



Comparator Sourcing Organisation

Disclaimer: The views expressed in this presentation are that of the author based on his experience and are meant for training and workshop purpose, they do not represent the views on the company.

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Little known facts about **Sourcing** Comparators from **Emerging Markets** with Confidence

By Dr. Piyush Gupta



Facts: Biosimilar Opportunity 2020

Sects: About Biologics

Global Regulatory Pathway

Comparator Examples From Market

Key regulations governing comparator sourcing

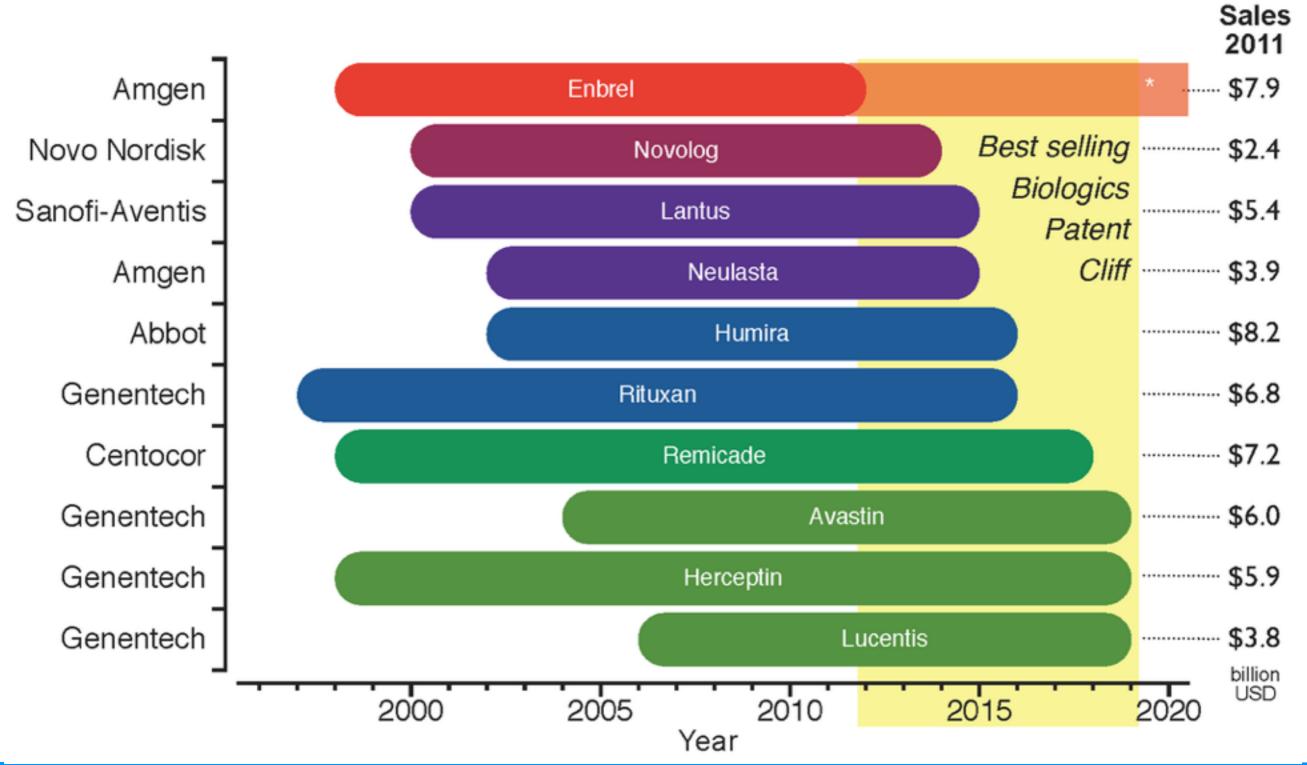
Comparator Souring Organisation - Roles and Services.



Facts: Biosimilar Opportunity 2020



Facts: Biosimilar Opportunity 2020 Patent Cliff



Calo-Fernández B, Martínez-Hurtado J (December 2012). "Biosimilars: Company Strategies to Capture Value from the Biologics Market". *Pharmaceuticals*. **5** (12): 1393–1408. doi **1**0.3390/ph5121393. PMC 3816668. PMID 24281342.

