Biosimilars:
Prospect for Competition and Saving
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Introduction

• Economics is based on incentives
• People and businesses respond to incentives
• The proper incentive system will lead to competition and biosimilar entry
• The incentives seemed to be aligning in U.S. market
• The market will evolve to be highly competitive
• As in the pharmaceutical market there will be a few winners and many losers
Some Terminology

- A biosimilar is “highly similar” to an originator or reference biologic
- Generally in United States, EU, Canada or Australia
- The term “biosimilar” is often misused
- Some claim to be biosimilars but are not
- Those not highly similar “noncomparable biologics”
- Biosimilars are not identical so they cannot be automatically substituted at the pharmacy level unless they are interchangeable.
- Requirements to be interchangeable are still being developed by FDA
- Biobetters are biologics that are superior
Benefits of Pharmaceutical Innovation

• Innovation increases the quality of life and promotes economic growth
• Pharmaceutical innovation has led to tremendous advances in the treatment of diseases
• Enhanced both the length and quality of life
• Lichtenberg: consumer welfare is increased considerably by the replacement of older drugs by newer more effective drugs
• Drug discovery often reduces medical expenditures
• Lichtenberg estimated that the reduction in inpatient spending was 4 times the prescription costs
• Drugs can increase workers’ productivity
• Public policy should and does encourage innovation
Biologic Development

• The development of a new biologic is a long and difficult process
• Taking on average between 10 and 15 years, with many of these efforts ending in failure
• R&D costs for one originator biologic have been estimated to be between $1.3 billion and $2.6 billion
• When taking failures into account, the costs could be as much as $5 billion each
Biosimilar Development

- Biosimilar development is expected to cost between $100 million and $200 million and take between eight to ten years.
- Celltrion has invested $112 million in the development of Remsima, a biosimilar for Remicade.
- Entry into the biosimilar market also requires establishing manufacturing facilities that must meet FDA requirements regarding “good manufacturing practices.”
- To overcome physician reluctance to prescribe biosimilars will require significant sales and promotion efforts.
Market Opportunities

- Revenues for biologics are growing at twice the rate of global drug revenues overall.
- Some estimates have biologics reaching 50% of pharmaceutical sales.
- U.S. sales in 2014 were around $200 billion and grew over 10%
- The U.S. is around 50% of biologics market
- Many biologics have sales of over a billion dollars
- Over 30 biologics have lost or will soon lose patent protection which represents $80 billion
- Given the potential market opportunity, there is expected to be an influx of biosimilars into the market
## Patent Expiration

<table>
<thead>
<tr>
<th>Drug</th>
<th>E.U</th>
<th>U.S.</th>
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<tbody>
<tr>
<td>Avastin</td>
<td>Jan. 21, 2022</td>
<td>July 4, 2019</td>
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<tr>
<td>Humira</td>
<td>April 6, 2018</td>
<td>Dec. 31, 2016</td>
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<tr>
<td>Aranesp</td>
<td>July 6, 2016</td>
<td>May 15, 2024</td>
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<tr>
<td>Herceptin</td>
<td>Expired</td>
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<td>Remicade</td>
<td>Expired</td>
<td>Sept. 4, 2018</td>
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<tr>
<td>Enbrel</td>
<td>Expired</td>
<td>Nov. 22, 2028</td>
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<tr>
<td>Rituxan/MabThera</td>
<td>Expired</td>
<td>Sept. 22, 2016</td>
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Barriers to Entry for Biosimilars

- Before passage of the BPCIA there was no pathway for biosimilar competition
- The FDA approval process requires a stepwise approach
- The FDA will based its decision on totality of evidence and a case-by-case approach
- There are many barriers that make entry of biosimilars more difficult than generics
- Biosimilars are much more costly to develop and the process takes much longer
- The cost of establishing a manufacturing facility has been estimated to be around $250 million
- The complexity makes expertise in manufacturing quite important
Barriers to Entry for Biosimilars Cont.

