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Despite Market Opportunities, Risks and Uncertainties Remain for Biosimilars®

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For Presentation on the Panel

The Growth Pathway for Future Bio Business in Korea

(Regulatory business development perspectives)

Delivered at the

Semi-Annual Conference of Korean Society for Biotechnology and Bioengineering (KSBB)

Changwon, South Korea

April 13, 2012

(Donated to the Institute for Trade, Standards and Sustainable Development (ITSSD))

ABSTRACT

The recent entry into force of the KORUS FTA, the ongoing public pressures to reduce healthcare costs and the impending expiration of brand name drug patents and exclusivities are expected to spur significant growth of the U.S. and global biosimilars industry through the end of the decade. However, USFDA concerns about the safety, efficacy and purity of these complex and variable molecules persist.

The recently promulgated draft proposed guidelines intended to implement the BPCIA's provisions and which reflect these concerns would, if adopted, likely raise regulatory uncertainties and result in delayed development of biosimilars and interchangeables, overall higher development, manufacturing, data generation and testing costs, reduced product profit margins, and lower than anticipated patient cost savings.

The BPCIA's mandatory patent settlement procedure, furthermore, is likely to raise additional litigation uncertainties, risks and costs for biosimilar applicants due to the difficulty of undertaking 'freedom-to-operate' clearances (including prior art searches) given the biotechnology-jurisprudence lag, USFDA Orange Book exclusion of process patents, pending non-published (provisional) patent risk, and broad and nested platform patents.

These risks and uncertainties notwithstanding, many biopharma companies have endeavored to capitalize on the perceived biologics trend by pursuing various individual, alternative and/or collaborative business strategies, focusing on, among other things the development of new innovative biologics, biosimilars and/or bio-betters, and the entering into of domestic, cross-border and/or cross-industry segment out-licensing arrangements, and marketing, distribution and/or joint manufacturing ventures.

I. Korea-US Trade Environment for Biologics and Biosimilars

A. KORUS-FTA Overview

1. History
2. IP Provisions Arguably Applicable to Biologics and Biosimilars
   a. Market/Data Exclusivity
      - Cannot authorize marketing of 'same' or 'similar' for 5 yrs. based on original product safety/efficacy data;
      - Cannot authorize marketing of 'same' or 'similar' for 3 additional yrs. if new clinical information relied upon to approve original product.
   b. Applies to chemically synthesized small molecule products;
   c. Arguably applies to complex biologic and biosimilar products ('highly similar' to reference product, notwithstanding minor differences in clinically inactive compounds and NO clinically meaningful differences in safety, purity, potency.).
   d. Article 18.9 – NO reliance on original drug approval in Korea for 5 yrs.; no reliance on drug approval in other country for 5 years.
   e. Article 18.9.4 - NO tying data protection to patent term – they are distinct IP rights;
   f. Article 18.9.5 – PATENT LINKAGE - NO generic/biosimilar drug approval during original product patent term – AFFIRMATIVE OBLIGATION OF government to investigate and confirm pending patents and to disclose generic/biosimilar applicant seeking marketing approval.
   g. Exchange of Letters Between Korean & U.S. Gov'ts:
      - Delayed implementation of Patent Linkage provisions for drug approvals from other countries. NO DUTY TO INVESTIGATE PENDING PATENTS RELATED TO DRUGS APPROVED IN OTHER COUNTRIES.
   h. Article 18.9.3/18.11 – WTO Declaration on Public Health Applicable to WTO TRIPS Agreement – Must make compulsory licensing of patented drugs available.

II. Korean Legal Environment for Biologics and Biosimilars

A. Korean Biosimilars Law Overview

1. KFDA July 2009 Biosimilars Guidelines for Market Authorization

   a. Need accumulated data on safety and efficacy to secure approval of biologic license.

b. Comprehensive 'Comparability' of 'raw material' & 'final manuf'd product' is required to establish 'biosimilarity'.
c. Comprehensive qualitative data package required, differing on case-by-case basis.
d. Less non-clinical and clinical data will be required IF quality 'comparability', on basis of safety, purity, efficacy is demonstrated.
e. Data extrapolation to other indications of use may be permitted if qualitative 'comparability' is demonstrated.
f. KFDA reserves authority to eliminate clinical studies for 'other indications' if certain additional conditions are satisfied.

2. Data Protection

a. No express data protection, but rather de facto data protection of original product data during the 4-6 year reexamination period for BOTH biologic and non-biologic products.

b. Difficult to effectively produce data & file biosimilar application before expiration of 4-6 yr. reexamination period.

3. Patent Linkage

a. **Recent amendments to Korean Pharmaceutical Affairs Act (PAA)** to implement Hatch-Waxman Act:
- Patentees must request KFDA to list patents in Korean 'Orange Book' if relate to medicinal use, product's approved active ingredient, and are directly relevant to safety, efficacy & quality information contained in approved drug application;
- Generic mfr. must notify NDA holder w/in 7 days of filing generic application of intent to launch on market;

b. **KFDA Proposals for PAA Amendments**:
- 12 month automatic stay of generic product approval to prevent generic applicant from entering market without prior patentee consent. (Shorter than Hatch-Waxman 30-month stay)
- Reward of 180 days Exclusivity to (generic) party who successfully challenges and invalidates pharmaceutical patent.

c. **Recent Amendments to Korean Patent Act**:
- Patent term extension to compensate for unreasonable regulatory delays of up to 4yrs. from application or 3yrs. from examination request.
- Patentee must petition KIPO for extension.
- **Consideration of** granting protective orders for trade secrets in litigation.