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Facts: Biosimilar Opportunity 2020 Patent Cliff

Biologic drugs with sales over \$100 billion set to loose patent by 2020.1

Over 3000 companies globally are in the race to develop Biosimilars / Biobetters

Over 1300 biosimilars candidates under development

The demand for Comparators / RLDs has been estimated at 500,000 units for phase 1 trial through Phase III trials!

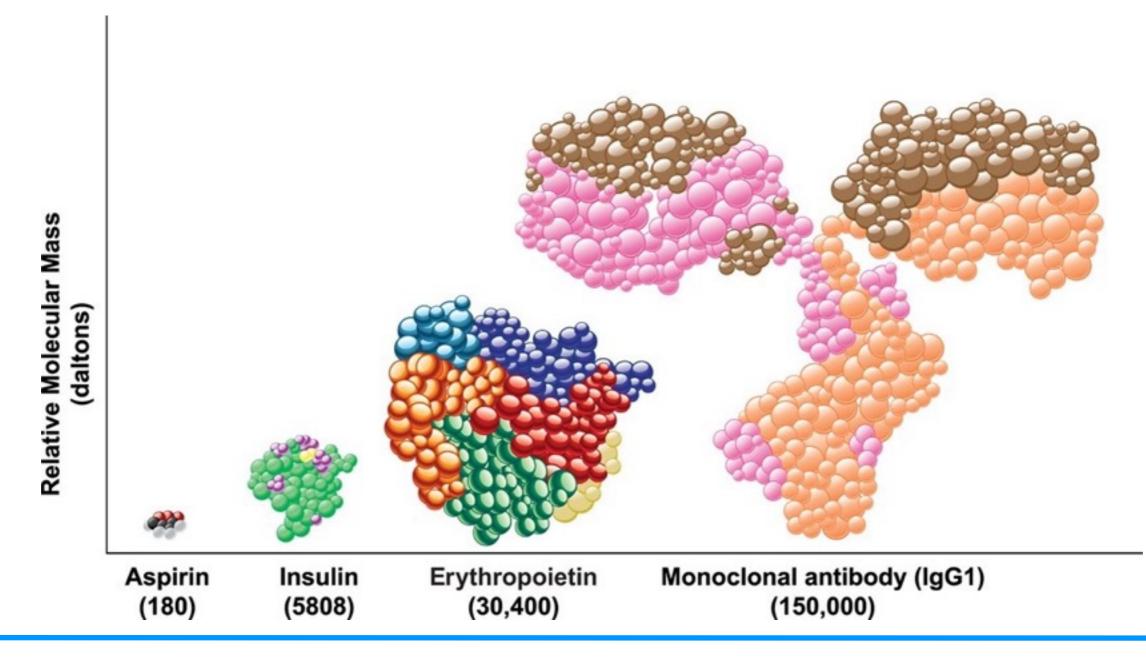


AFacts: About Biologics



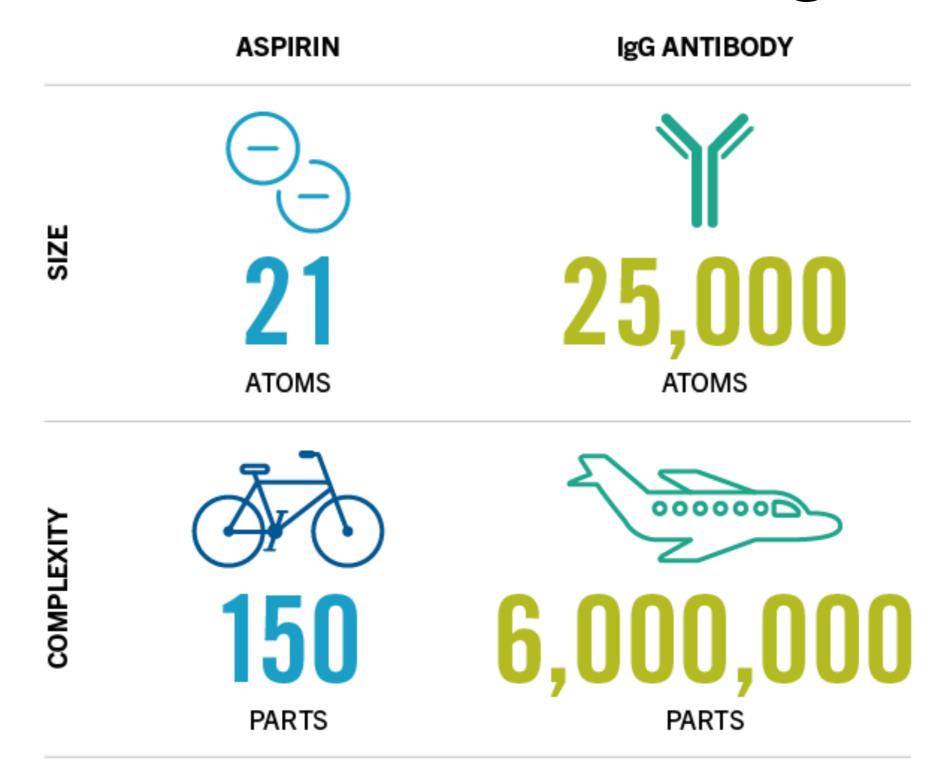
Facts: About Biologics

If Aspirin's molecular mass is 180 daltons, that of a Biologic such as mABs is more than 150,000 daltons





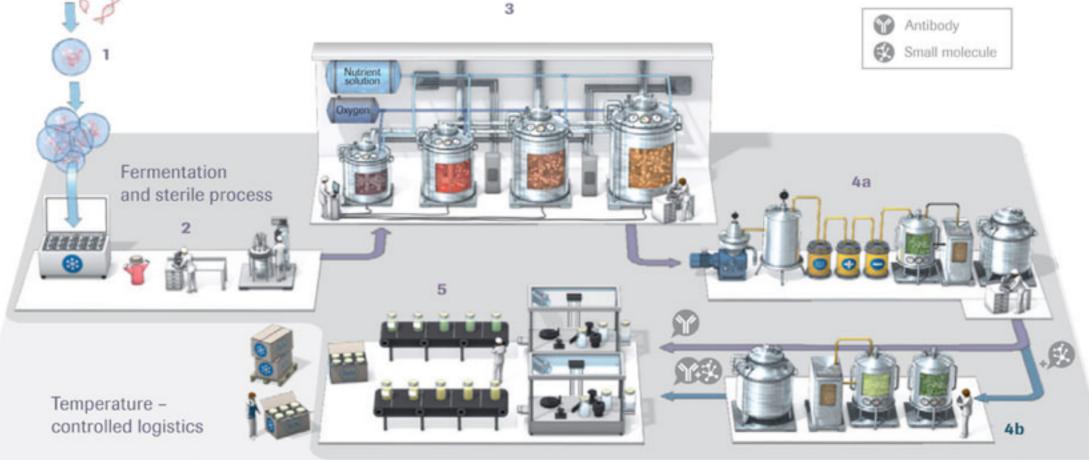
Facts: About Biologics



https://cdn.gene.com/assets/content/feature_asset_image/ 0074 How_Hard_Can_It_Be_Inline_01_sizecomplexity_1280x600_crop.png



Facts: About Biologics - complex manufacturing process



1 Cell line

Specific human genes are inserted into bacterial or mammalian cells to create a unique master cell line that yields the target antibody (biologics drug substance). This master cell bank is frozen for storage.

4a Purification

The antibody is separated from the biomass (cells, culture medium and waste products) leading to a pure solution. The centrifugation, purification and concentration steps are specific to each desired antibody.

2 Culture

For production, cells are removed from the master cell bank, cultured in a liquid growth medium and transferred to larger vessels as the cells multiply.

4b Conjugation

Additional steps for antibody-drug conjugates: The antibody is combined with a highly potent small molecule and again purified and concentrated.

3 Fermentation

The cell culture is transferred to progressively larger bioreactors. Special nutrient medium is added. Its unique composition is optimised for each cell line and enables production of the desired antibody.