- Companies experienced in biologic manufacturing will have a learning curve advantage which translates into a cost advantage
- Entrants into biosimilars are likely to be large, biologic originators for other reference products
- Marketing costs could be substantial, especially in the early days as producers have to educate providers and patients about biosimilars
- Many biologics are infused, the buyers are physicians or hospitals so that marketing efforts may be less than expected
- Biosimilars are not exact copies, presently their approval requires clinical trials
Barriers to Entry for Biosimilars Cont.

- These trials can be quite expensive
- Also 85 percent of clinical trials were already being delayed because of difficulties in obtaining sufficient patient recruitment
- The highly similar but not identical nature of the biosimilar makes obtaining interchangeability status difficult
- The lack of interchangeability will preclude automatic substitution at the pharmacy level
- Physicians will then have to authorize substitution
EU Market Experience

- In generic market the originators did not respond to competition
- In biologics, the originators have actively responded in a variety of ways
- Lowering price, developing second generation biologics (biobetters), patent extension, better devices and reducing the frequency of dosages
- Each country has a unique reimbursement system with different incentives for biosimilar use
- Over much of Europe, there has been little financial incentive for the patient, the physician or the pharmacists to opt for lower priced biosimilar products
- This is changing
Biologics among the Highest Priced Drugs

• Biologics are among the highest priced drugs
• The annual price for Soliris in 2015 was $536,529 and Naglazyme was $485,747
• These are the two most expensive biologics
• The tenth most expensive, Revlimid, had an annual price of $128,666
• Some of these expensive biologics are so-called orphan drugs and are used for a small patient population
• So need high price to get return on investment
Biosimilar Prices

• Given the higher costs of biosimilars one would not expect prices to decrease as much as in generic market
• In the EU biosimilar competition has resulted in price decreases of around 20 to 30 percent
• Many biosimilars are being produced by brand name companies which because of their reputation should be at less of a competitive disadvantage than early entrants into the generic market
Pricing Policies

- EU has tendering which has resulted in some huge discounts 72% in Norway (Orion Resima/Remicade)
- Hospital or plan purchase, generally regional, 45% discount in France (Hospira Inflectra/Remicade)
- NICE least expensive drug including biosimilars should be used for RA
- Originators have responded in some markets by cutting price
- Originator strategy can’t cut prices too much in individual country which could lead to lower prices in all countries
- So profit maximum strategy can be different for different products
Celltrion

- Celltrion has dual distributorship in EU
- If one distributor can discount at 72% and purchasing from Celltrion
- What is Celltiron’s cost of production and what are they selling it for to distributors?
- Celltrion does not care what discounts are because it is getting its price
- Greater discounts more sales for Celltrion
Complexity

- Complexity of biologic/biosimilar marketplace
- As complex as biologics are: its market is just as complex
- Laws and regulations, competitors, decision makers: payers, providers, patients
- Seen how difficult it is to get law, develop pathway, approval process and patents issue
U.S. Market

- U.S. more complex private and public payers
- Medicare Part D not allowed to negotiate for discounts
- Medicare Part B controversy over one J-code for biosimilars and reference product with average selling price
- Reimbursement markup for biosimilars is 6% of selling price of reference product.
- Medicaid special discount
U.S. Market Cont.

- Private payers can act like tendering similar to what happened in Hepatitis C market with discount of around 46%
- Zarxio entered with 15% discount same as when it entered in EU when launched in EU in 2009
- Not surprising since with generics don’t see big discounts when only one competitor
- Bigger discounts come with more competitors
- Prices higher in U.S. than EU so discounts can be greater
- So how low can prices go?
Patents and Exclusivity

- Most of the developed nations have patent periods of 20 years
- Allow for extensions of up to 5 years if regulatory approval takes long time.
- EU exclusivity: 8+2+1 years Data +Market+ New Indication
- Canada and Japan 8 years exclusivity
- U.S. 4 year data and 12 year market
Type 1 and Type 2 error

- Much debate over the length of market exclusivity for biologics
- The debate centered around 7 or 12 years
- Difficult to determine the optimal exclusivity time period
- It can and almost certainly will differ significantly by drug
- Decided that 12 year exclusivity was appropriate
- Raises the issue of a type 1 and type 2 error
Type 1 and Type 2 error Cont.