III. U.S. Legal Environment for Biologics and Biosimilars – BPCIA Abbreviated Approval Pathway

A. U.S. Political/Constitutional Uncertainties

1. Current Challenges to U.S. Healthcare Law May Impact Availability of BPCIA

a. Patient Protection and Affordable Care Act (PPACA) w/in which BPCIA was enacted.

b. If not severable and declared unconstitutional, BPCIA dies.

c. If severable, and remainder found constitutional, BPCIA lives.

B. U.S. Market/Data Exclusivity-Related Regulatory Uncertainties

1. Post-Enactment Debates Regarding Reference Product 'General' Exclusivity

a. Cannot **accept** biosimilar application until after **4 yrs.** from reference product approval/licensure.

b. Cannot approve market authorization of biosimilar until after **12 yrs.** from reference product approval/licensure.

c. 'Market Exclusivity' – General concept is that others are prevented from filing a biosimilar application.

d. 'Data Protection' – General concept is that others are prevented from relying on original product data (clinical, non-clinical, trade secrets) as basis for their application.

e. Market Exclusivity/Data Exclusivity is a separate IP right granted/administered by USFDA, not USPTO.

f. Congressional and industry debate over definition and scope of these exclusivities.

- *See* Lawrence A. Kogan, *The U.S. Biologics Price Competition and Innovation Act of 2009 Triggers Public Debates, Regulatory/Policy Risks, and International Trade Concerns*, Kluwer Law, Global Trade & Customs Journal, accessible online at: http://www.itssd.org/GTCJ_6(1112)_Lawrence%20A%20Kogan%20-%20FINAL.pdf.

- Do 4 yr. & 12 yr. periods run successively or concurrently? The better interpretation is:
    - During yrs. 1-4, reference product is granted BOTH 'market exclusivity' w/re to biosimilar applications AND 'data exclusivity' w/re to data used to support application;
    - During yrs. 5-12, reference product retains 'market exclusivity', but loses 'data exclusivity'. Biosimilar applicant can generate data and include within biosimilar application beginning in yr. 5.

- EU treatment of exclusivities:
    - During yrs. 1-8, 'Data Exclusivity' – NO biosimilar application can be submitted and, by implication, can rely on reference product data;
    - During yrs. 9-10, 'Market Exclusivity' - NO biosimilar product can be placed on market/
    - During yr. 11, 'Market Exclusivity' – NO biosimilar can be placed on market if there is demonstration of a new indication bringing 'significant clinical benefit'.

2. Post-Enactment Debates Regarding Evergreening of Brand Name Exclusivity

    a. USFDA –
    - **NO separate 4yr./12yr. market/data exclusivity granted** to any biological product supplement or any subsequent biologic license application for:
        - NON-structural changes to biological product resulting in 'new indication, route of administration, dosing schedule, dosage form, delivery system device, strength;
        - STRUCTURAL changes NOT resulting in change in safety, purity or potency.

    b. PhRMA – Sought unsuccessfully for coverage of supplements or subsequent BLA under original reference product exclusivities if a member of an 'affiliated group'.

3. BPCIA 'Interchangeability' Exclusivity

- 1 year exclusivity;
- Available for 1st 'biosimilar' if can show higher similarity;
- Not yet defined in terms of 'science';
- Available after earlier of:

- 1 yr. after 1st commercialization/marketing of 'interchangeable'; OR
- Earlier of several dates if biosimilar involved in patent litigation.

C. U.S. Patent-Related Regulatory Litigation Uncertainties

1. General

a. New BPCIA mandatory dispute settlement procedure triggered by the acceptance for review of a filed biosimilars application that potentially covers a reference product patent.

b. Under Hatch-Waxman Act applicable to generics, the offering to sell, use, make or import a U.S. patented invention for uses reasonably related to seeking an USDA regulatory approval was NOT deemed an 'infringement'.

c. New BPCIA dispute settlement procedure consists of three stages:

- Pre-Litigation Information Exchange;
- Early Stage Litigation;
- Late Stage Litigation

2. Pre-Litigation Information Exchange (6 month process could extend to 200 days)

a. Biosimilar Applicant (BA) provides Reference Product Sponsor (RPS) with 'information' on 'confidential' basis w/in 20 days of application filing date. 'Information' consists of:

- Biosimilar application copy;
- Description of proposed biosimilar mfg. process;
- Additional 'information' RPS requests;
- 'Other' 'confidential' information BA deems relevant to prove NO patent infringement.

Information shall be given on a 'confidential' basis to:

- RPS;
- RPS' inside counsel;
- RPS' outside counsel.

