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 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

Patent Expiration		
	E.U	U.S.
Avastin	Jan. 21, 2022	July 4, 2019
Humira	April 6, 2018	Dec. 31, 2016
Aranesp	July 6, 2016	May 15, 2024
Neulasta	Aug. 21, 2017	Oct. 20, 2015
Herceptin	Expired	June 18, 2019
Remicade	Expired	Sept. 4, 2018
Enbrel	Expired	Nov. 22, 2028
Rituxan/MabThera	Expired	Sept. 22, 2016

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, Revlmid, 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