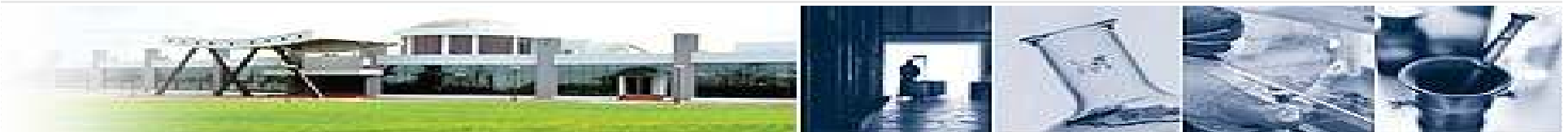
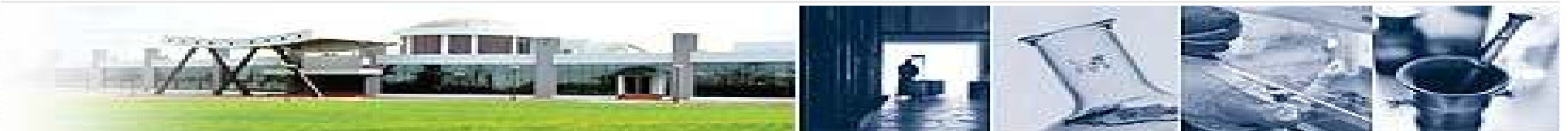

Biosimilars & Compendial Opportunities

Samir Sangitrao
USP-IPC 8th Annual Scientific Meeting
Hyderabad
11th Feb 2009



Agenda

1. Current scenario - Biosimilars
2. Biosimilar Analytics and Monograph requirements
3. Monograph in Biosimilar development
4. Regulatory expectations
5. Agency Vs Compendial requirement
6. General chapters required
7. When can monographs benefit Biosimilar companies



Current Scenario: Biosimilars

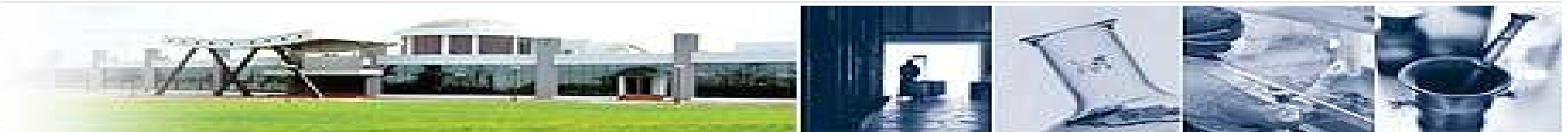
Biosimilar - medicine which is similar to authorized biologic product.

EU: Established & used pathway, >10 approvals so far

US: Various Bills and legislation tabled. Pathway expected soon "Hope is on President Obama"

Rest of the World

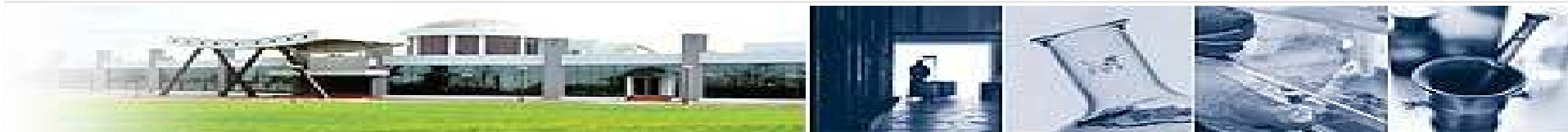
- Canada, Australia, Japan, etc., actively considering a pathway
- India, China & Latin American countries pathway exists
- WHO guidance to harmonize authorization req. (final draft)



APPROVED BIOSIMILARS

	Number of Brands Approved			
	US	EU	China	India
Insulin			✓	8
G-CSF		4 (2)	✓	12
PEG-GCSF				1
EPO alfa / zeta		7	✓	13
IFN alfa / beta		2	✓	7
hGH	1	2	✓	4
Streptokinase				3
MABs				1