- If BA's confidentiality breached BA entitled to injunction agnst RPS.

b. RPS responds to BA information w/in 60 days of receipt. RPS provides following information:

- Lists patents 'believed' to be infringed if biosimilar product used, sold or imported into U.S.
  - Process Patents; AND
  - Patents claiming drug or a use of it.
- Specific patents on list RPS is prepared to license to BA.

c. BA responds to RPS information w/in 60 days of receipt. Provides following information:

- Responds to each patent on RPS' list; OR
- Provides own list of RPS patents against which believes a patent infringement can be asserted;
- Provides factual & legal substantiation of position(s), patent claim-by-claim.

d. RPS responds to BA's list w/in 60 days of receipt.

- Lists subsequently acquired or licensed patents w/in 30 days of execution of agreement;
- Provides factual & legal bases of positions, claim-by-claim, regarding infringement.

e. Bottom-Line of New Procedure:

- Minimalistic statements likely to be made by both parties due to tight deadlines, long lists of patents, and binding nature of any statements made in litigation. NOT VERY HELPFUL.

3. Early Patent Litigation Negotiations/Information Exchange (45 day process if agree)

a. **15 days** Good faith negotiations required concerning which patents to litigate.

b. If agreement reached, RPS must commence litigation **not later than 30 days**.

c. If NO agmnt. reached, BA notifies RPS of patents it believes shld be litigated, and **w/in 5 days** of notice both parties exchange lists of identified patents that each seek to litigate.

d. Once litigation is commenced, BA must notify USFDA of suit **w/in 30 days of receipt of complaint**.

- **245+ days** for Pre-Litigation and Early Stage Litigation phase of BPCIA procedure reduces patent certainty, especially w/re to newly issued or licensed patents, AND raises the risks surrounding a biosimilar product launch.

4. Late Stage Patent Litigation/Pre-Commercialization – 3 Available Remedies:

a. Preliminary Injunction (PRI)

- RPS may seek following BA's 180 day advance notice of 1st commercialization, BUT BEFORE commercialization;
- PRI effective until court decides patent infringement/validity/enforcement issues;
- Applies to any pre-litigation or litigation **listed** patents;
- RPS may use PRI to add subsequently acquired or licensed patents to litigation patent list w/in 30 days of execution of agmnt IF reasonably could be infringed.

b. Declaratory Judgment (DJ) (limited availability; favor RPS)

- Can be used to seek infringement/validity/enforcement determination concerning ANY patents included on initial and supplementary patent lists;
- BUT, NOT available to either party:
  - IF BA has timely provided RPS with copy of biosimilar application and other 'confidential' 'information';
  - UNTIL RPS receives BA's 180-day advance notice of 1st commercialization.
- RPS may seek DJ where BA failed to perform any of the following acts:
  - Provide biosimilar application, mfg. process information, patents or patent positions, 180-day advance notice of 1st commercialization;
  - Timely: exchange or respond to RPS patent lists, notify USFDA of patent litigation, provide 180-day 1st commercialization notice.

- NO similar remedy available to BA for RPS failure to perform in dispute procedure.
- BA may seek DJ after it files 180-day notification of 1st commercialization in effort to control litigation, by selecting venue, forum and patents to litigate.
- BA may escape temporary injunction and being prevented from using a patented mfg. process under BPCIA b/c:
    - Process patents not included in USFDA published patent list ('Orange Book');
    - BPCIA does not require RPS to identify its patents in advance of biosimilar competition (UNLIKE Hatch-Waxman Act requirement to list for publication patents that can reasonably be infringed by generics);
    - BPCIA does NOT YET authorize USFDA to deny approval of biosimilar application NOT disclosed to RPS.
        - BUT USFDA could potentially regulate
        - Hatch-Waxman Act authorized USFDA to deny generic approval if generic applicant failed to certify to all Orange Book-listed patents.
- RPS must rely on judiciary to 'stay' release of biosimilars onto the market. (There is NO automatic 30-day 'stay' of Abbreviated New Drug Application (ANDA) as Hatch-Waxman grants if a timely infringement action is filed).
- **RPS' sole BPCIA remedy is to bring DJ action and seek injunction**. **CANNOT block USFDA approval of biosimilar**.

c. Permanent Injunction (PMI)

- RPS may seek PMI to prevent patent infringement **after** 1st commercialization of biosimilar, until patent expiration, if:
    - RPS obtains final non-appealable court judgment of infringement in BPCIA litigation; AND
    - Biosimilar product has not yet been approved b/c RPS product exclusivity has not expired.

5. Recap – Patent Infringement Remedies

a. PRI – to prevent commercialization or importation
b. PMI – to prohibit infringement once commercialized/imported
c. Money Damages – to compensate where commercialization/importation has occurred.
    - Will be limited to a 'reasonable' royalty if:

- RPS fails to bring timely infringement action (w/in 30 day period) concerning listed patents;
- RPS brings timely infringement action but later sought dismissal w/o prejudice OR failed to prosecute in good faith.

d. NO REMEDY – If RPS fails to include patent on pre-litigation or litigation lists.

