GNH INDIA™

Global Leader. Local Partner.

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.

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

By
Dr. Piyush Gupta

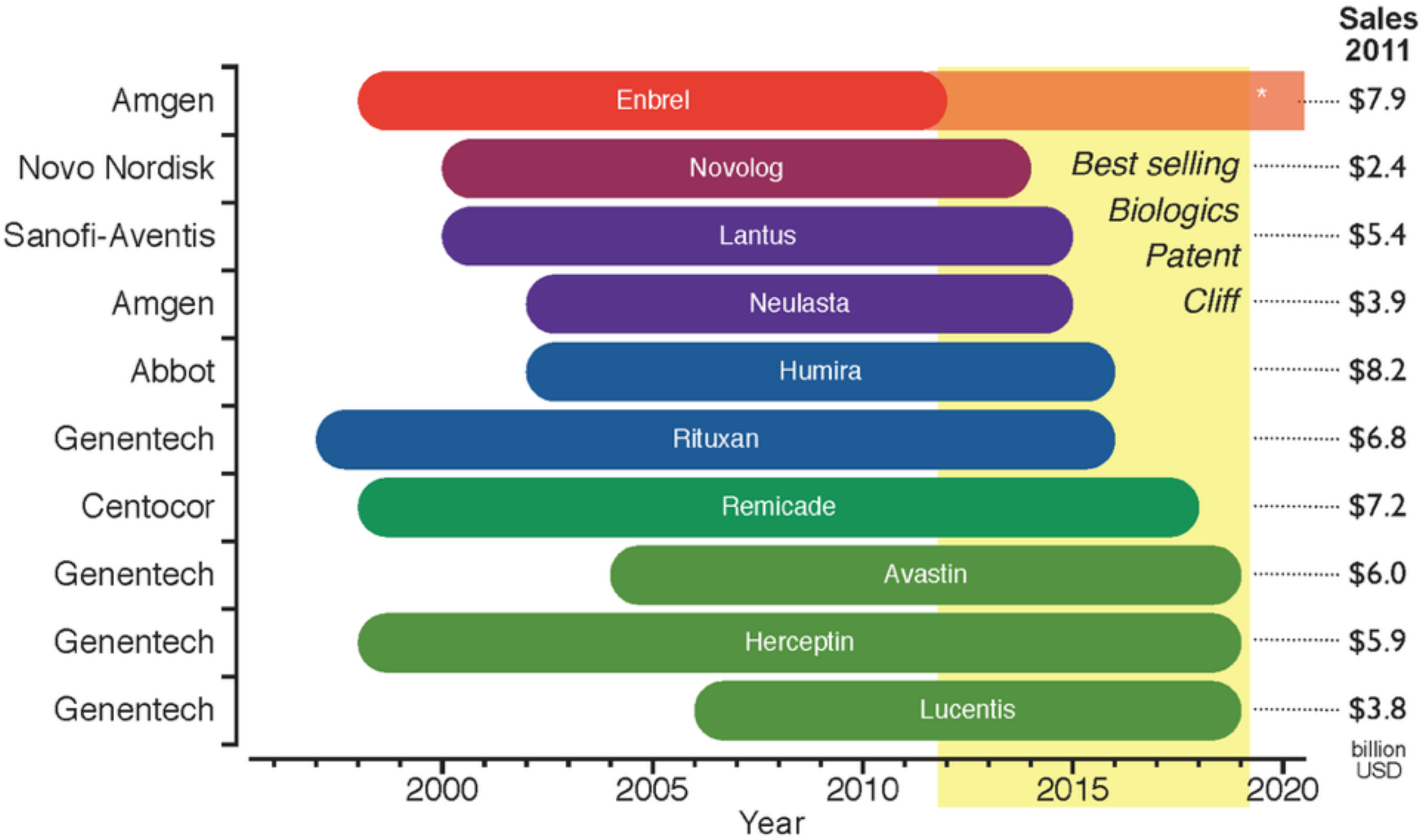
Index

- Facts: Biosimilar Opportunity 2020
- Facts: About Biologics
- Global Regulatory Pathway
- Comparator Examples From Market
- Key regulations governing comparator sourcing
- Comparator Souring Organisation - Roles and Services.

Index

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:10.3390/ph5121393 . PMC 3816668 . PMID 24281342 .

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

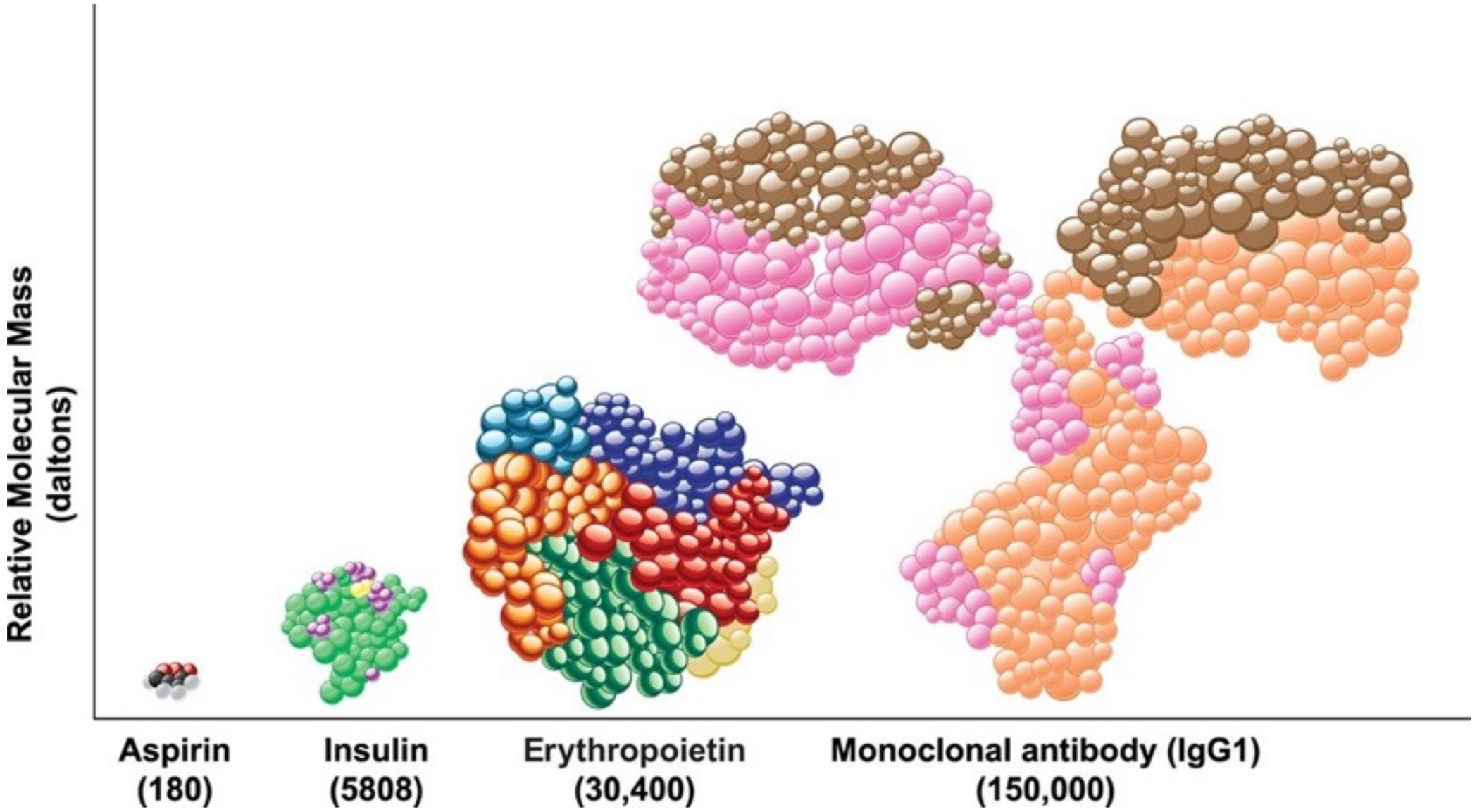
- The demand for Comparators / RLDs has been estimated at 500,000 units for phase 1 trial through Phase III trials!