5 Formulation, filling and packaging

The drug substance is formulated into a stable dosage form (sterile liquid or powder), filled into vials or syringes, and packed for shipping.



Facts : Biologic Manufacturing

Every Biologic product displays a certain degree of variability even between different batches of the same product.

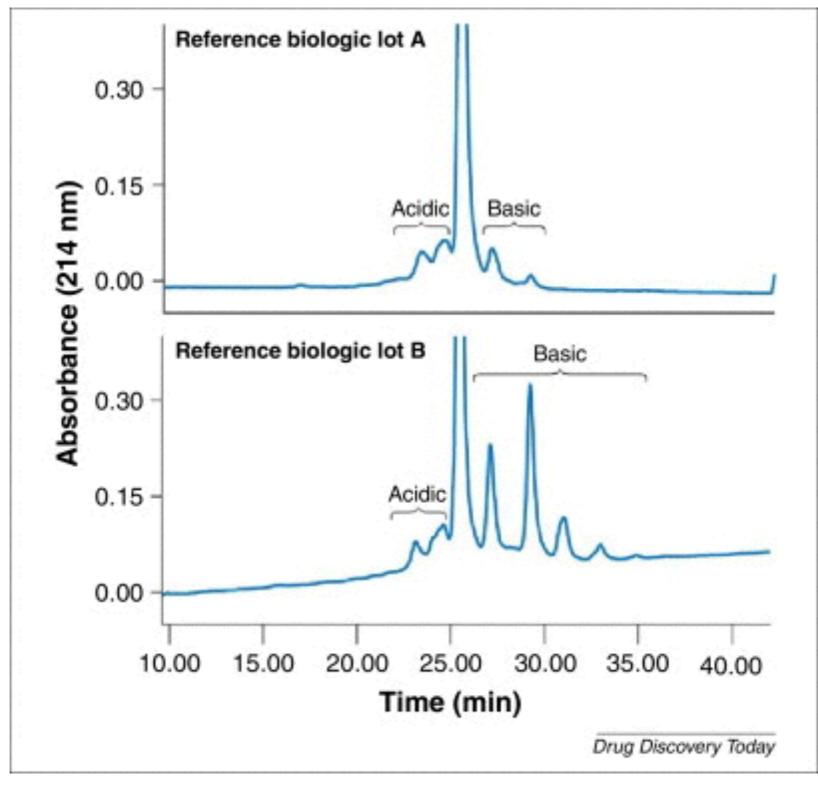
Even minor changes in production process have to approved by NHAs

SFor 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



Facts: Inherent Variability



http://biosimilars.elsevierresource.com/system/files/articles/assets/S135964461500121X/21/gr3.jpg