6. BPCIA's Implications for Patent Licensing

a. BPCIA's failure to have USFDA require that RPS list all relevant patents in advance of biosimilar competition places BA at competitive disadvantage. INCREASES LITIGATION RISK

b. BA will find it difficult and costly to conduct 'prior art' patent searches, especially considering USFDA 'Orange Book' excludes 'process patents'.
- For biologics and biosimilars, the mfg. process is defining of the final product;
- mAbs and certain therapeutic proteins may be highly dependent on proprietary mfg. systems.

c. BAs will face greater uncertainty in undertaking 'freedom-to-operate' clearances due to:
- Biotech jurisprudence lag;
- Pending non-published patents;
- Nested platform patents.
- Freedom-to-Operate Clearance:
  - Seeks to proactively identify potential barriers and/or risks of infringement relating to product or process launch, including patents, trade secrets, 3rd party licenses, country-by-country;
  - Impacts R&D and commercialization strategies;
  - Helps to avoid willful infringement allegations and to reduce litigation costs.

d. Patent Owners could be adversely impacted by RPS failures to include patents on pre-litigation or litigation lists.
- PRI denied to RPS if patent not on lists;
- No standing for patent owner to sue if patent not on list;
- BPCIA does not require BA to provide 'confidential' 'information' to patent holder even if has rights to assert patent or participate in infringement litigation. BA *may* provide patent owner with info.
- BPCIA does not require RPS to share 'confidential' 'information' received from BA with patent owner.

e. Patent owners/exclusive licensors can be disadvantaged by RPS failures to:
- Timely file BPCIA litigation – NO PRI;
- Prosecute litigation in good faith – LIMITED MONETARY DAMAGE;

f. Patent owners/exclusive licensors may wish to become affirmatively involved with RPS in BPCIA dispute settlement process;

g. Patent owners/exclusive licensors may wish to reconsider which technologies to patent and which to keep as 'trade secrets'.

D. U.S. Market Authorization Regulatory Uncertainties Remain Despite Recent Proposed USFDA Guidance

1. USFDA Issues 3 Guidance Documents Proposing How Agency Will Implement BPCIA

2. Key Questions Remain

3. Scientific Considerations for Establishing and Evaluating Biosimiliarity

a. USFDA **Negative** Regulatory Presumptions:

Due to the complexities of biological products as compared to chemical generic products, the risk that changes in biologic product can change during mfg., and the risk that protein mfg. processes can affect product safety or effectiveness, demonstrating 'biosimilarity' to a reference product is more complex than assessing product 'comparability' after mfg. changes.

MORE data & info is needed to establish 'biosimilarity' than to establish 'comparability' of mfr.'s post-mfg. and pre-mfg. change products.

b. USFDA **'stepwise approach'** to developing data in support of biosimilarity:

At each step, sponsor must evaluate degree of 'residual uncertainty' about proposed 'biosimilarity' and address such 'uncertainty' via extensive analysis, characterization & direct 'side-by-side comparison' between proposed biosimilar & reference products, identifying quantitative and qualitative differences.

c. USFDA **'risk-based totality of evidence approach'** in evaluating demonstration of 'biosimilarity':

- Will determine type & amount of analyses & testing needed to demonstrate biosimiliarity on product-specific basis.
- Will exercise discretion to determine whether any data & test element is Unnecessary in biosimilar application.
- Encourages meetings with biosimilar sponsors to review product development plans & to establish milestones for reference in future Agency meetings.

d. USFDA may permit a biosimilar application to establish an acceptable **'scientific bridge'** – to use data derived from animal or clinical studies comparing a proposed U.S. biosimilar product to a non-U.S. licensed reference product. But must show 'scientific justification' of relevant data. USFDA most comfortable considering non-U.S. product comparative data if biosimilar marketing approval already obtained in another market (e.g., EU).

4. Quality Considerations for Establishing and Evaluating Biosimiliarity

a. Biosimilar applications should contain a chemistry, mfg., and control (CMC) section providing sufficient information on product characterization, adventitious agent safety, process controls & specifications.

b. Animal studies may be used to establish a relevant **'scientific bridge'** between a non-U.S. licensed reference product and a U.S. licensed reference product, and to show 'comparability' between biosimilar and U.S. reference product. Analyses, non-clinical and clinical pharmakinetic and pharmacodynamics studies.

c. USFDA may consider patentable or licensable 'expression systems' – technologies (biological materials and know-how) needed to genetically modify organisms to manufacture proteins and other products.