Index

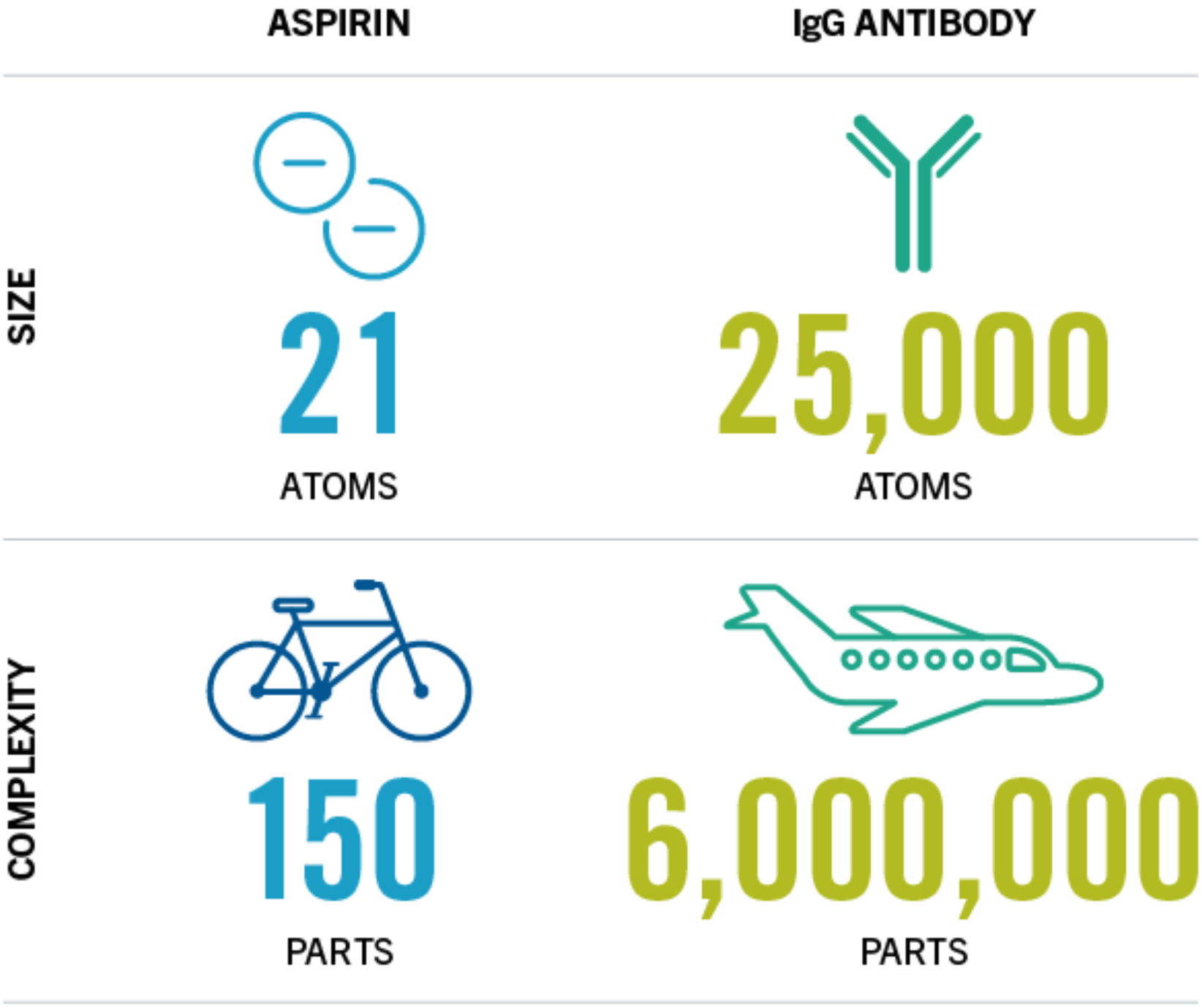
Facts: About Biologics

Facts: About Biologics

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

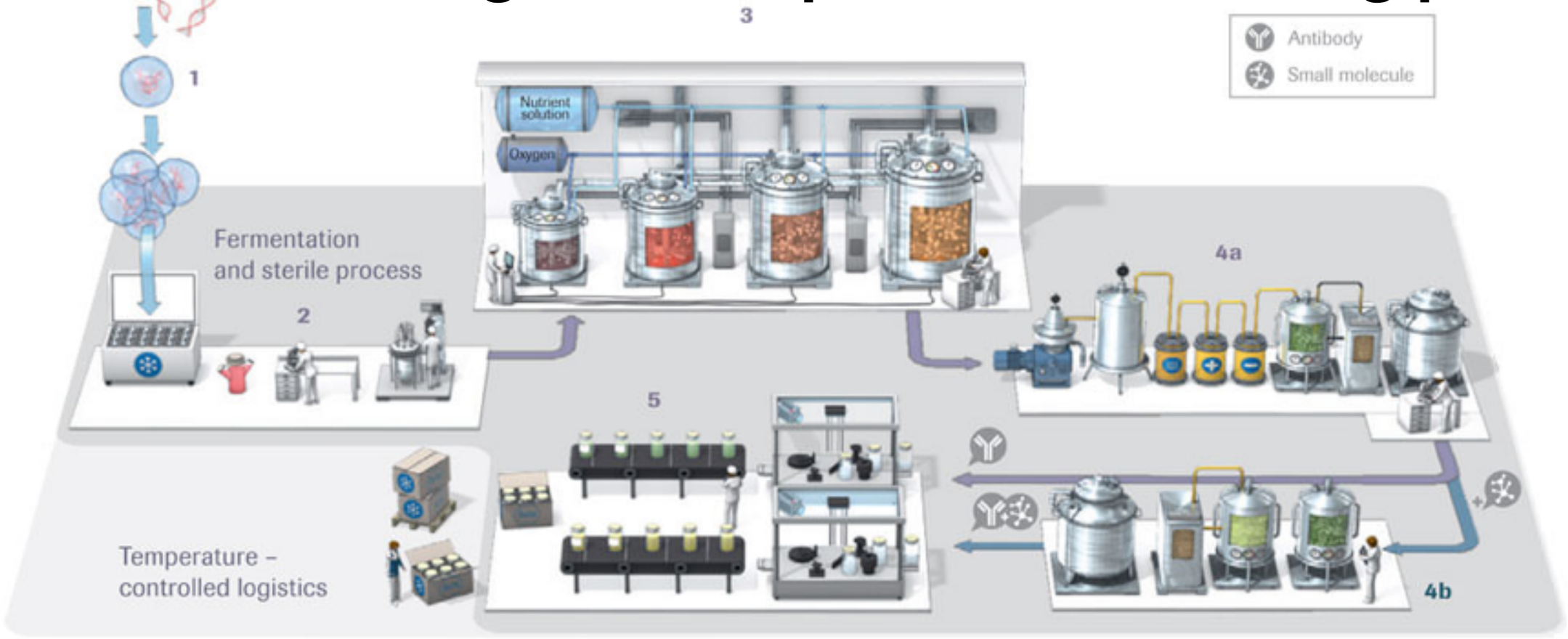


Facts: About Biologics



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.

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.

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.

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.

4b Conjugation

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

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.

