatin (LIPITOR) and Pfizer
- Development – Warner Lambert/Parke Davis
- Pfizer marketed Lipitor and later bought Warner Lambert
- Was not first statin on market, first was Merck's lovastatin and simvastatin
- Pfizer sold Lipitor from 1996 to 2012 made more than \$125 billion



Price Squeeze

- Extension Patents expired 2012
- Watson and Ranbaxy produced
- Now same compound sold as Stator, Atovastatin Teva, Litova, Torid, Atoris, Atorlip, Mactor, Lipvas, Sortis, Torvast, Torvacard, totalip and Tulip and the Pfizer generic brand Zarator.

The Price

- During Pfizer exclusive cost of Lipitor was slightly more than \$200 per month or \$6.75 per pill
- Now cost is less than \$10 per month or about \$0.31 per pill
- Cost reduction of 2200% (22X reduction)
- WHAT IS BOTTOM LINE?
- As Carl for Choice Hotels (Comfort Inn) says:
“LOWEST PRICE GUARANTEED”

Remember the U.S. FTC Prediction from 2013?

- BIOSIMILARS Competition Will Not Be Like Brutal Generic – Branded Pharmaceuticals
 - U.S. FTC forecasted 2013/2014 that
 - Only 2-3 entrants per biological reference product (BRP)
 - RPS will likely retain 70-90% market share
 - Biologics Competition will resemble Brand to Brand Pharma competition rather than Brand to Generic competition
 - Predictions lead to better profitability for Reference and Biosimilar Companies
 - Competition will not be based on price alone

Is That All There Is? (Peggy Lee)

If you copy and sell a Biological, will you earn...



Cost Drivers for Biosimilars

Will Costs Become Lower?
YOU BET!

Univercells - Production

- Single-use high-cell density bioreactor, in perfusion mode, for continuous process & chaining clarification & capture operating in continuous mode.
- Palivizumab example: CAPEX 5 units: 1 unit produced 100 kg/year (1 batch 15.3 kg x 8 batches/year) \$14 million and 40 FTEs
- \$39/gram
- NO large storage tanks, filtration equipment, chromatography columns, large pumps

Courtesy of and reproduced from seminar of Richard DiCicco, Harvest Moon Pharmaceuticals

Big Cost Driver - Production

Rotative Biologic Contactor (1)

These unit steps:

- Media prep
- Culture
- Cell harvest
- Concentration
- Capturing
- Viral clearance

Integrated into a
continuous process



But Wait!

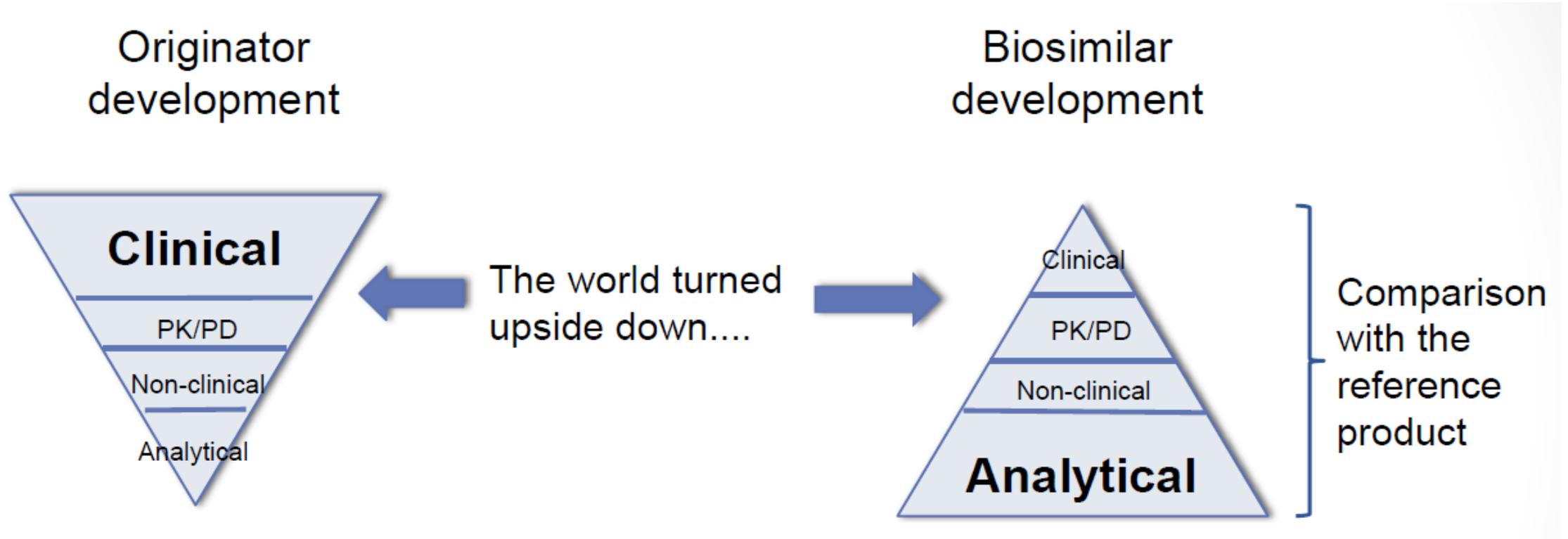
- Prelim to Worrying about Production Costs