Global Regulatory Pathway

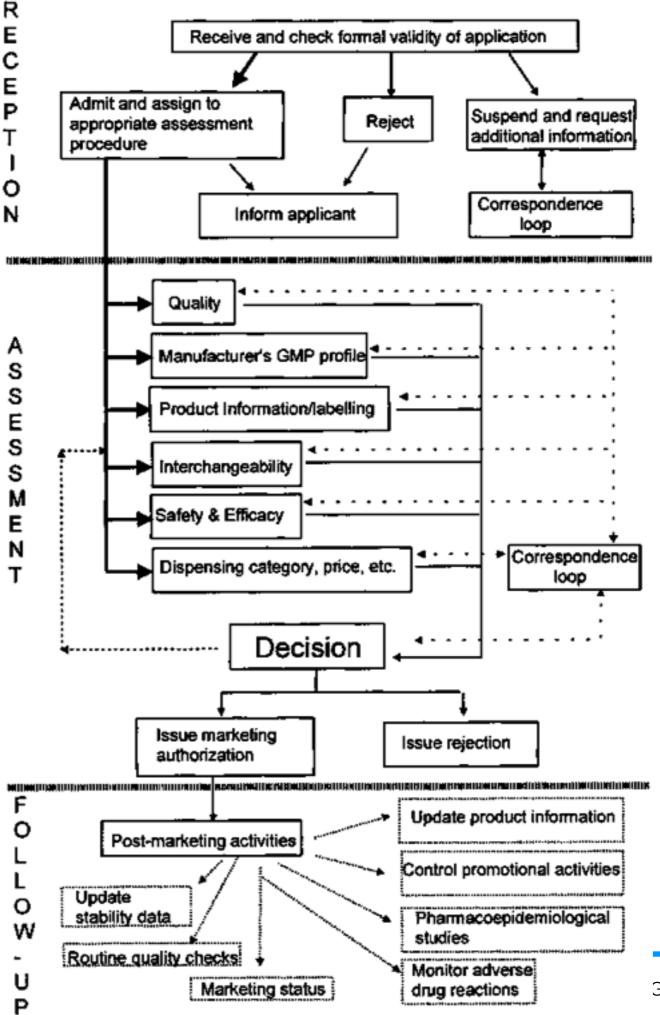


How does a Biologic travel from SRA to Emerging Market





Global Regulatory Pathway

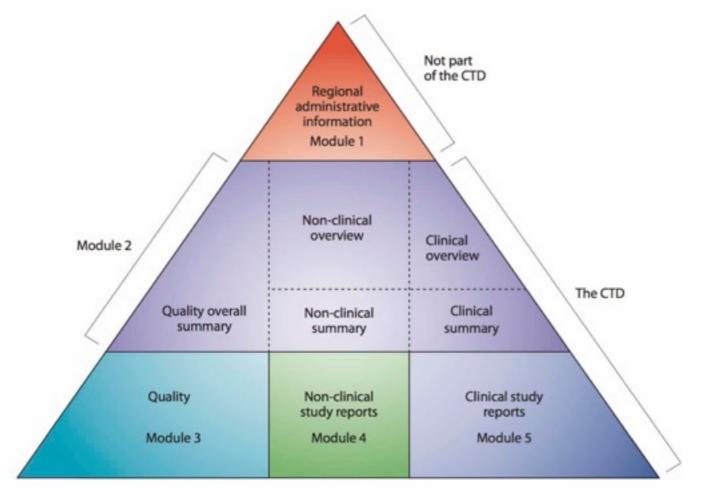


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Pathway to Emerging Markets: Product registration

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.

Module 1 - CPP and FSC



What does a CPP look like ?

	CERTIFICATE OF A PHARMACEUTICAL PRODUCT ¹
	This certificate conforms to the format recommended by the World Health Organization (Explanatory Notes and General Instructions attached)
	Exporting (certifying) country: Switzerland
	Importing (requesting country): India
	1. Proprietary name (if applicable) and dosage form:
	 a) in Switzerland: Ristova 100 mg/10 ml and 500 mg/50 ml, concentrate for solution for infusion b)* in the importing country: * not verified by the certifying authority
	 Active ingredient(s)² and amount(s) per unit dose: Complete composition including excipients is attached: X yes □ no
	Rituximab 100 mg/10 ml Rituximab 500 mg/50 ml
	1.2 Is this product licensed to be placed on the market for use in the exporting country? ³
	yes
	1.3 Is this product on the market in the exporting country?
	yes Ino, product destinated to be exported solely
	2A.1 Number of product licence ⁴ and date of issue:
	62'757 01, 02 April 17, 2012
	2A.2 Product licence holder (name and address):
	Roche Pharma (Schweiz) Ltd. Schoenmattstrasse 2 4153 Reinach, Switzerland
	2A.3 Status of licence holder ⁵ :
	C

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 Swiss Agency to Therapeutic Froducts
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 Swissmedic | Hallerstrasse 7 | Postfach | CH-3000 Bern 9 | www.swissmedic.ch | Tel. +41 31 322 02 11 | Fax +41 31 322 02 12
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Regulatory - Registration

Module 1 - General Information:

One of the most important requirement of module 1 is CPP (Certificate of Pharmaceutical Origin). CPP is a certificate developed under WHO (World Health Organisation) Certification scheme in 1975 and most recently revised in 1997.Detailed information can be read here : <u>http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/</u>

CPP requirement as adopted by Indian CDSCO: here : <u>http://www.cdsco.nic.in/writereaddata/Guidance%20documents.pdf</u>.
CPP is a mandatory certificate in all CTD dossiers and is taken as a proof of QSE (Quality, Safety and Efficacy) of the product and also as an evidence of GMP.