Picture : http://www.roche.com/supply_resp_2.jpg

Facts : Biologic Manufacturing

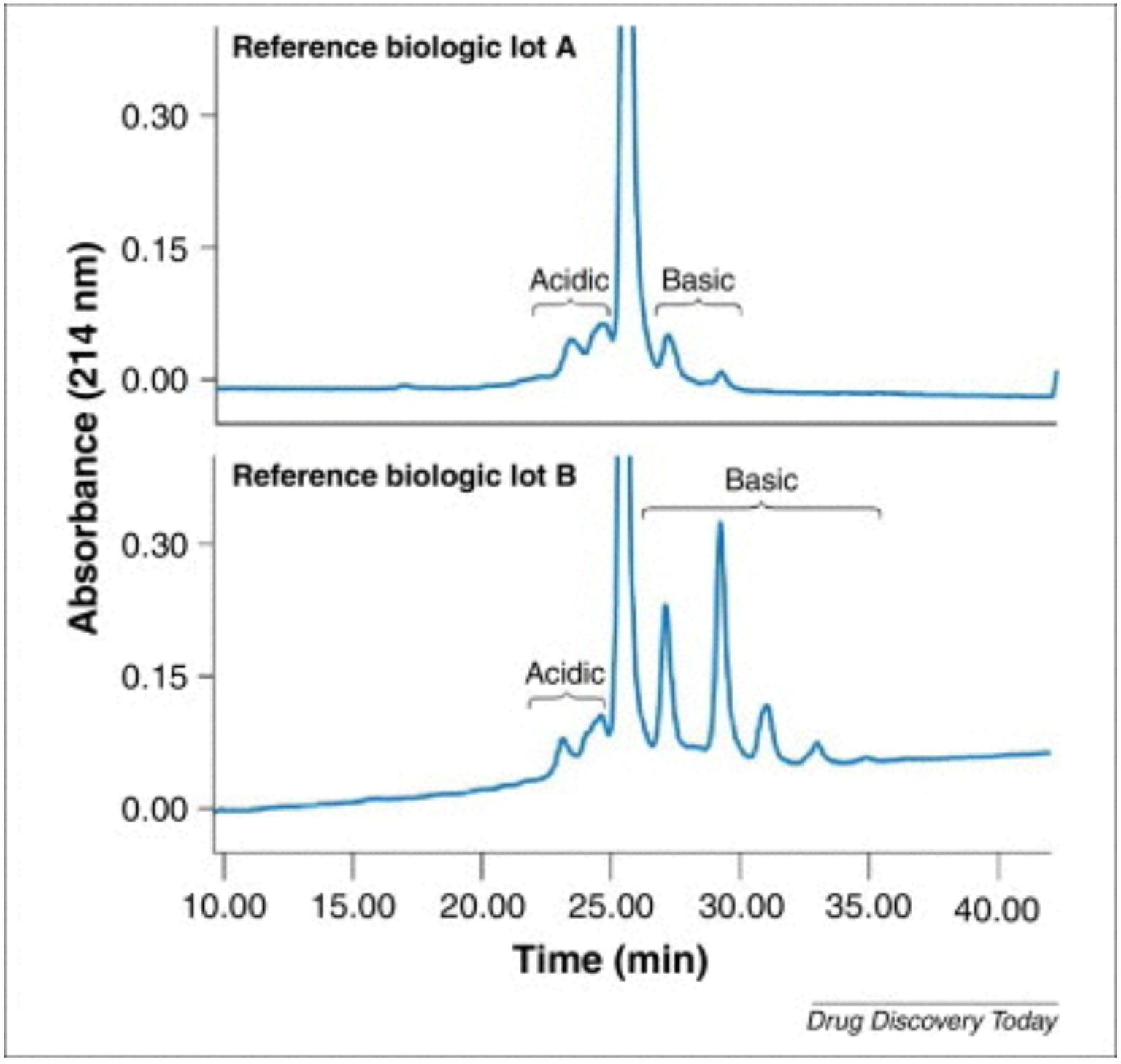
- Every Biologic product displays a certain degree of variability even between different batches of the same product.

- Even minor changes in production process have to approved by NHAs

- 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]

Facts: Inherent Variability

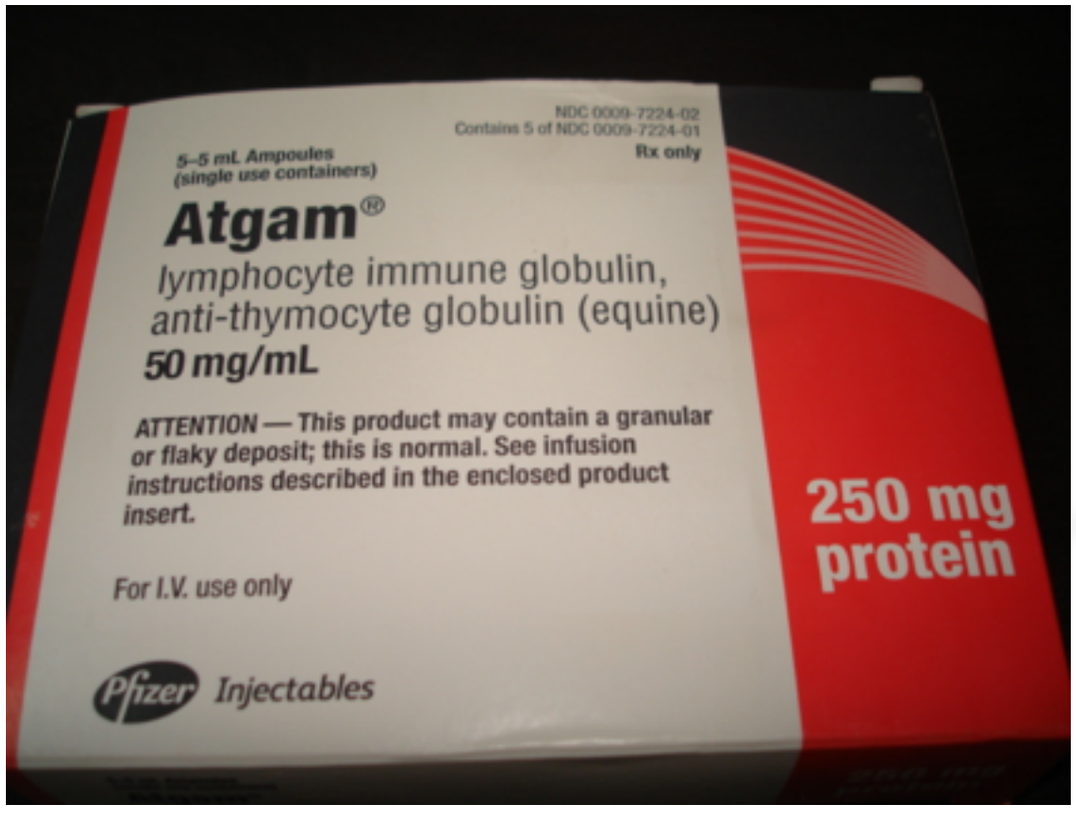


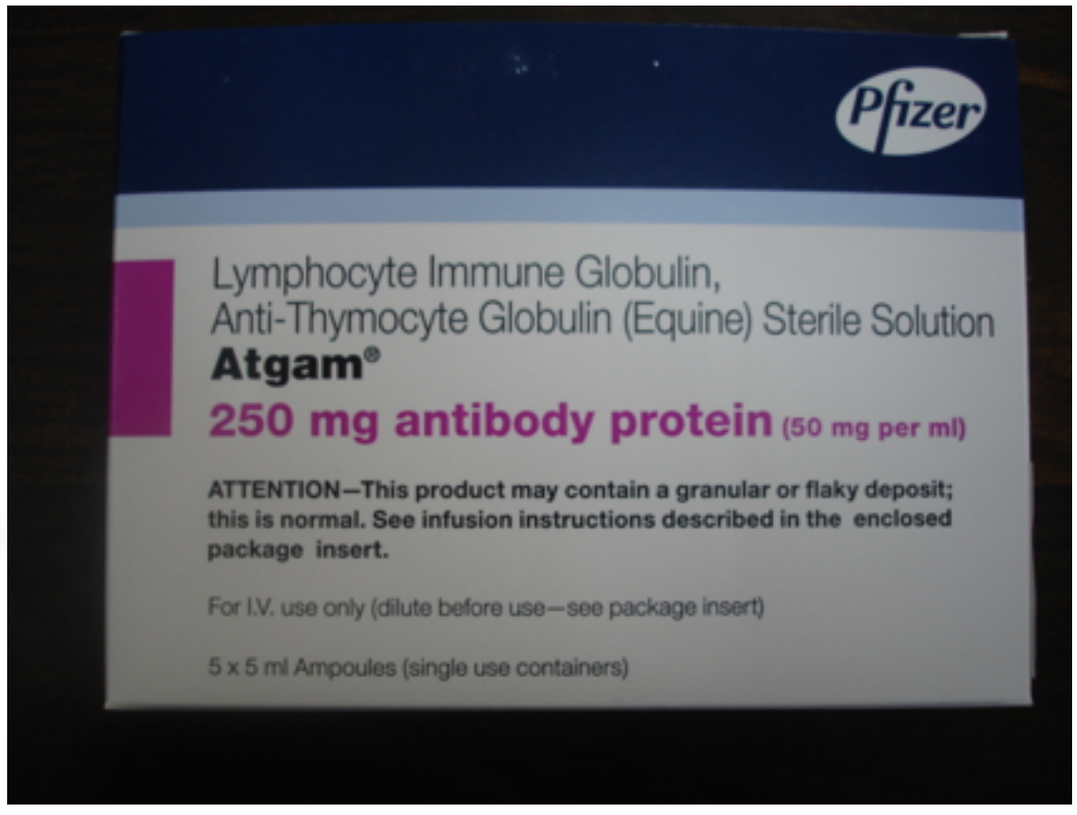
http://biosimilars.elsevierresource.com/system/files/articles/assets/S135964461500121X/21/gr3.jpg