- What About Clinicals?
- Could choose the big seller
 - Like Etancercept - Enbrel by Amgen, a fusion protein
 - Like infliximab – Remicade by Janssen, a chimeric Mab
 - Like Herceptin – Genentech, a Mab
 - Like Humira – adalimumab by AbbVie –a Mab
- Need Clinicals for proof of BioSimilar Status

- ARE CLINICALS A BARRIER?



Recall This Depiction of Scope Needed for Biostudies



Do Real BioSimilar Clinicals Follow this Ideal?

TNF Example without Processing Improvement

Dev't Cost Center	2007	2016
Animal Studies	2,000,000	0
Phase I pK (120 HV's)	16,000,000	5,000,000
Phase III confirmatory (n=600)	50,000,000	30,000,000

Point: Cost of clinicals will continue to drop just like production cost

Courtesy of Richard DiCicco, Harvest Moon Pharmaceuticals



Example II BIOSIMILARS

- ETANERCEPT aka ENBREL
- Patent set to expire 2012 in US but 2nd patent issued – will expire 2028
- Price US - \$2225 per month
- Under Amgen patent US
- US patent expires 2028

What will happen when US patent expires?

Example II BIOSIMILARS

- COPY producers of ETANERCEPT
 - AryoGen Pharma Iran; Avesthagen, India; BioXprese Therapeutics, Switzerland; Celltrion, South Korea; CIPLA, India; Clover Bio pharm, China; Coherus BioSciences, USA; Hanwah Chemical, South Korea; Intas Pharma, India; LG Life Sciences, South Korea and Japan; mAbxience, Spain; Momenta, USA; Mycenax, Taiwan; Probiomed, Mexico; Protalix, Israel; Sandoz, Switzerland; Samsung/ Merck, South Korea; Shanghai Celen, China; Shanghai CP Guojian Pharma, China; YL Biologics (Lupin), India
- 24 potential producers of Biosimilar Etanercept
- What will happen when US patent expires?
- EP patent expired 2015.
- Price in EP already half: Switzerland \$1017 per month

What are the Risks and Future for BioSimilarars?

- Most likely the future is just like Generic Pharmaceuticals
- COMPETITION
- Completely price driven
- Lowest production cost will win the day – A School of Sharks!!!
- You are swimming in the BioSimilarars Shark School



What is your Future?

- WHAT IS YOUR FATE?
 - Success, Failure what does it mean?
- Timing
 - Generics 3 to 4 years
 - Biosimilars – little short of 8 years

Is There an Alternative?

- Move On To  **BIOBETTERS**
SUPERGENERICS
- Think Three Steps Ahead
- Exclusivity and better product = competitive advantage
- Get your own patents
- MAY BE BLASPHEMY

BUT The Future is SuperGenerics and BioBettors

What is the hidden benefit of Generics/BioSimilarars?

- Significant Clinical data is needed no matter what!
- Consider Sandoz's BioSimilar Zarxio Multi country; Phase 3 Foreign and US clinicals, Reams of clinical data
- Consider Celltron's BioSimilar Remsima - Reams of clinical data

LESSON:

- If you developed a BioSimilar OR Generic:

YOUR RESEARCHERS POSSESS NOW POSSESS THIS EXPERTISE!

The Hidden Benefit

- **FAULTS OF COPYING**
 - Duplicated something that was developed long ago
 - Generics – 10 to 14 years ago
 - BioSimilarars – 15 to 20 years ago.
- **YOUR RESEARCHERS KNOW TODAY’S RESEARCH CUTTING EDGE**
 - THEY ARE SMART AND NOT 20 YEARS BEHIND IN KNOWLEGE
 - THEY KNOW THE BIOLOGY AND CHEMISTRY
 - THEY HAVE IDEAS HOW TO MAKE BETTER
 - THEY ARE CONSTRAINED BY “COPYING”
- They know how to make your **PRODUCT** better, cheaper, more effective

SuperGenerics and BioBetter

- The pioneer product is “stalking horse” e.g., a guide
 - Your researchers have expertise and likely know how to make the drug, biological better
 - May be structural variation
 - May be pharma formulation



“It turns out we’ve only got enough money for R or D.”

