National Centre for Biotechnology Information estimates that Biologic drugs having sales of over $100 Billion will loose patent by 2020.[1]

Over 3107 companies in the race to develop bio similar! *

Will every developer be able to get hold of Comparators to prove “Similarity” of their product to innovators from SRA markets such as US / EU ?

Don’t let comparator drug derail your Billion Dollar Dreams!

Lets BUST some myths about sourcing from Emerging markets to maintain your development pipeline……

WHITE PAPER

LITTLE KNOWN FACTS ABOUT COMPARATOR SOURCING FROM EMERGING MARKETS AND ASSOCIATED TIME AND COST SAVINGS.

BY

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Disclaimer : Information within this paper is based on authors experience and expertise. The paper represents the views of the author for training and workshop and not that of the company.

Facts:

Several Block buster Biologic drugs are going off patent by 2020 as per reports in public domain.

Biologics are extremely complex to manufacture.[2]

For example: If Aspirin is made of 21 atoms, a biologic drug Enbrel® is made up of over 20,000 atoms.

Every biological product displays a certain degree of variability, even between different batches of the same product, which is due to the biological expression system and the manufacturing process.[3]

Even minor changes in the production process have to be reported to the national health authorities and approved by them.

For example, Genzyme opened a new large plant in an attempt to produce Myozyme (alglucosidase alfa), but the FDA did not consider the product in the new plant to be the same as Myozyme.[4]

Instead, Genzyme had to get approval from the FDA through a BLA (Biologic licensing application) for an entirely new biologic, Lumizyme (alglucosidase alfa), which was produced at the new plant. This resulted in a better biologic with new exclusivity.[5]

Current Status:

Comparators are an integral part of the development process for a Biosimilar product.

Comparator sourcing has become an “Achilles Heel” in biosimilar development process due to:

a) Comparator is the only component which is not under developers / sponsors control, its a third party product for which the development has to reply on others for procurement.

b) As competition to develop Biosimilar has increased, there are now 100s of companies all competing against each other for comparator stocks.

Over 3700 developers worldwide are trying to develop over 1307 Biosimilar candidates. In Phase I trial alone a minimum of 400 units of comparator drug is required to be tested on healthy patients against the Biosimilar under development. This takes the demand to 1307 x 400 = 522,800 units of Innovator drug in Phase I trails alone!

Can US / EU markets alone supply such quantities ??

Historically biosilimar development is full of stories about trials getting stuck, delayed, abandoned due to non-availability of comparators.

Regulatory Senario

At the core of Comparator sourcing are two words with different interpretations which lead to confusion and cost escalation: **“Sourced” and “Licensed”**

Let’s examine the **Difference between “Sourced” and “Licensed”. To the Dictionary:**

source

sɔːs/ verb: past tense: sourced; past participle: sourced

obtain from a particular source.

"each type of coffee is sourced from one country

licensed

ˈlʌɪs(ə)nst/ adjective: licensed;

having an offical licence.

"a licensed taxi operator”

Term used in guidelines issued by NHAs is “Sourced” from SRA (Stringent Regulatory Authority) markets. These are defied as North America, EU, Australia. For the purpose of this paper we will refer to US / EU as SRA countries.

The confusion occurs because we the industry **interpret** “Sourced from” **as** “Licensed in” SRA countries.

Since comparator sourcing is largely an outsourced activity done by CROs, Sponsors are unable to pass on industry specificknowledge such as the ‘product registration process’, CTD dossiers or the role of CPP or CoPP (Certificte of Pharmaceutical Product) nor the enormous amount of effort that goes into product registration to their outsourcing partners.

Sourced can mean Manufactured or Originate in SRA country.

While licensed means “for sale in the pharmacies” of a particular country.

Working Example:

In order to explain this difference better lets consider the following example for Rituximab.

Rituximab is manufactured by Roche Diagnostics in Germany and sold in Global markets including India under various brand names by Hoffman LA Roche.

In the EU, it’s marketed as “MabThera®”, while in India it’s marketed as “Ristova®”

In order for Roche to market it’s product in India it will have to undergo a process called “Product registration” at the Indian NHA called CDSCO (Central Drug Standards Control Organisation)

Product registration is a process followed by NHAs to obtain all Administrative, Non Clinical, Clinical, CMC and QSE details about the company and the product before granting marketing authorisation within their territory.

These registration requirements are commonly fulfiled in a CTD dossier / eCTD format.
CTD dossier normally has 5 modules - refer to **CTD triangle below.**

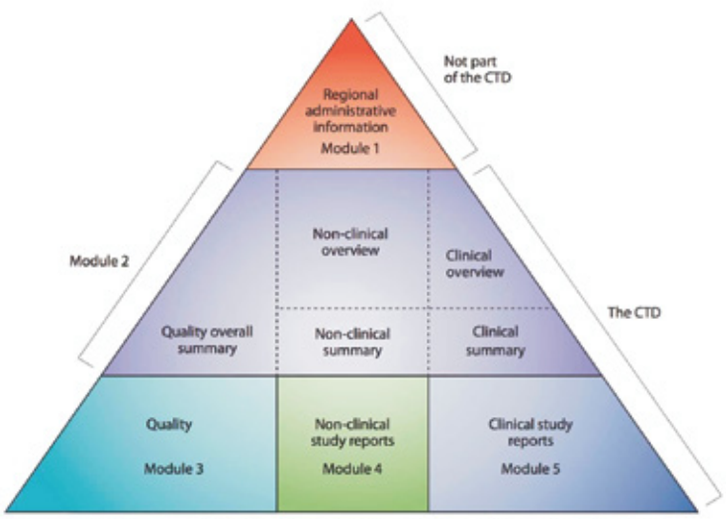
Module 1 - General Information:

One of the requirement of this module is for certificte called: CPP (Certificte of Pharmaceutical Product). CPP is a certificte developed under WHO Certifiction scheme in 1975 and most recently revised in 1997.