Index

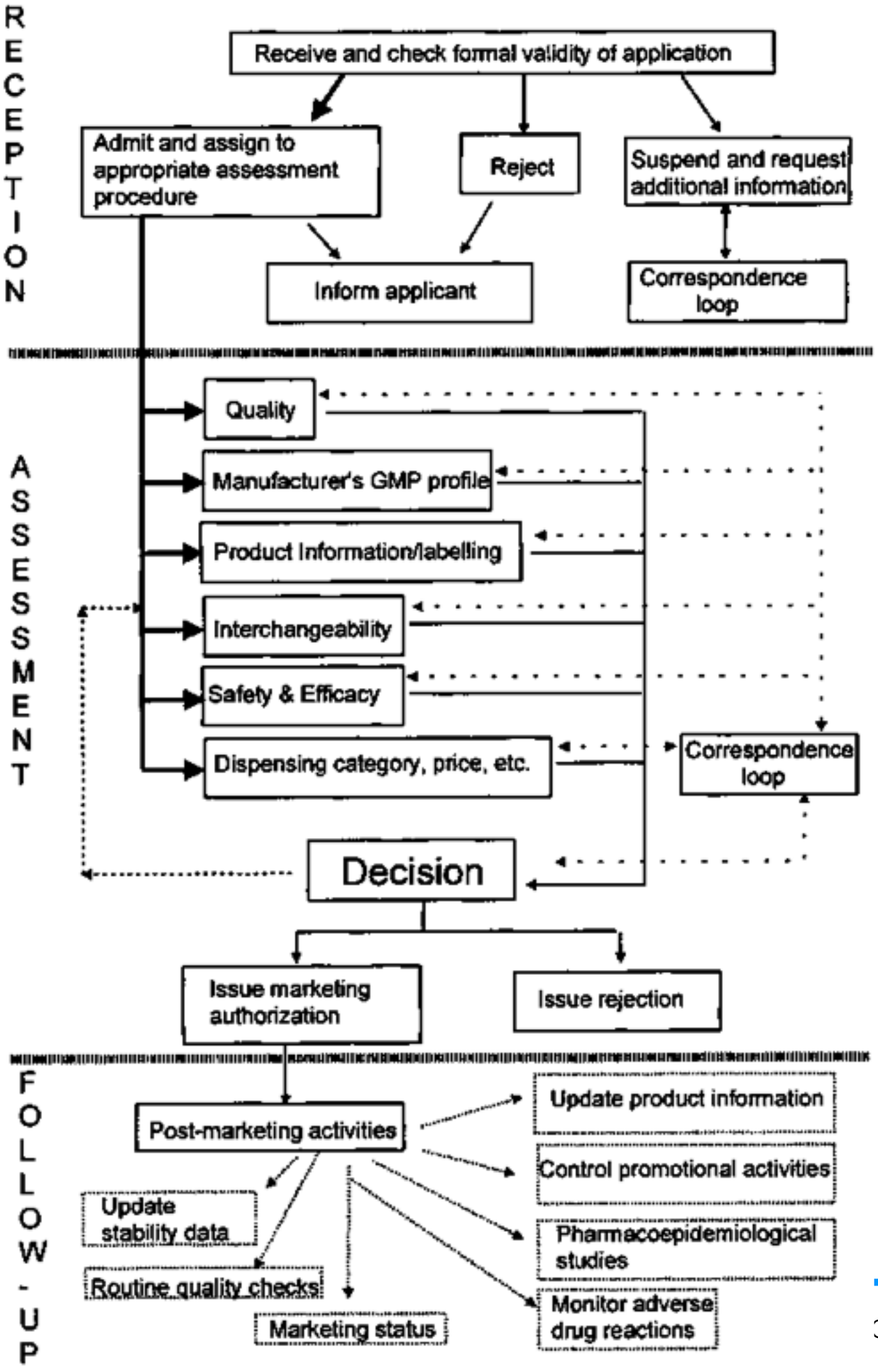
Global Regulatory Pathway

How does a Biologic travel from SRA to Emerging Market

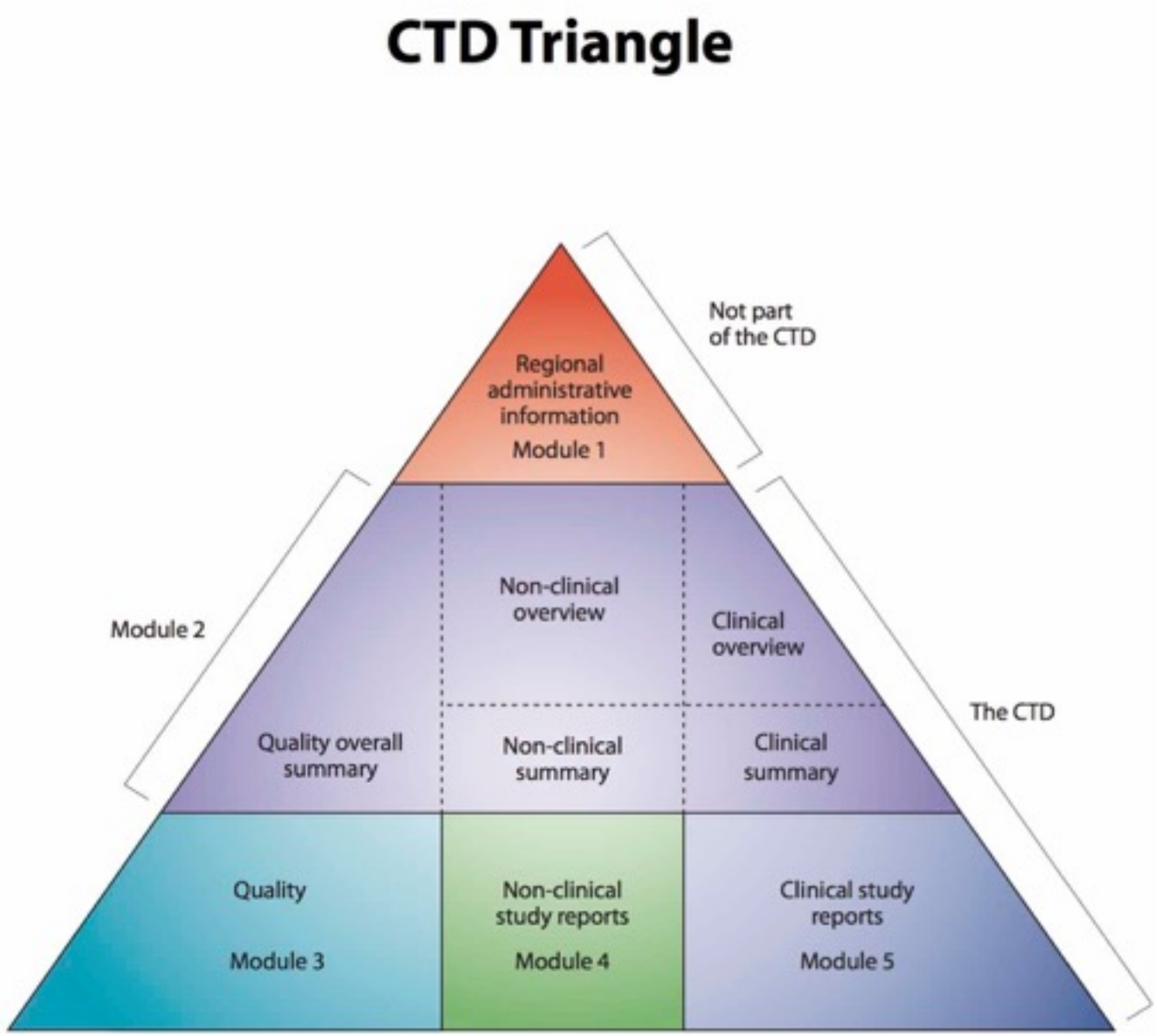




Global Regulatory Pathway



Pathway to Emerging Markets: Product registration



The CTD triangle. The Common Technical Document is organized into five modules. Module 1is 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 ?

swissmedic

No. of Certificate 12 0615 104

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

1.1 Active ingredient(s)[2] and amount(s) per unit dose:
Complete composition including excipients is attached: ☒ *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** ☒ **no,** 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

Regulatory - Registration