5. Biosimilars Q&A

a. Diff't *formulations* permitted IF: NO major diffs in clinically inactive components & NO clinically meaningful difference in safety, potency, purity between biosimilar and reference products;

b. Diff't *delivery system or container closure system* permitted IF: meets 'biosimilar' statutory definition, adequate performance data provided, studies show compatible for use w/ final formulation of reference

product & NO clinically meaningful difference in safety, potency, purity of biosimilar and reference products;

c. Can be licensed for fewer than all administration routes of reference product, IF: NO clinically meaningful difference in safety, potency, purity between biosimilar and reference products;

d. Can be licensed for fewer than all presentations (strengths, delivery device or container closure systems) of reference product;

e. Can be licensed for fewer than all conditions for use for which reference product licensed. Can use data extrapolated from one use to support another use IF: provide 'sufficient scientific justification'.

f. Can show biosimilarity IF: adequate head-to-head **'comparison'** based on use of analytical, pre-clinical animal, clinical pharmacokinetic **(PK)** and pharmacodynamics **(PD)** studies and demonstrate necessary 'bridging' data relevant to a non-U.S. licensed reference product.

g. NO DISCUSSION OF NECESSARY DATA FOR ESTABLISHING 'INTERCHANGEABILITY'.

h. Clarified definition of 'protein' w/in definition of 'biological product'.

BPCIA – Defines 'Biological Product' as:

"**any** virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, **protein (except any chemically synthesized polypeptide)** or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."

USFDA Guidance – Defines 'Protein' as:

"any alpha amino acid polymer with a specific defined sequence that is *greater than 40 amino acids in size*."

Implication: - A polymer composed of 40 or fewer amino acids is NOT deemed a protein, but a peptide, and thus is NOT a 'biological product' unless meets other requirements of definition (e.g., peptide vaccine). Thus will be regulated as a drug under FD&CA and subject to a 'New Drug Application'.

USFDA Guidance – Defines 'Chemically Synthesized Polypeptide' as:

"any alpha amino acid polymer that is *made **entirely** by chemical synthesis and is less than 100 amino acids in size*".

Implication: - Unless a chemically synthesized polypeptide otherwise meets definition of 'biological product' will be regulated under FD&CA.

E. Industry Critique of Cautious USFDA Approach Insufficiently Addressed in Recent Proposed Guidance

1. USFDA Experience With Biologics Manufacturing Changes Should Control Biosimilars Review

   a. Argue that USFDA presumption that biosimilars are less 'safe' than reference product triggers unnecessary costs and delays, serves as disincentive for innovation and frightens patients.

2. Regulatory Conservatism Can Impede Innovation and Increase Development Costs

   a. Fosters company reliance upon existing products from which to extract value.

   b. Fosters company use of 'risk-minimization' strategies to avoid mfg. changes engendering regulatory challenges.

   c. Facilitates over-building of data dossiers (production of largely NON-actionable industry data) to enhance likelihood of approval.

3. Precaution-Leaning Regulatory Model Retards Biosimilars Market Penetration in Europe

4. USFDA's **Scientific 'Comparability' Approach** for Evaluating Manufacturing Changes Can be Applied to Biosimilar Pathway

   a. USFDA head-to-head comparisons to evaluate product pre-mfg. and post-mfg. changes that can impact product safety and efficacy, to establish 'interchangeability'.

   b. Head-to-head comparisons rarely entail clinical trials.

   c. Understands original biologic products undergo changes over time, including when mfg. changes undertaken.

d. Understand that originator product attribute changes can occur within an acceptable range of variation **('goal posts')** – these can be used to evaluate **'comparability'** of a biosimilar.

e. Original mAb variability over time is slight with same mfg. process. But even if undertake mfg. changes, there is an acceptable range of variation **('goal posts')** based on which biosimilar **'comparability'** can be established.

f. Once **'goal posts'** are established, use of iterative/repetitive process to establish biosimilar 'comparability' based on physiochemical and biological characterization can proceed.

g. **'Goal Posts'** approach dependent on analysis of multiple batches of reference product mfd. in past and over time.

h. If product attributes fall outside **'goal posts'** process steps are modified to generate attributes that fall w/in 'goal posts'.

i. Abbreviated development justified when biosimilar product attributes are 'highly similar to reference product.

j. If ANY biosimilar attributes differ from reference product, 'scientific justification' of presume safety/efficacy is necessary AND additional pre-clinical and clinical studies demonstrating similarity necessary.

5. Industry's Use of BPCIA Abbreviated Biosimilars Pathway Depends on USFDA's Resort to this Scientific Approach

6. Biosimilar Sponsors Must Consider Increased R&D and Testing Costs Related to USFDA-Required Studies

a. Each country's laws default to need for a reference product previously approved by local regulatory authority – little acceptance of 'scientific bridge'. DUPLICATIVE CLINICAL DEVELOPMENT PROGRAM

b. Repeat of clinical studies where data shows indistinguishable reference products in U.S. & EU unnecessary. Though USFDA guidelines allow for **'scientific bridging'** in certain instances from animal or clinical studies if show 'scientific justification' and 'relevance' of comparable data of non-U.S. licensed reference product back to U.S. reference product, for comparison with biosimilar.

IV. Global Biopharmaceutical Market Response to Political, Legal, Regulatory Uncertainties Regarding Biosimilars

A. Industry Emphasizes the Significant Costs of Developing Original Biologics and Biosimilars

1. Estimated development cost for innovative biologic drug can exceed $1.2B.

2. Lengthy clinical trials & studies and associated time delays will likely result up to 100 times greater development cost than generics ($100-$200M rather than $1-5M.