Comparator Examples From Market



Sourced from USA

Lymphocyte Immune Globulin, Anti-Thymocyte Globulin (Equine) Sterile Solution Atgam[®]

250 mg antibody protein (50 mg per ml)

ATTENTION—This product may contain a granular or flaky deposit; this is normal. See infusion instructions described in the enclosed package insert.

For I.V. use only (dilute before use-see package insert)

5 x 5 ml Ampoules (single use containers)

® Trademark
Proprietor: Pfizer
Enterprises SARL
Manufactured by:
Pharmacia & Upjohn
Company*
Kalamazoo, MI
49001, USA
* Division of Pfizer Inc. NY, NY 10017, USA

Imported and marketed by: Pfizer Products India Private Limited, Shree Arihant Compound, Kalher Village, Bldg.No. D7, Gala No. 2,3 & 4, Bhiwandi, Thane-421302



Authorised in USA

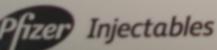
NDC 0009-7224-02 Contains 5 of NDC 0009-7224-01 Rx only

5–5 mL Ampoules (single use containers) **Atgam**[®]

lymphocyte immune globulin, anti-thymocyte globulin (equine) 50 mg/mL

ATTENTION — This product may contain a granular or flaky deposit; this is normal. See infusion instructions described in the enclosed product insert.

For I.V. use only





250 mg

protein



Sourced from France



Manufactured by: Sanofi Winthrop Industrie 1, rue de la Vierge, Ambares Et Lagrave, 33565 Carbon Blanc, Cedex- France Importer: Sanofi-Synthelabo (India) Ltd., City Link Warehousing Complex, Bldg No. 3, Gala No. 6A, S. No. 120-121, Village Vadpe, Taluka - Bhiwandi, Thane - 421302. Regd. Office: 54/A, Sir MV Road, Andheri (E), Mumbai -93, India.



Authorised in France

AXOTERE®

20 mg/1 ml

solution à diluer pour perfusion concentrate for solution for infusion

docetaxel

Perfusion intraveineuse Intravenous perfusion

sanofi aventis

Composition: Each ml of concentrate contains 20 mg docetaxel as trihydrate. One vial of 1 ml of concentrate contains 20 mg of docetaxel. Excipients: polysorbate 80, ethanol anhydrous and citric acid. Read the package leaflet before use.

Ready to add to infusion solution.

CAUTION: Withdraw the required amount of this docetaxel concentrate (20 mg/ml) from the vial and add it directly into the infusion solution. See accompanying preparation guide.

Do not store above 25°C. Store in the original package in order to protect from light. Keep out of the reach and sight of children. Single-use vial. Intravenous use. To be administered under the supervision of a physician experienced in the use of cytotoxic agents. Use immediately the medicine once added into the infusion bag. If not used immediately, in-use

storage times and conditions are the responsibility of the user and would normally not be longer than 6 hours below 25°C including the one hour infusion.



RESPECTER LES DOSES PRESCRITES/ USE THE DOSE AS PRESCRIBED

Uniquement sur ordonnance/ Prescription only medicine

Aventis Pharma S.A. 20, avenue Raymond Aron 92165 Antony Cedex / France

Fabricant / Manufacturer: Aventis Pharma Dagenham Rainham Road South Dagenham, Essex RM10 7XS / United Kingdom.