Module 1 - General Information:

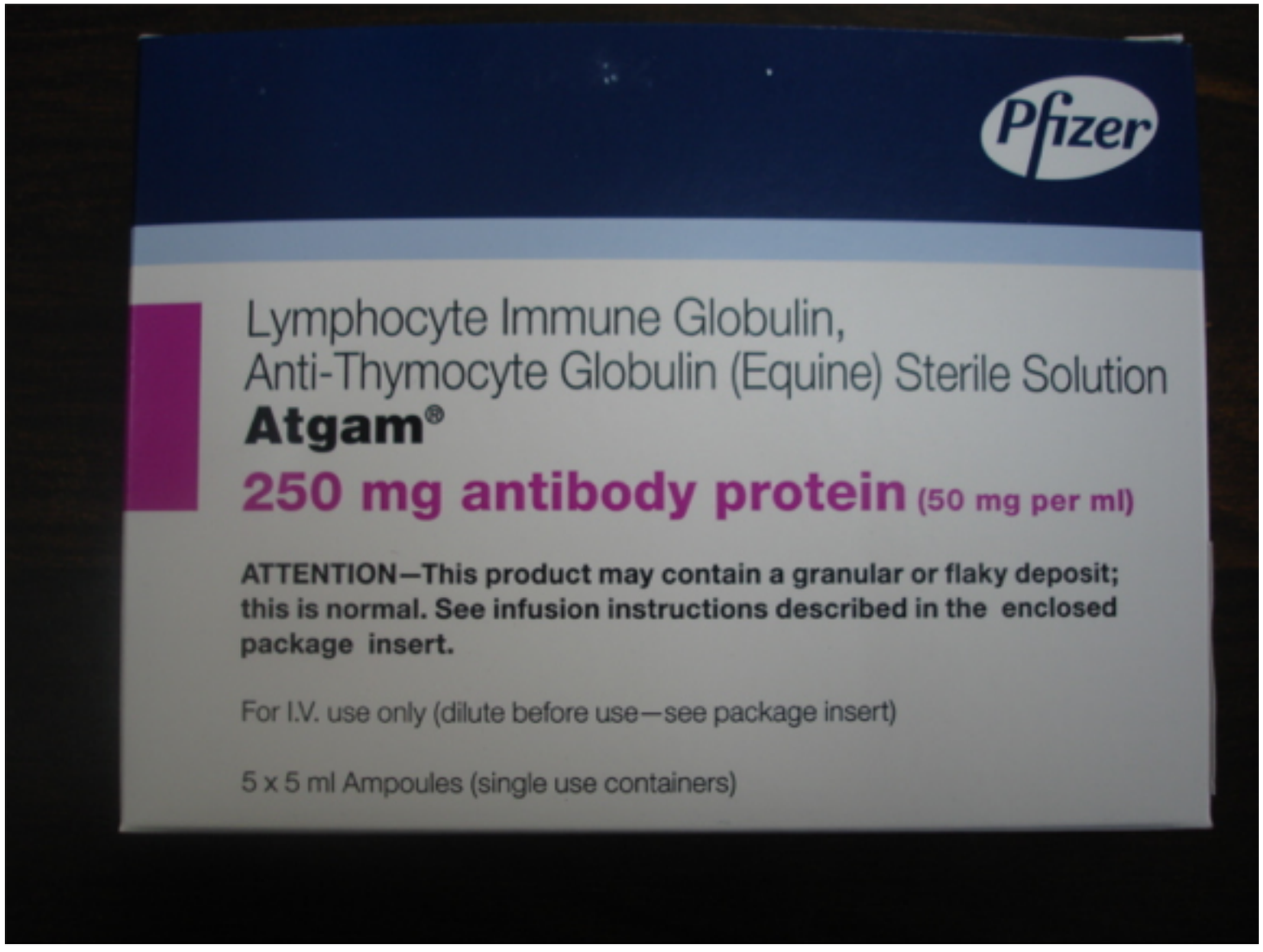
One of the most important requirement of module 1 is CPP (Certificate of Pharmaceutical Origin). CPP is a certificate developed under WHO (World Health Organisation) Certification scheme in 1975 and most recently revised in 1997.Detailed information can be read here : http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelin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

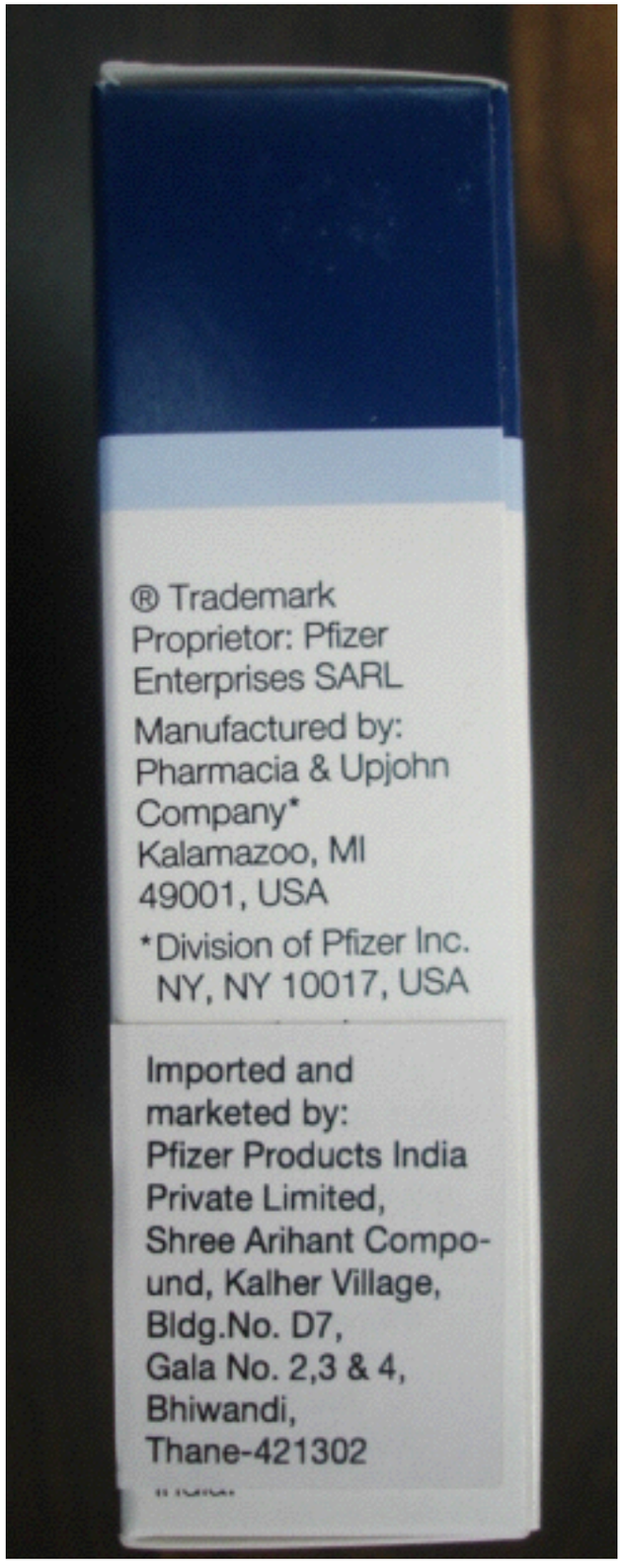
CPP requirement as adopted by Indian CDSCO: here : http://www.cdsco.nic.in/writereaddata/Guidance%20documents.pdf. CPP is a mandatory certificate in all CTD dossiers and is taken as a proof of QSE (Quality, Safety and Efficacy) of the product and also as an evidence of GMP.