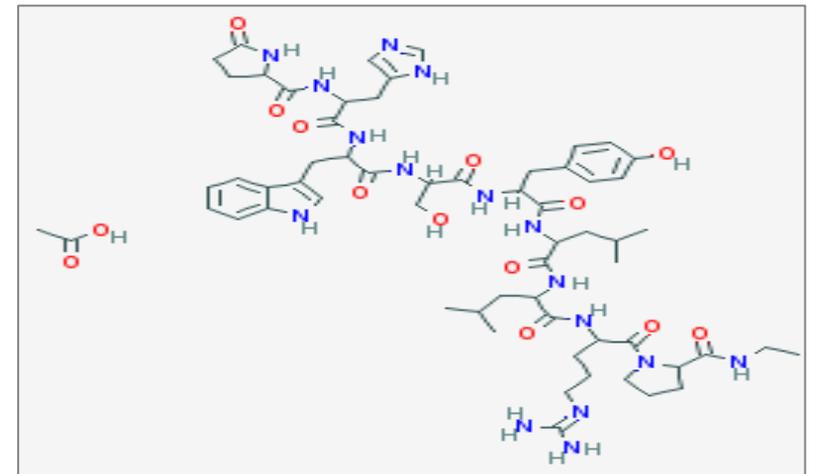
How to Design Anew

Consider THE SUPERGENERIC
ELIGARD®
An Anti-Prostate Cancer Drug



What is Active in Eligard?

- Active is Leuprolide Acetate
- Leuprolide Acetate is a nonapeptide that lowers testosterone level to below baseline
- It is the chemical castration drug, an LHRH superagonist
- Product encapsulated in preformed microparticles of bioabsorbable polymer already on market as Lupron Depot



What is Eligard?

- Eligard is a liquid formulation that upon subcutaneous injection *in situ* forms a single body implant
- It is not preformed multiple microparticles
- *In situ* Implant is bioabsorbable polymer with Leuprolide Acetate



ELIGARD BioBetter Design

- EXAMPLE OF SUPERGENERIC OR BIOBETTER
- The Eligard monolithic (single body) implant produces 4X effect with half dose as does Lupron Depot
- Single injection of Eligard lasts 6 months
- Lupron Depot max is 3 to 4 months
- Patient acceptance: injection is painful and requires clinic visit
- Would you want to visit twice a year or four times a year and get stuck deep with this needle?



Strategy



- Patents Provide Exclusivity
- Strategy
 - File Patents at early date
 - File before technical or clinical or biological data are published Create Patent thicket
 - Product Structure, Composition, Second tier product structures Pharma composition, Method of treatment, Dosing, Unit dose, Dose regimen, Pharma formulation as in soln, capsule, tablet, Route of admin, Polymorph, Polymorph in combo with foregoing, Drug combinations, Process to make, Product by process, Kit, others.
 - Develop data for each kind of patent that is unique.
 - Consider invention by selection
 - Consider formulation, polymorph, other evergreen possibilities

Expert's Lesson



- What about IPR?
- IPR EARTHQUAKE has happened
 - No Longer Broadest Reasonable Interpretation of claim terms
 - Now is Philips Interpretation just like Fed Dist. Ct.
- Future is NOW better for patent holder in pharma/bio field
- Use EverGreen Strategy
- Let your researchers develop product variation
- Be cognizant of functional reasons showing why the SAR relationship does not predict result.

SUPERGENERICS & BIOBETTERS

- **Avoid Being In SHARK SCHOOL**
- Early choice with reiteration
- EXPENSE OF PRODUCTION AND CLINICAL BECOMING PRECIPITOUSLY LOWER
- Technology for making a biobetter, copy cat, or functionally similar product is superior to technology of 5 years ago – when the pioneer product was made
- This is a winning factor for BioBettters and SuperGenerics!
- Developments not made in vacuum; can use related product clinicals and properties as guide
- Better properties and patent position = \$\$

QUESTIONS & DISCUSSION



Jim Nelson *B.S., Ph.D., J.D.*

Phone: (612) 373-6939

Email: anelson@slwip.com