Authorised in USA

Paclitaxel (protein-bound particles) for injectable suspension

Abraxane* for Injectable Suspension



68817-134-50

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Realitaxel (protein-bound particles) for injectable suspension

Abraxane* for Injectable Suspension

100 mg Single Use Vial For I.V. Use Only

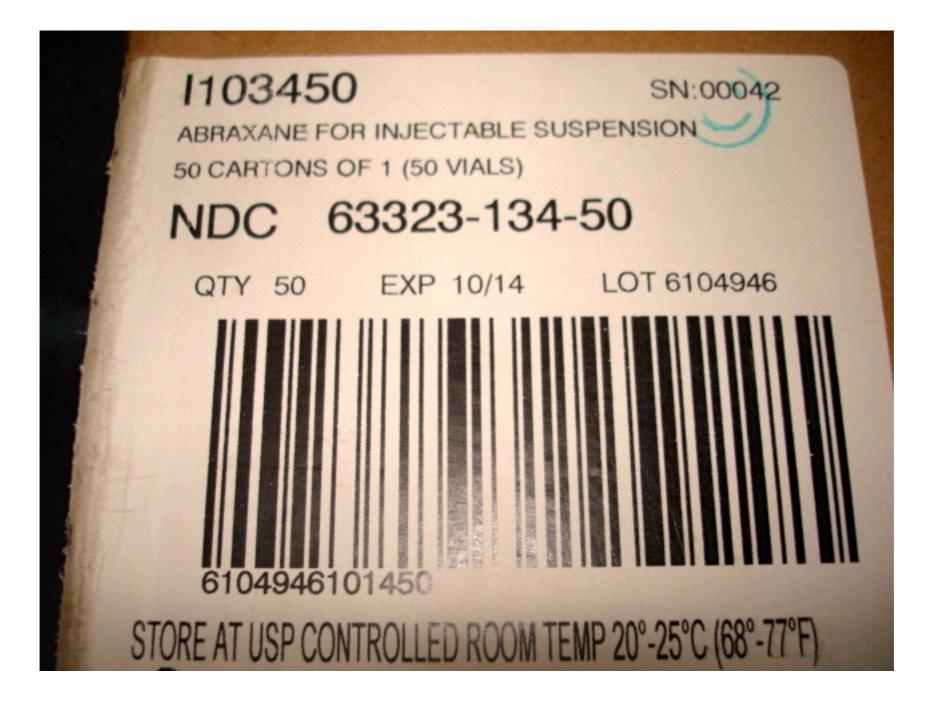
Functional properties differ from other paclitaxel products. DO NOT SUBSTITUTE.

Biocon



Authorised in USA







Taking a product from SRA to Emerging Market



Is this possible without CPP, eCTD, Registration pathway?



Key regulations governing comparator sourcing



Regulatory Senario - USA

A Important act governing Biologic and Biosimilar Trade:

Biologic price competition and innovation act. <u>http://www.fda.gov/downloads/Drugs/</u> <u>GuidanceComplianceRegulatoryInformation/</u> <u>ucm216146.pdf</u>

Over 110 reference made in this act to "Reference" product (Comparator).

Important restriction: (5) General Rules (A) - One reference product per application.



Regulatory Senario - EU

A Important act governing Biologic and Biosimilar Trade:

Suidelines on Similar Biological Medicinal product: http://www.ema.europa.eu/ docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

Section 3.2: Choice of reference product:

Restriction: "The reference medicinal product must be a medicinal product authorised in the EEA, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended"

"However, with the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials, it may be possible for an Applicant to compare the biosimilar in certain clinical studies and in in vivo nonclinical studies (where needed) with a non-EEA authorised"



Comparator Souring Organisation



CSO - Comparator Sourcing Organisation

Sourcing of Reference drugs / Comparators has become an " "Achilles Heel" of this industry.

Ask for 1000 pack - Sorry we offer only 50.

Ask for 3 batches - Sorry we have only 1 batch.

Ask for CoA - Sorry not provided.

Because Sponsors and CROs should be able to focus on trials.



CSO - Comparator Sourcing Organisation

CSO such as GNH India a specialised wholesaler of Drugs who understand the complex global regulatory frame work and can help Sponsors and CROs cut cost

We navigate the treacherous path of comparator sourcing for you, so you could **FOCUS** on Development.

A 1000 packs - Done

🔅 3 Batches - Done

CoA, CoC, Pedigree dossier, Temperature record, Recall Agreement - DONE

Ship to Timbuktu - Done

Cost effective sourcing from Emerging markets can bring this down to 5 - 10%