Index

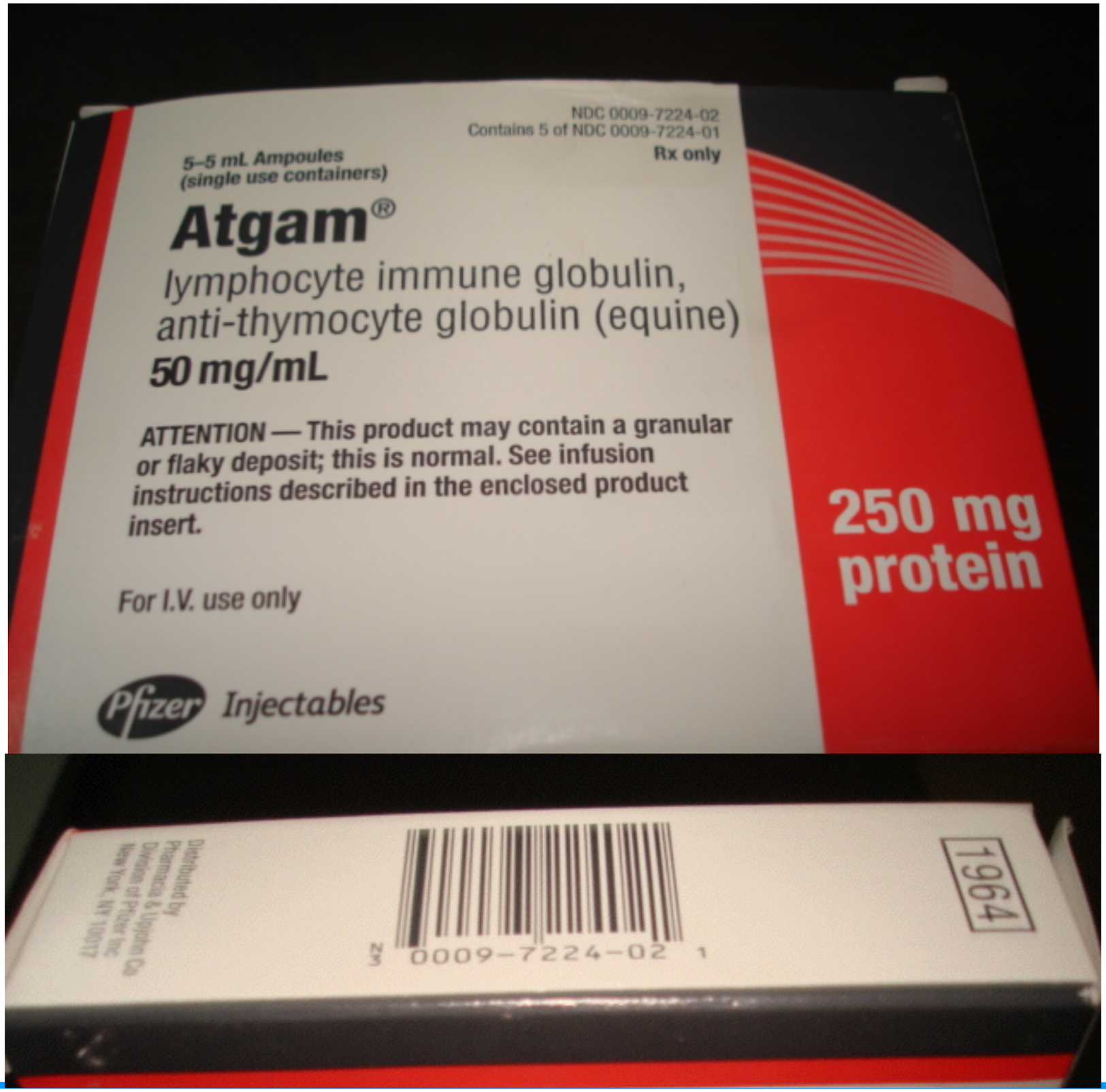
Comparator Examples From Market

Sourced from USA

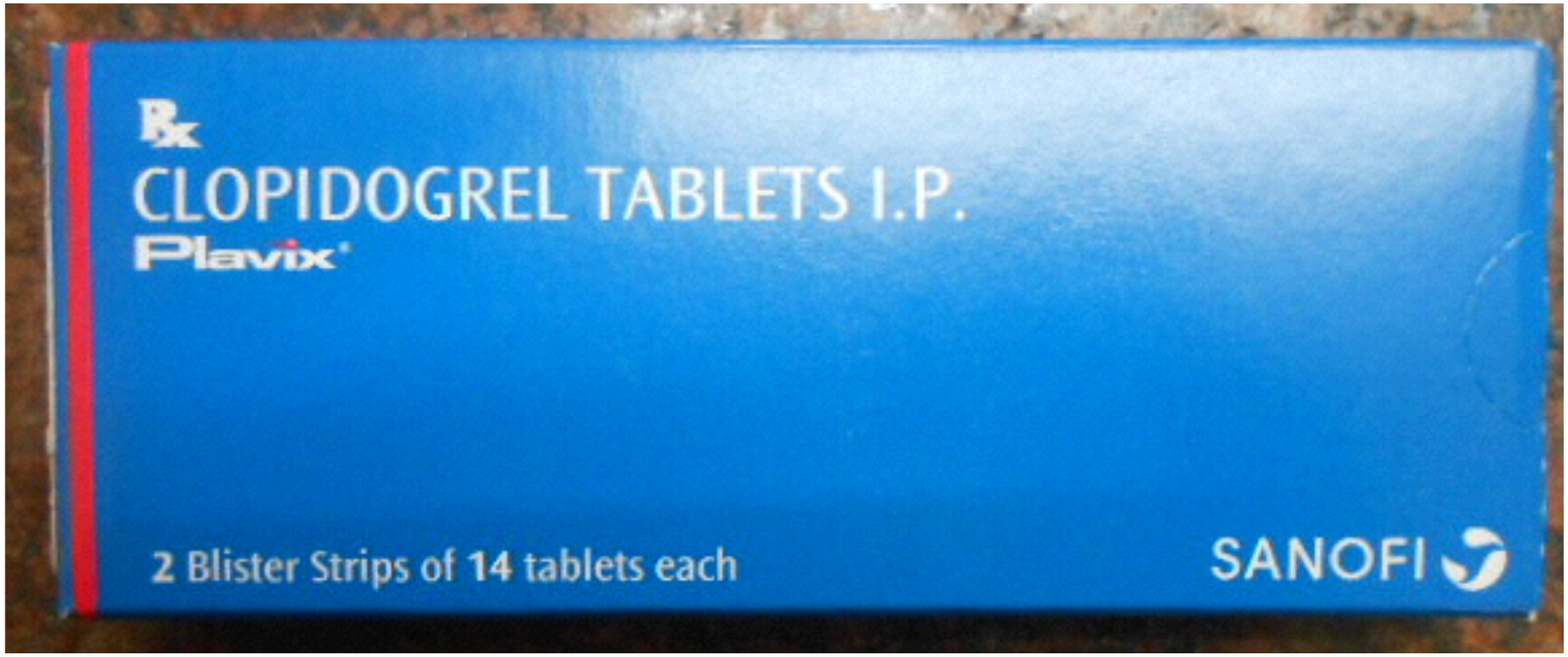


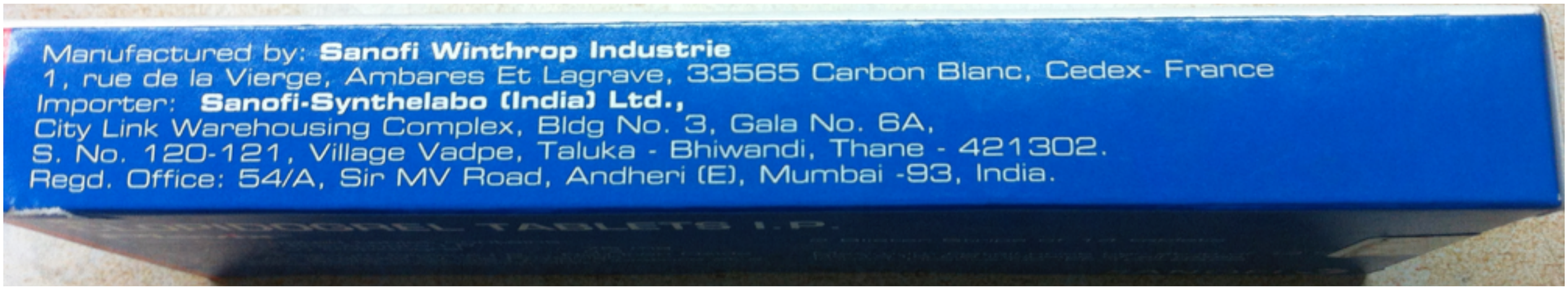


Authorised in USA

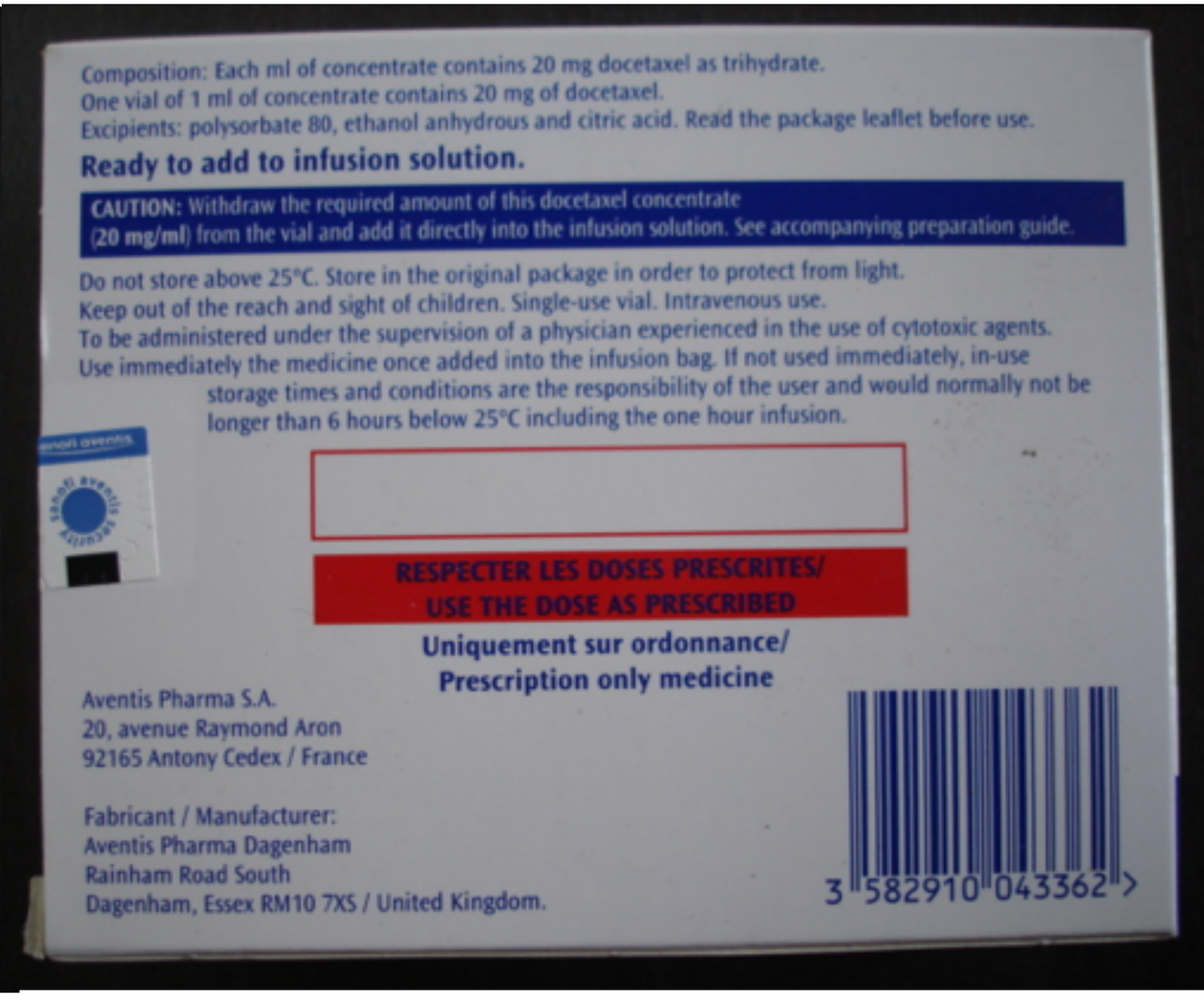


Sourced from France

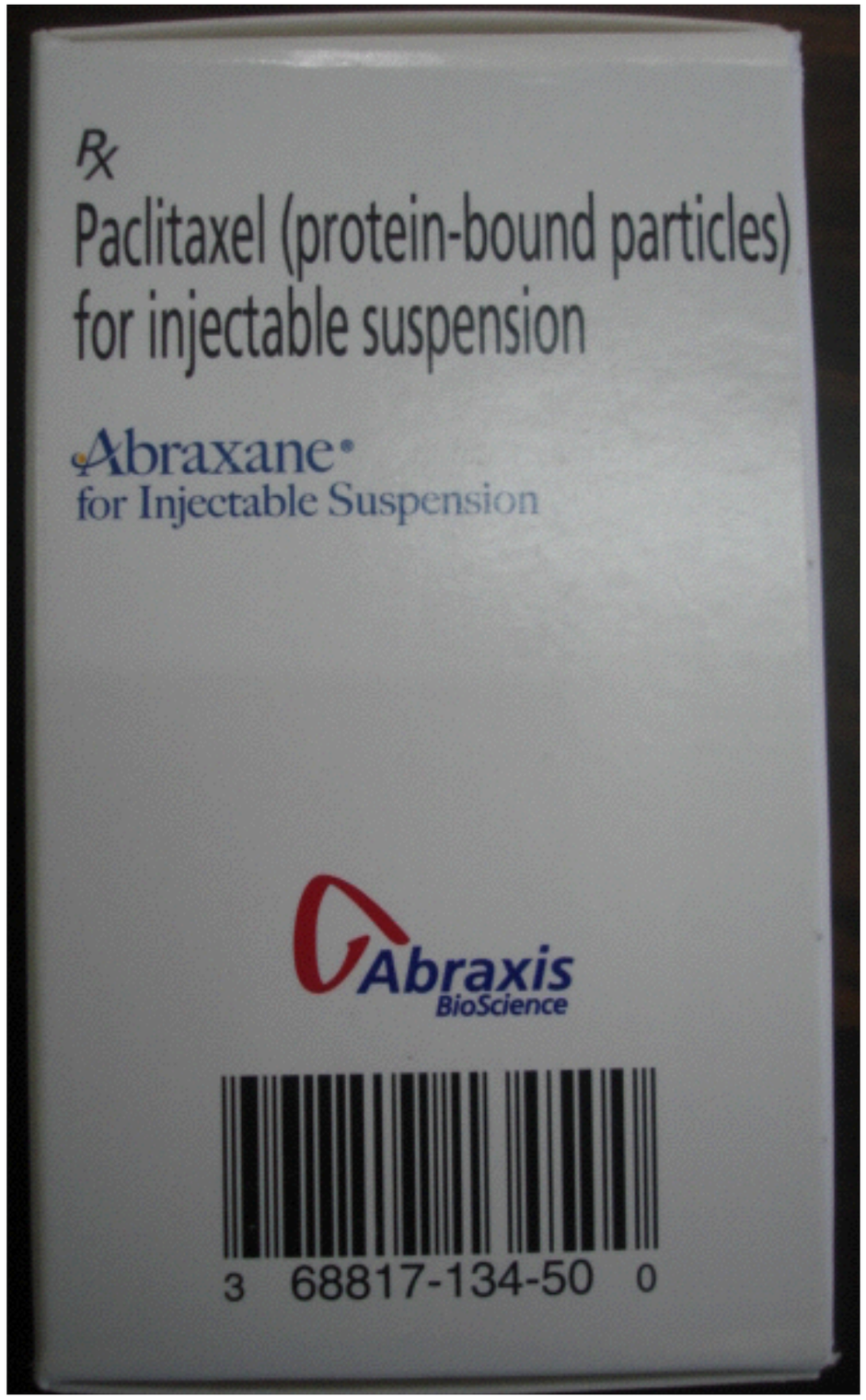




Authorised in France

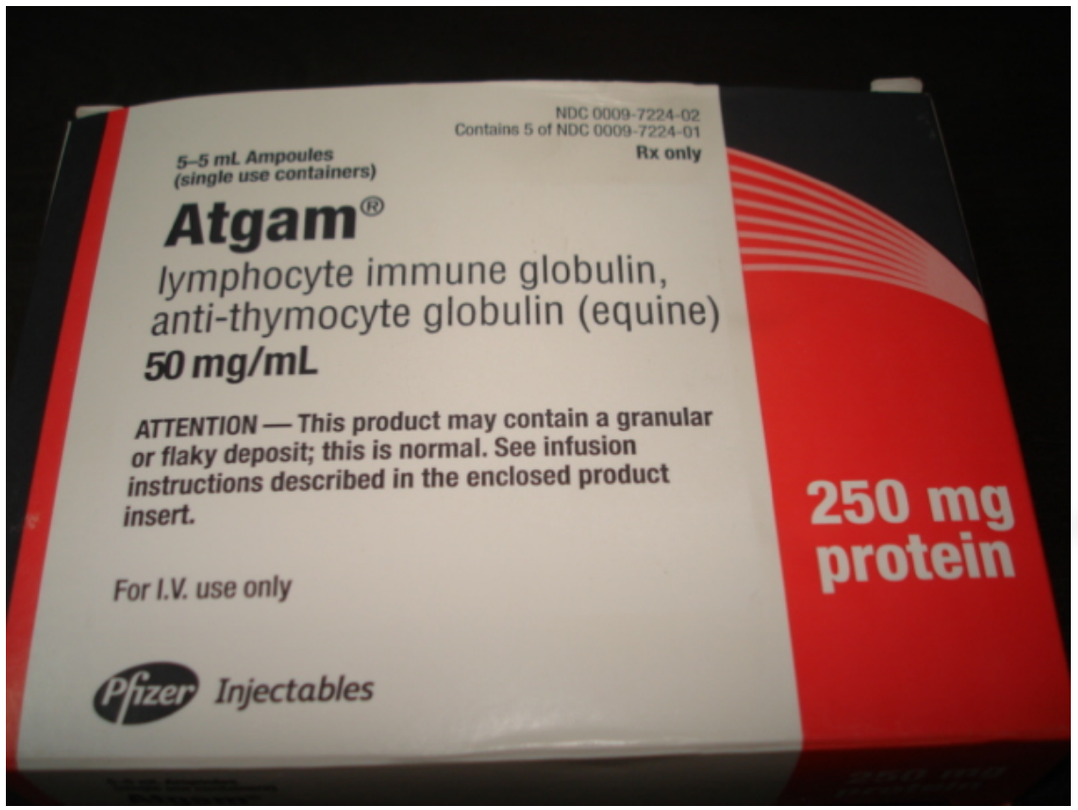