3. Estimated cost of building large biologic mfg. facility is between $200-500M, coupled with need to secure USFDA GMP/cGMP authorization.

4. Higher Sales & Marketing costs likely for biosimilars than for generics due to need to educate physicians and consumers about safety of biosimilar products.

B. Government and NGO Studies Emphasize the Relatively Lower Price Savings from Biosimilars

1. NO more than 10% to 30% for at least 1st five years of ramp up of biosimilars market (unlike 40%-80% price savings for chemical generics). Only one estimate of 50% price reduction thereafter.

C. Lower Market Penetration To-Date in Europe & U.S. Betray Regulatory Conservatism and Related High Development Costs

1. High entry costs
2. NO real competition - Only 2-3 biosimilar entrants – usually large deep-pocketed companies
3. NO steep price discounting
4. NO automatic substitution between original biologic and biosimilar
5. Average course of treatment for 6 approved biosimilars has ranged from $35,000 to $135,000

V. Possible Strategies for Korean Biosimilar Product Companies (Clear Industry Segment Lines are Fading)

A. Follow ‘Big Pharma’ & ‘Big Generics’ Leaders and Undertake Bio-Betters & Biosimilars Development Alone?

Considerations of Benefits and Risks Associated with Bio-betters:

- Same class drug as existing biopharmaceutical, but with some molecular, chemical or other improvement over original OR a new delivery system:
  - (half-life/less frequent dosing; more potency; less toxicity)
- USFDA likely to regulate as novel biologic;
- An immediate biologic license application (BLA) available – NO 4yr. wait as for biosimilars;
- USFDA to require clinical phase III to demonstrate superior efficacy;
- 12 yrs. exclusivity vs. 1 yr. exclusivity for 'interchangeable' biosimilar;
- Reduced clinical development risk or costs NOT guaranteed even though NOT a completely new molecule.
- 'Big Pharma' advantages: (mfg., testing economies of scale; global clinical trial know-how; higher cost barriers to entry to smaller competition).

1. Rely on Biologic License Application (BLA) for 'Improved' Reference Products ('Bio-Betters') Rather Than Biosimilars?

   a. *Merck* (U.S.)

   b. *Sandoz/Novartis* (Switzerland)

   c. *Pfizer* (U.S.) (2009)
   Acquired Wyeth, in large part, to compete in bio-betters AND biosimilars. To improve Genentech's Rituxan (lymphoma drug), and to improve Roche's Enbrel (rheumatoid arthritis) drug.

   d. *AstraZeneca* (UK)
   Acquired MedImmune (U.S.) to focus on bio-betters.

   e. *Lilly* (U.S.); *Amgen* (U.S.); *GlaxoSmithKline* (UK); *Aventis* (France)

2. Rely on Biosimilars Pathway?

   'Big Pharma' – Examples:

   a. *Merck BioVentures (MBV)* (U.S.) (2008)

   Dedicated division to R&D of biosimilars (including with respect to own biologic reference products), following its acquisition of the mfg. facility and biosimilar candidates of U.S. biopharma firm Insmed, its acquition of the rights to produce generic forms of Amgen's filgrastim and pegfilgrastim (used to prevent infections of patients undergoing chemotherapy), and its prior 2006 acquisition of the biotech firm GlycoFi with its humanized yeast platform.

'Big Generics' – Examples:

a. *Teva* (Israel) (2009)
First filed a biosimilars application for neutroval, a biosimilar form of Amgen's filgrastim and neupogen, which stimulates white blood cells, and pursued work on a biosimilar version of Genetech's rituxan. USFDA accepted the application in Feb. 2010.

b. *Hospira* (U.S.) (2010)
Announced that its clinical trials entered into Phase I for erythropoietin (EPO), its biosimilar form of Amgen's Epogen, during July 2010. During January 2012, announced it had enrolled its first patient in EPO clinical Phase III testing program.

c. *Sandoz (generic arm of Novartis)* (Switzerland) (2010)
Announced its increasing capacity in biomanufacturing and its decision to pursue biosimilars applications for U.S. biosimilars launches. Has positive track record with Omnitrope (recombinant human growth hormone) – THE 1st biosimilar approved in EU & U.S. Also has Zarzio and Binocrit biosimilar forms of Amgen's figrastim and Johnson & Johnson's epoetin alfa in EU market. Had a Phase II trial in place for its biosimilar form of Genentech's Rituxan.

c. *Celltrion* (South Korea)
Initiated clinical trials of CT-P13, its biosimilar form of Genentech's Rituxan.

d. *Dr. Reddy's* (India); *Cipla, Wockhardt* (India); *Shandong Xinhua Pharmaceutical Group* (China)

B. Follow 'Big Pharma' & 'Big Generics' Leaders and Form Cross-Industry & Cross-Border Bio-Betters & Biosimilars Development, Manufacturing, & Commercialization Collaborations?