- If too short a period were chosen, a type 1 error
- Originator firms would have less time to obtain a return on investment and less incentive to innovate
- Some beneficial biologics may not be developed
- If the period of exclusivity was too long, a type 2 error
- There would be less competition and less access due to higher prices during the exclusivity time period
- Optimal public policy should err on the side of innovation
Legal Issues in U.S.

• First biosimilar approved in U.S. in March 2015
• Entry delayed until Sept. 2015 because of legal issues
• Entry 180 days after approval
• Need to know final composition and approved uses of biosimilar
• Patent Dance not necessary
• Patent holder can sue for infringement
Patent Issues

- Patent issues are:
- confusing whether generics or biosimilars
- Logic versus legal
- Mostly understand the legal issues concerning patents
- But logical has always puzzled me
- Valid patent: patent office gives a patent but may not be valid
- Seems easy to get patent which leads to patent litigations
- Need to fix this inconsistency
- Infringement: whether generic or biosimilar:
- Claiming product is exact copy (generic) or highly similar (biosimilars) but somehow not infringing on originator
Interchangeability

• Presently unlikely to file for interchangeability in initial FDA hearing
• Before a biosimilar gets interchangeability probably 2 or 3 other biosimilars in market
• One year market exclusivity for first interchangeable but still competing with originator and non-interchangeable biosimilars
• High cost of switching studies for clinical trials
• Very little competitive advantage especially in physician administered (no automatic substitution: physicians decide)
• How much will switching still be an issue when finally approved?
Interchangeability Cont.

- Do payers care if interchangeable?
- Are they willing to pay a price premium?
- If not will get on formulary if lower priced but if originator matches price it will get market
- Non-interchangeable may set lower price
- Risk of failure: going from highly similar to very highly similar
- If do not get interchangeability will it be bad PR
- Product be perceived as not high quality thus hurting your market share
First Mover Disadvantage

- Most markets first mover has advantage
- Advantage: can come in at higher price
- As more biosimilars enter price will decrease
- Disadvantage: Higher cost of entry
- FDA approval: more uncertainty and thus high costs of preparation for approval process
- Legal issues and costs due to potential patent issues
- Cost of educating physicians and patients concerning what a biosimilar is and the quality of biosimilars
- Later movers can free ride on all of the above
Incentivizing Market Acceptance

- Biologics are coming under greater scrutiny because of their high prices.
- Stakeholders (physicians, patients and payers) will greatly influence the biosimilar market.
- The U.S reimbursement system is more complex than EU with roles for both large private payers and public payers.
- Biosimilar uptake in the EU has been successful when stakeholders have the right incentives.
- High biologic prices could lead to pressure by payers to switch to lower priced biosimilar
Incentivizing Market Acceptance

• For example, Germany has encouraged the use of biosimilars and has experienced some of the highest market shares for biosimilars
• Bundling of payments for providers so that they receive a fixed price for treatments would encourage the use of less expensive inputs, including biosimilars
• Many biologics are physician administered; bundling would be easily adopted for these biologics
• Similarly, the growth of Accountable Care Organizations, encouraged by the ACA, where providers earn higher profits for cutting costs, would seem to encourage the use of biosimilars
Incentivizing Market Acceptance

- Reference pricing, which make patients pay out of pocket for prices above the insurance reimbursement rate, can encourage patients to seek biosimilars.
- Medicare has ACOs and is considering reference pricing and bundling.
- In the U.S. market, third party private payers will have the ability to negotiate the best deal for their clients and may utilize a tier system.
- In the U.S. a bidding process for exclusive arrangements could be utilized to encourage more competition and might lead to more rapid expansion of the use of biosimilars, similar to the hepatitis C chemical drug market.
- The uptake of biosimilars could proceed faster than the experience in the EU and other developed markets.
Hatch-Waxman (Generics)

• Thirty years ago, the U.S. was faced with similar concerns as it developed regulatory framework for generic chemical drugs entry
• The resulting Hatch-Waxman Act was intended to balance competition and innovation as is BPCIA
• The major public policy goal was to enhance competition from generics, which would lead to lower prices, but still provide the originator with the incentive to innovate
• The Hatch-Waxman Act has been successful in a number of ways
Hatch-Waxman (Generics) Cont.