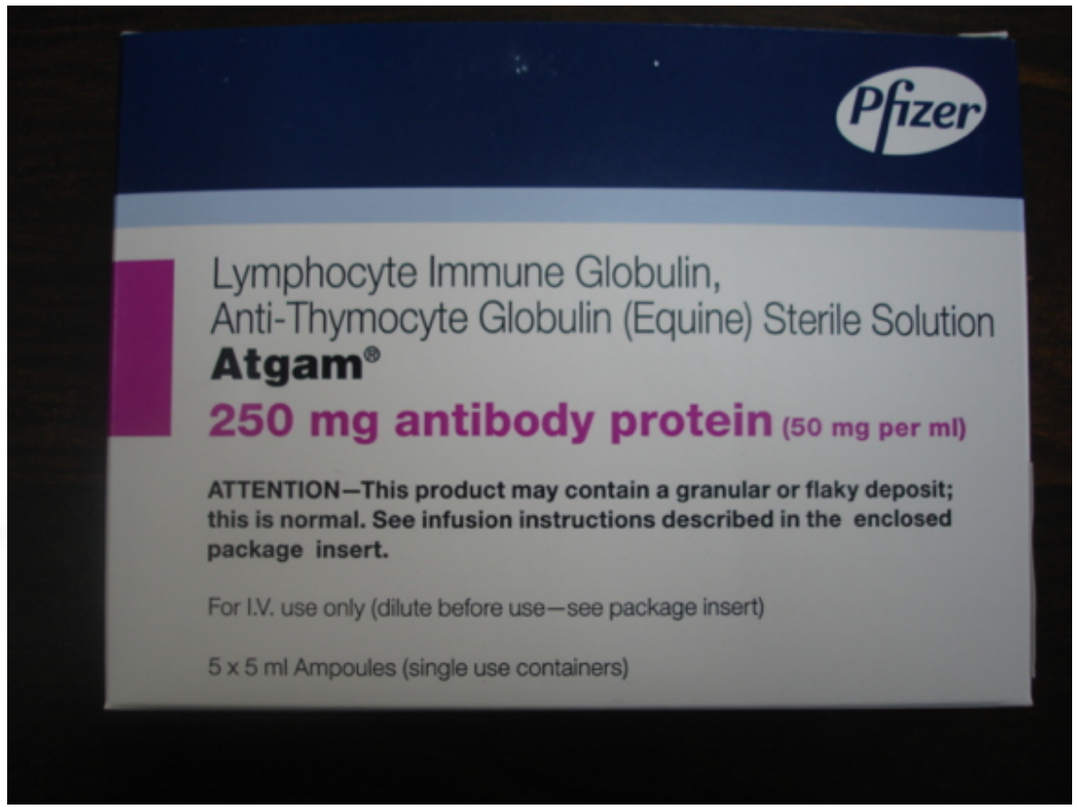
Authorised in USA



Authorised in USA

Taking a product from SRA to Emerging Market





Is this possible without CPP, eCTD, Registration pathway ?

Index

Key regulations governing comparator sourcing

Regulatory Senario - USA

- Important act governing Biologic and Biosimilar Trade:

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

- 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

- Important act governing Biologic and Biosimilar Trade:

- Guidelines 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 non-clinical studies (where needed) with a **non-EEA authorised**”

Index

Comparator Souring Organisation

CSO - Comparator Sourcing Organisation

Why CSO ?

- 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%**