1. Examples:

a. *Teva* (Israel)/*Lonza Group* (Switzerland) (2009)
Agreed to jointly develop, manufacture and sell **biosimilars**, following Teva's 2009 acquisition of CoGenesys to establish a biosimilars platform. Teva is known for its R&D and production capabilities, while Lonza Group is recognized as one of the largest producers of active pharmaceutical ingredients (APIs) for biologics. Teva publicly acknowledged that despite the size of the prospective market,

biosimilars development is long and risky proposition, considering the regulatory uncertainties, high entry barriers, including the complexity of developing and producing the drugs, and the high cost. This JV set into motion a number of competing JVs toward the end of 2011, considering that patents for biological drugs with $54 billion in aggregate sales are due to expire by 2020.

b. *Baxter Int'l* (U.S.)/ *Momenta Pharmaceuticals* (U.S.) (2011)
Will work together to develop **biosimilars** to treat cancer and autoimmune deficiencies. Momenta receives payments upfront and upon meeting development milestones, as well as, royalties with a profit-share option on four drugs, for which Baxter will cover clinical trials, manufacturing and commercialization costs.

c. *Merck BioVentures* (MBV) (U.S.)/*Paraxel* (U.S.) (2011)
MBV and Paraxel CRO will jointly develop **bio-betters** and biosimilars. Paraxel will establish a unit dedicated to MBV joint activities.

d. *Merck* (U.S.)/*MedImmune* (U.S.) (2011)
Entered into a 15-yr mfg. capacity-sharing agmnt using MedImmune's MD factory which had already been making **biosimilars** for Merck.

e. *Samsung* (South Korea)/*Quintiles* (U.S.) (2011)
3 Samsung units entered into strategic JV with Quintiles CRO, pursuant to which a biopharma mfg. plant would be constructed in the Incheon Free Economic Zone in Songo, Incheon, South Korea to provide biopharma contract mfg. services.

f. *Biogen Idec* (U.S.)/*Samsung Biologics Co.* (South Korea) (2011)
JV established to develop **biosimilars** for multiple sclerosis, building on Samsung/Quintiles agmnt. Biogen already has significant mfg. presence in North Carolina, U.S.

g. *Gedeon Richter* (Hungary)/*Stada* (Germany) (2011)
Stada secured non-exclusive distribution rights for Gedeon Richter-developed **biosimilar** forms of Idec Pharmaceutical's rituximab and trastuzumab in Europe and Commonwealth of Independent States (CIS), excluding Russia.

C. Pursue Collaborations Specifically Focused on Development of Biosimilar Monoclonal Antibodies for Treatment of Cancers and Immune Deficiencies (mAbs)?

1. Biosimilar Therapeutic Monoclonal Antibodies ('mAbs') Are Deemed High Value Biologics

    a. High ROI Expected from mAbs Focus on Oncology and Immune Deficiency Therapies;

    b. 57 mAb biosimilar candidates are currently in development versus only 46 therapeutic protein candidates.

2. Two Examples

    a. Rituxan (rituximab) (non-Hodgkins lymphoma, lymphocytic leukemia, rheumatoid arthritis);

    b. Herceptin (trastuzumab) (metastatic breast cancer)

3. Collaboration for Development of Biosimilar mAbs is Highly Recommended

    a. Small firms specialize in biosimilar development; Big pharma/biotech have resources to run trials, submit filings, and market drugs; CROs/consulting firms have expertise in clinical trials planning/execution & regulatory strategy.

    b. *Roche* (Switzerland)/*Emsure Pharmaceuticals* (USA) *(subsidiary of Emcure Pharmaceuticals Ltd., India*
    Emcure to manufacture/distribute Herceptin & MabThera for Indian market.

    c. *Xencor*, Inc. (U.S.)/*Boehringer Ingelheim* (Germany)
    Xencor proprietary protein design automation platform to be used for bio-better mAbs. Xencor covers pre-clinical & clinical studies & retains commercial right to produce. Boehringer to provide all mfg. & product supply from pre-clinical thru Phase I trials, and holds mfg. rights to supply clinical & commercial material if go beyond Phase I.

    d. *Merck BioVentures (MBV)* (U.S.)/*Hanwa Chemical* (South Korea)
    Merck to clinically develop & commercialize globally Hanwa's biosimilar version of Roche's Enbrel mAb, exclusively licensed to Amgen, approved for RA, psoriasis. BUT, Amgen awarded patent for a fusion protein it incorporated w/in Enbrel, which can block biosimilar development. It places value of MBV agreement into question.

    e. *Amgen* (U.S.)/*Watson Pharmaceutical, Inc.* (U.S.)

Joint agmnt to build biosimilars business focused on mAbs. Amgen will assume lead in R&D, mfg., initial commercialization. Watson will contribute almost one half billion dollars and commercialization, life cycle mgmt. expertise.

f. *Mabxience* (*biosimilar division of Chemo*) (Switzerland)/*NATCO Pharma Ltd.*, (India)
NATCO will test, file dossier registrations, secure market authorizations, manufacture and commercialize in India and other Asian countries, 3 Chemo biosimilar mAbs in oncology segment (trastuzumab, bevacizumab, rituximab) and 1 chemo biosimilar mAb in autoimmune segment (etanercept).

f. *Celltrion* (South Korea)/*Hospira* (U.S.)

