# GENERIC DRUGS AND BIOSIMILARS

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# Background

- Biologics have shown huge potential in **curing the unmet demand of small drug molecules.**
- The pharmaceutical industry has placed an **increased emphasis** on developing **biopharmaceutical-based drugs** (biologics)
- The global biologics market is expected to reach $220 billion by 2019.
- By 2020, **patents on several biologics** with global sales of more than US$67 billion **will expire**.
- Biosimilars or “similar biologics” are expected to become an **important economic and therapeutic driver of the Indian pharmaceutical market.**
- Biosimilars offer **new therapeutic options** with the **potential for cost savings** to the healthcare system.

# Generic Drugs and Biosimilars

**Generic Drug:**

- "a drug product that is comparable to a brand/reference listed drug product in dosage form, strength, quality and performance characteristics, and intended use."

**Biosimilar/Similar Biologic**

- "A biological product/drug produced by genetic engineering techniques and claimed to be 'similar' in terms of safety, efficacy and quality to a reference biologic, which has been granted a marketing authorization in India by the Drug Controller General of India (DCGI) on the basis of a complete dossier, and with a history of safe use in India." (-Indian Draft Guidelines)

# Generic Drugs and Biosimilars

**“reference biologic” (an innovator product)**

- “A comparator biological product/drug used for head-to-head comparability studies with a similar biologic in order to show **similarity in terms of safety, efficacy and quality.** Only a biological product that was licensed on the basis of a full registration dossier can serve as reference biologic.”

**Important Considerations**

- A similar biologic can only be developed against a **licensed reference biologic** that has been approved using a complete data package in India.
- However, if a reference biologic is not authorized in India, it must have been licensed and widely marketed for at least four years (post-marketing) with significant safety and efficacy data in a country with an established regulatory framework.
- Nonetheless, this four year period can be waived or reduced in the event that no medicine or palliative therapy is available or in the event of a national healthcare emergency.

# Generic Drugs and Biosimilars

**Other Considerations**

- The rationale for the choice of the reference biologic should be provided by the manufacturer of the similar biologic in the submissions to DBT and CDSCO.
- A similar biologic cannot be used as a reference biologic.
- The reference biologic must be used in all comparability testing.
- The dosage form, strength and route of administration of the similar biologic must be the same as that of the reference biologic.
- The active ingredient of the reference biologic and the similar biologic must be shown to be similar.

# Generic Drugs and Biosimilars

**Comparison**

- Biologics are 200 to 1,000 times the size of a small molecule (generic) drug, and far more **structurally complex**.
- Biologics and biosimilars are **manufactured in living cells**, then **extracted and purified,** whereas small molecule drugs and generics are manufactured purely via chemical synthesis.
- Given the complexities attached to biologics and biosimilaes regulatory authorities have outlined **robust data requirements to demonstrate similarity**
- Biosimilar manufacturers will **generally need to generate data from lab testing, non-clinical testing and clinical testing** to show that the biosimilar they have developed will provide the same therapeutic benefit and risks to patients as the reference product.
- Because the **cost to develop and manufacture biosimilars**, particularly high-quality biosimilars, is **considerably higher than for small molecule generics**, cost reductions are expected to be more modest for biosimilars than what is sometimes realized for small molecule generics.

# Generic Drugs and Biosimilars

| PROPERTIES | GENERICS | BIOSIMILARS |
|---|---|---|
| SIZE | Small | Large |
| MOLECULAR WEIGHT | <500-900 Daltons | 4000 to >140,000 Daltons |
| STRUCTURE | Simple and well-defined | Complex with potential structural variations |
| MANUFACTURING | Predictable chemical process to make identical copy | Specialized biological process to make similar copy |
| COMPLEXITY | Easy to fully characterize | Difficult to characterize due to heterogeneity |
| STABILITY | Relatively stable | Sensitive to storage and handling conditions |
| ADVERSE IMMUNE REACTION | Lower potential | Higher potential |
| MANUFACTURING QUALITY TESTS | ≤ 50 | ≥ 250 |
| APPROVAL REQUIREMENTS | Small clinical trials in healthy volunteers | Large clinical trials in patients |

Source: Amgen Biosimilars

# Variance in Uses and Effects

- Biosimilars may have **different uses** - for new patients, for existing patients, and potentially for pharmacy-level substitution
- Each biosimilar will **differ in terms of product label**, including **relevant pharmacology and clinical data,** which will be influential in guiding correct use of biosimilars.
- Based on the nature and extent of totality of evidence, some biosimilars may be approved **for all diseases** that the reference product is approved for while other biosimilars may be approved **only for the disease for which it was tested in clinical trials** or a subset of the reference product indications of use
- Biologic medicines have the potential to **present unique risks** when switched back and forth
- It is imperative for healthcare providers to understand key aspects of each biosimilar, including functional data and/or clinical data to make a choice whether to 1. **initiate a new patient**, 2. **transition a stable patient**, or 3. **support automatic substitution to a biosimilar**.

# Biosimilars-Patent Landscape

**Patent Strategy**

- The goal of the biosimilar applicant in developing its biological product is thus **to design around patent claims of the RP sponsor**
- The patent strategy of the reference product (RP) sponsor, on the other hand, is **to craft claims that capture not only the reference product itself but the entire biosimilar landscape**.
- Secondary patents, including those that cover variations in product, combination therapies, second and subsequent indications, new routes of administration, formulations, manufacturing processes, expression systems, diagnostic and pharmacologic assays, and underlying research tools and platform technologies accordingly have acquired added significance in the context of biosimilars.