Detailed information can be read here : http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certifiction/guidelines/en/

CPP requirement as adopted by Indian NHA - CDSCO here : http://www.cdsco.nic.in/writereaddata/Guidance%20documents.pdf

CTD Triangle



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

CPP is a mandatory certificte in all CTD dossiers and is taken as a proof of QSE (Quality, Safety and Efficcy) of the product and also as an evidence of GMP.

In case CPP is missing, the manufacturer has to undertake Clinical validation, Safety, Efficcy studies in destination market as well as the manufacturing facility will have to be inspected by the inspectors form the NHA in order to obtain marketing authorisation. This means additional Population Trial cost in Destination market and Arduous Inspection process at the plant.

The presence of CPP helps cut down registration time by bypassing Population trials, plant inspection and assuring the destination NHA: that the product being registered in RoW / Emerging markets has the same QSE profie as the one in Origin.

Upon satisfactory scrutiny of the CTD dossier by the NHA, Marketing authorisation is granted.

So before reaching Emerging Markets - The Innovator drug has proved to NHAs that it's the same drug in origin and destination.

Considering the "Facts" stated in beginning of this paper, do you think it makes commercial sense for a manufacturer to have:

a) Multiple Biologic manufacturing facility for the same product ? OR One for SRA countries and another for Emerging markets ?

b) Keeping in mind the complex manufacturing process, inability to control inherent variations and associated approval process with their NHA for even minor process changes, do you think the manufacturer will alter the manufacturing process, product structure, quality, specifiction to differentiate the product in SRA country as compared to an Emerging market due to different selling prices ?

Commercial Facts:

Cost of branded Rituximab 500mg in Germany is about 3600 Euros / vial while in India it's 1100 Euros. Due to differential pricing policy adopted by all manufacturer globally.

For a Bio-similar development process where comparator cost constitutes over 20% of the cost, this can mean considerable cost savings and shorter time to market due to ease of availability of comparators from Emerging markets as compared to SRA markets.

Regulators are looking for comparator which come from the same site as the reference innovator.

Origin of a comparator can be easily proven by inspecting: product pack, leafet, SPC and information available on NHA's website.

So is there any difference in drugs "Sourced" from Germany as compared to "Licensed" in Germany ?

Answer : No and Yes

NO: There's NO difference.

The registration process involving CTD dossiers are pretty cumbersome and thorough.

The process is designed to pick out variations and differences and every submission has to be Legalised, Notarised, Apostille, etc….

Any variations, result's in deficencies letters, rejection or even inspections. Manufacturers are very careful to avoid these and follow a principle of **One product One Dossier.**

Products specially Biologics and large molecules involving complicated manufacturing process come from a common site and are marketed world wide.

YES: Yes, the difference is in their labelling, box warnings and Pack language.

A product licensed in SRA will be a country specificpack.

The pack will be in local language - for the example used above it will be a German pack

Will carry German PZN number and any warning or specificinstructions mandated by German regulator at the time of granting Marketing authorisation.

Advantages of sourcing from Emerging markets.

Key advantages :

1. Price: Pharma majors follow a differential pricing strategy in SRA and Emerging markets - this can be used to the advantage of the developer

2. Quantity: Quantities of 500s, 1000s etc… are easily available in Emerging markets such as India as compared to SRA markets due larger population pool.

3. Batches: Multiple batches / Single batches requirements are easier to meet them from Emerging markets as compared to SRA markets.

Conclusion:

The difference between Sourced and Licensed is clear.

“Sourced” can be manufactured in SRA country but also sold in other Emerging markets - it does not loose it’s QSE or GMP parameters merely by the fact that it’s sold in Emerging markets.

To be able to sell in Emerging marketed the product has undergone a thorough administrative scrutiny to ensure that product is same in Origin and Destination.

While “Licensed” is a country specificpack, meant for “ **A**” particular market.

Concerns:
Such as counterfeit, Pedigree, Supply chain integrity, GDP compliance etc… can be effectively addressed by working with Qualifid wholesalers such as GNH India, who are among very few from India to be certifid by SGS France for their WHO GDP practise.

Meet us at the PCT loft 21 - GNH India

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* References are maintained by the author and can be obtained by contacting him

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OUTSTANDING EXPORTS AWARD

WHAT MAKES US UNIQUE

- Global Full line Pharmaceutical wholesaler
- 1,35,000 Product Lines
- Shipping to over 180 countries

ADVANTAGES

- Direct manufacturer's billing
- Shortest pedigree trail to manufacturer
- CoA, CoO, TSE / BSE Certificates with Purchase
- Validated Cold chain shipping process
- WHO cGDP Certified Warhouse operations
- ISO Certified QMS

SPECIALIST IN

- Comparator suppliers
- Clinical Trial Supplies
- Parallel Lines
- Name Patient supplies
- Orphan Drugs
- Unlicenced Medicines
- Hospital Lines
- Shortage Lines
- Discontinued Lines
- MOH Tendering
- Cold chain & Controlled Ambient
- Vaccines