Hospira will distribute 8 Celltrion biosimilar mAbs in the U.S., Europe, Australia, New Zealand and Canada when biologic patents expire. (Celltrion developed/developing biosimilars for Remicade & Herceptin, and rituximab, trastuzumab, infliximab). **Hospira has U.S. mfg. capacity b/c of prior acquisition of biosimilar filgramstim**.

g. *Celltrion* (South Korea/*Egis* (Hungary)

Egis to distribute/market 8 Celltrion biosimilars, focusing on treatment of oncology, autoimmune & inflammatory diseases, in 5 Commonwealth of Independent States (CIS) including Russia. Celltrion to use Egis' distribution in 12 other countries of Central & Eastern Europe (CEE).

h. *Celltrion & Celltrion Healthcare* (South Korea)/*Hikma* (Jordan)
Hikma to distribute/market, under Hikma brand, 9 Celltrion biosimilars in Middle East/North Africa (MENA) markets. Hikma has ability to jointly develop & manufacture for supply in MENA region.

D. Exploit Biosimilars, Invest in Innovation and Learn From the Mistakes of 'Big Pharma' and 'Big' Generics?

1. Biosimilars Market Predicted to Suffer Setback After 2020

a. Fewer new biologics with large sale potential going off patent.

b. Many new competitors will enter market and force prices/profits down.

2. Prudence Dictates That Biosimilars Companies Find a Path Towards Innovation – Consider one or more of possible options:

   a. Aggressively in-license & acquire technologies // do NOT attempt to invent everything;

   b. Adopt global mindset – look far and wide for investments;

   c. Invest in and in-license novel methods of antibody production;

   d. Pursue bio-betters cautiously – even the market leaders have not been able to create viable bio-betters.

   e. If have large mfg. capacity, consider becoming a contract mfg. organization (CMO) to produce antibodies for other companies.

E. Seek Investors to Help Fund Product Development and Secure Licensing of 'Specialized' 'Bio-betters' and/or Biosimilars?

1. Seek Drug Development Partnerships With 'Big Pharma'?

   a. *Biogen Idec* (U.S.)/ *Stromedix, Inc.* (U.S.)
   Biogen providing funding of Stromedix mAb re: fibrotic disease, making payments upfront and upon meeting development/approval milestones.

   b. *Biogen Idec* (U.S.)/ *Isis Pharmaceuticals* (U.S.)
   Biogen providing funding for Isis spinal muscular atrophy treatment, making payments upfront and upon meeting development/approval milestones. Holds exclusive worldwide commercialization option with payment of license fees.

   c. *Biogen Idec* (U.S./*Portola Pharmaceuticals* (U.S.)
   Biogen providing funding for Portola's oral inhibitor (autoimmune) program for rheumatoid arthritis and lupus, making payments upfront and upon meeting development/approval milestones. Holds exclusive worldwide license to co-develop oral pills and Portola equity stake.

   d. *Merck* (U.S.)/*Exelixis* (U.S.)
   Merck providing funding for Exelixis' preclinical delta inhibitor and related compounds, making payments upfront and upon meeting development/approval milestones for multiple indications. Holds exclusive worldwide license to delta R&D program.

2. Seek Development and Commercialization Funding from Venture Capital Firms?

   a. *Itero Pharmaceuticals, Inc.* (U.S.)
   Backed by Panorama Capital, SV Life Sciences and VentureEast to develop biosimilars and bio-betters. During July 2010, licensed a biosimilar for treatment of female infertility to *Watson Pharmaceuticals*.

   b. *Femta Pharmaceuticals, Inc*. (U.S.)
   Backed by Latterell Venture Partners and BioAtla, LLC to develop/license therapeutic mAbs having application in areas of inflammation, autoimmune disease & oncology. BioAtla, LLC, a protein/engineering company, offering R&D and mfg. services, developed Fetma's initial drug pipeline. Femta looking at bio-betters.

   c. *PolyTherics Ltd*. (UK)
   Backed by Imperial Innovations Group, Capital Fund Longbow Capital to provide improved solutions (targeted modifications) to protein and peptide-based drugs via a proprietary platform. Developing two bio-betters for clinical development out-licensing & commercialization. In 2010, development/commercialization license with Celtic Pharma (Bermuda); In 2012, acquired Warwick Effect Polymers (UK) with protein modification platform.

3. Seek Development and Commercialization Funding from Non-Conventional Sources Such as Islamic Financial Institutions?

   a. *See* Lawrence A. Kogan, *Gauging The Opportunities and Challenges Surrounding Shariah-Compliant Technology-Related IP Financing*©, Presentation Delivered at the 22nd Annual Meeting & Conference of the Inter-Pacific Bar Association, "Legal Trends, Thoughts and Times" (March 2, 2012), accessible online at: accessible at:
http://www.itssd.org/Gauging%20The%20Opportunities%20and%20Challenges%20Surrounding%20Shariah-Compliant%20Technology-Related%20IP%20Financing%20-%20IPBA-KLG-New%20Delhi%20(2012).doc