- It took some time for U.S. consumers to accept generics
- Presently, 84% of the small-molecule chemical market in the U.S. consists of generic drugs
- Third party payers have induced patients to use generics by lower out of pocket payments
- Many consumers still believe that generics are simply an insurance company device to save money
- Generic drugs have saved over a trillion dollars in healthcare costs between 2002 and 2011
Consumer Welfare Gains

- It is important to note that the primary policy objective is to increase consumer welfare.
- The market share of biosimilars is not a fully informative metric.
- The relevant welfare benchmark is not price of the biosimilar relative to the reference product, but the comparison price before competition.
- The increase in quantity due to lower prices increases access.
Potential Gains from Biosimilar Competition

• Prices of biosimilars will be about 25 to 30 percent less than their reference products.
• The savings to consumers and society could be much greater in the case of biosimilars because of their higher prices.
• Revimid which treats multiple myeloma and whose annual cost in 2015 was $128,666
• A 30 percent saving on this drug would be about $38,600
• Lipitor, one of the world’s blockbuster drugs lost patent protection in 2011
• The annual cost for a 20 mg regimen of treatment with Lipitor in 2011 was $1939
Potential Gains from Biosimilar Competition Cont.

• Even if the generic price were 90 percent below that of Lipitor, annual per patient savings would be $1745
• Biosimilar competition is also expected to result in substantial benefits.
• In EU one study estimated that biosimilars will have saved between 11.8 billion and 33.4 billion Euros in 8 EU countries, from 2007 to 2020
• Another study estimated annual savings of 1.6 billion Euros across Europe from a 20% price reduction in the five most popular patent free biologics.
• A RAND study estimated that savings from biosimilar competition could save $44.2 billion in the U.S. over 10 years
Strategies

• Issue of strategy: which markets to enter, greater potential profits in blockbusters but more competition so higher discounts, potentially less profits and may have no return on investment

• Medium revenue markets initially less potential profit but could have less entry and lower discounts so may get higher profit
Return on Investment

- Can biosimilars get return on investment?
- Many firms making huge investments to develop biosimilars
- Cost of R&D, manufacturing, clinical trials and other costs
- Have price competition and many competitors
- Many biosimilars and biobetters being developed
- In 2013 21 Herceptin, 27 Enbrel, 35 Rituxan biosimilars being developed
- As of Feb. 2015 50 biosimilars for 15 reference submitted inquiries to the FDA
- Originators developing 2nd generation
- Price competition from originators
- In EU there are five brand-name competitors in the human growth hormone market and two biosimilars
- Many firms making huge investments to develop biosimilars
- How many biosimilars will enter each market?
Ironic Relationship

• Ironic relationship between generics (biosimilars) and originators companies
• The generic market (biosimilars) would not exist without the originators market
• Nothing to copy
• The branded market is also helped by the existence of generics
• The generic market decreases the price of older drugs.
• Allows for higher priced newer drugs
• Consumers benefit from both
Conclusion

• Historically, EU generic market not as strong as U.S. so expect greater uptake in U.S.
• In U.S. many stakeholders are serious about controlling healthcare costs
• Payers promising tough negotiations for expensive drugs
• All the factors point to highly competitive market but will take some time to develop
• Access will increase
Conclusion

- Products highly similar so not much difference if any in therapeutic effect
- Small producers will not survive, need to partner
- Most markets will have 5 to 6 biosimilar competitors that are well established branded companies