# Biosimilars-Patent Landscape

**The Disclosure Issue**

- When drugs made by engineered organisms go off patent, **it isn't easy for other companies to start making a generic version.** For one thing, there is no legal requirement for the patent holder to give his engineered organism to anyone else.
- Other companies will have to try to replicate the engineered organism, and because the **patents do not fully describe the organism** (**some deliberate obfuscation to protect profits is involved**), they will not wind up with a perfect copy.
- In favourable circumstances other companies would be **able to reproduce the most salient features of the engineered organism** and the resulting active ingredients would have equivalent effects on patients.
- In recognition of the fact that there is inherently **more variation when trying to replicate a formerly-patented drug made by an engineered organism than for drugs made by chemical synthesis**, there is the use the term "biosimilar" instead of just "generic."

# Biosimilars-Patent Landscape

**Are Biosimilars Patentable?**

- Given the substantial variance in the manufacturing process and significant variance in structure, enhanced efficacy or improved products they may qualify for patents (in the light of novelty and inventive step including criterion set by Sec. 3(d))
- Patenting biosimilars before the expiration of the original patent might raise several questions for the original manufacturer as well as the biosimilar manufacturer.
- The original manufacturer draft the original patent in a way that provides protection against a wide range of similar products
- The biosimilar manufacturer tries to ensure that the similar product is new and inventive to make it patent eligible
- However, **in the absence of case law** both manufactures are somewhat in an unclear and ambiguous situation when it comes to **estimate the scope of claims of biopharmaceuticals**

# Regulatory Pathway for Biosimilars

- Biosimilars present more challenges than conventional generics and thus marketing approval is also **more complicated**.
- The **overall risk is modest** with biosimilars, but regulatory pathways are required because of **structural complexity, manufacturing process and risk for immunogenicity**.
- India being one of the most preferred manufacturing destinations of biosimilars, issued "**Draft Guidelines on Similar Biologics"** in June 2012
- The Indian guidelines on similar biologics address the **pre-marketing and post-marketing regulatory requirement** (i.e., "comparability exercise"), and also address the requirements related to manufacturing process and quality control.
- Recently, on **27th June, 2016**, these guidelines were revised by CDSCO and Union Health Ministry so as to enhance and improve the journey of the regulatory pathway for their marketing authorization in the country.

# Regulatory Pathway for Biosimilars

- As per the latest guidelines, the reference biologic used to compare the biosimilar needs to be licensed in a country that has adopted the technical requirements for pharmaceuticals for human use which are prescribed by **the International Council for Harmonization (ICH)**, in case it is not marketed/ licensed in India.
- As per Draft Guidelines, Phase III trials on biosimilars should include minimum 100 patients for evaluation, whereas Phase IV trials need at least 200 evaluable patients.
- In case of **biosimilars used to treat orphan or severe diseases** and the **disease with limited therapeutic options**, the Draft Guidelines allows to conduct clinical trial on a smaller population size.
- The Draft Guidelines are published to make the process for marketing approval in India smoother and simpler for the journey of a biosimilar in India

# Regulatory Pathway for Biosimilars

- **The Review Committee on Genetic Manipulation** of the Genetic Engineering Approval Committee (GEAC) with the permission of DCGI, approve clinical trials to be conducted in India related to biosimilar therapeutic products.
- The biosimilar has to demonstrate comparable data of non-clinical studies viz., pharmacokinetics and toxicology (safety pharmacology, reproduction toxicology, mutagenecity and carcinogenicity) and clinical studies (efficacy and tolerability for each indication) before it gets approval for all indication of the reference medicine
- There is need to use well-designed clinical trials to establish biosimilarity. **The challenge with biosimilars is to know the differences which matter clinically**. The specific product given to the patient should be clearly identified.

# Herceptin Episode: Regulatory Puzzle

- Swiss pharmaceutical giant Roche's Trastuzumab is a biological drug used primarily for treatment of HER 2 positive breast cancer. In India, Trastuzumab is sold under the brand names Herceptin®, Herclon™ and Biceltis®.
- Indian drug maker Biocon, in partnership with the US-based generic drug maker Mylan Pharmaceuticals, have come up with products which they argue is "biosimilar," that is, a biological product that is highly similar but not same as the original biological product, i.e. the "biologics."
- Roche took the matter to court. A legal battle has been going on since 2014.
- "Based on Roche's plea, the Delhi High Court on April 28, 2016 maintained that the approvals to Biocon's CanmaB AND Mylan's Hertraz were **'not on the basis of the adherence of the guidelines' and 'rules framed under the Drug Act,'**
- The Delhi High Court Division Bench on April 28, 2016, has directed, that the position as prevailing till 24th April 2016 (i.e. before passing of the 25th April judgment by the Single Judge Bench) shall continue to operate till the next date of hearing.

# Important Questions

Whether Indian Patent System provides a viable mechanism for Biosimilars?

Does it creates the possibility for patentability of Biosimilars?

Is Section 3 (d) an impediment in ensuring the patentability of biologics?

Does the research ecosystem in India is efficient enough to promote biologics?

Is the regulatory fora for biologics meets the need?

# Conclusion

Thank YOU