Marketing Authorization (Positive Opinion)



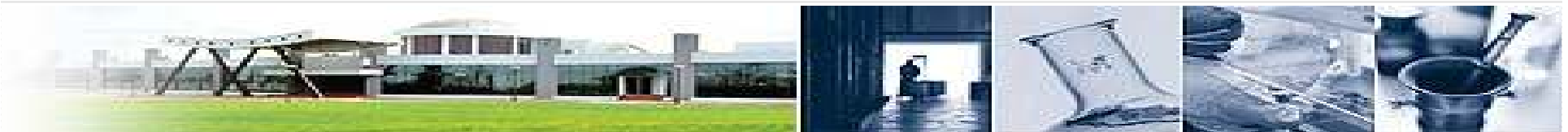
Biosimilar Analytics

Primary Structure

- Amino acid sequence
- N & C terminal sequencing
- Peptide map
- Isoforms
- Glyco analysis
- Mass spectroscopy

Secondary and Tertiary Structure

- Circular Dichroism
- Fluorescence
- Analytical ultra centrifuge
- Differential scanning calorimetry
- Nuclear magnetic resonance



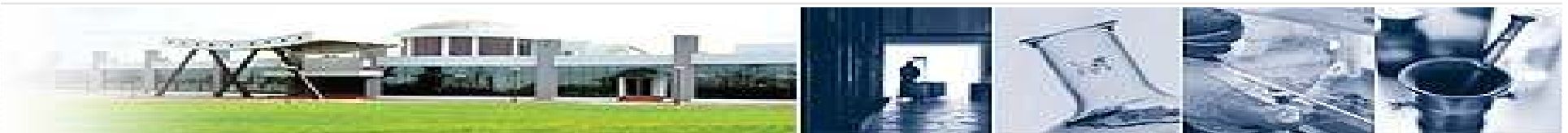
Biosimilar Analytics

Bioassay

- In-vitro
- In-vivo
- Receptor binding
- Reporter gene

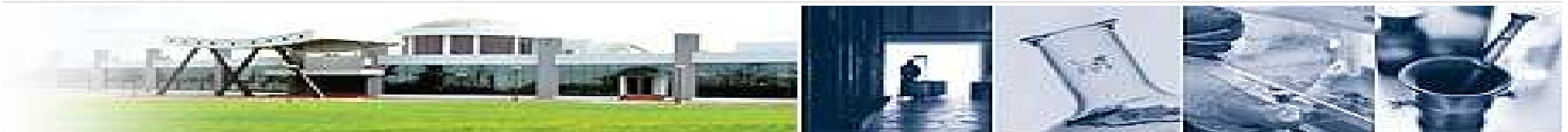
Impurities

- Process related: Host cell protein and DNA, Endotoxin
- Product related: Aggregates, oxidised, reduced, deamidated, Size variants, charge variants, isoforms



Biosimilar different from Generic Pharma

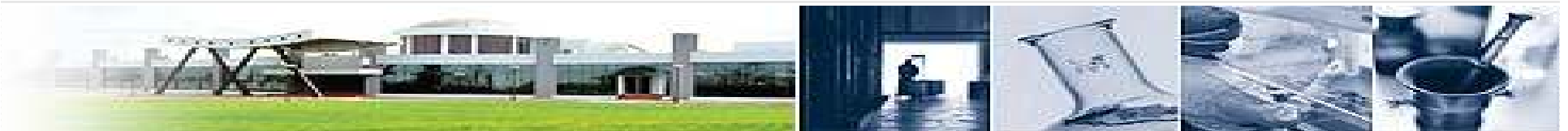
- ❑ Come from complex process
- ❑ Proteins are complex, heterogeneous & unstable in nature
- ❑ Large number of Process and product related impurities
- ❑ Degradation pathway not clearly understood
- ❑ Biological activity
- ❑ Impurities are immunogenic in nature
- ❑ All variants difficult to characterize



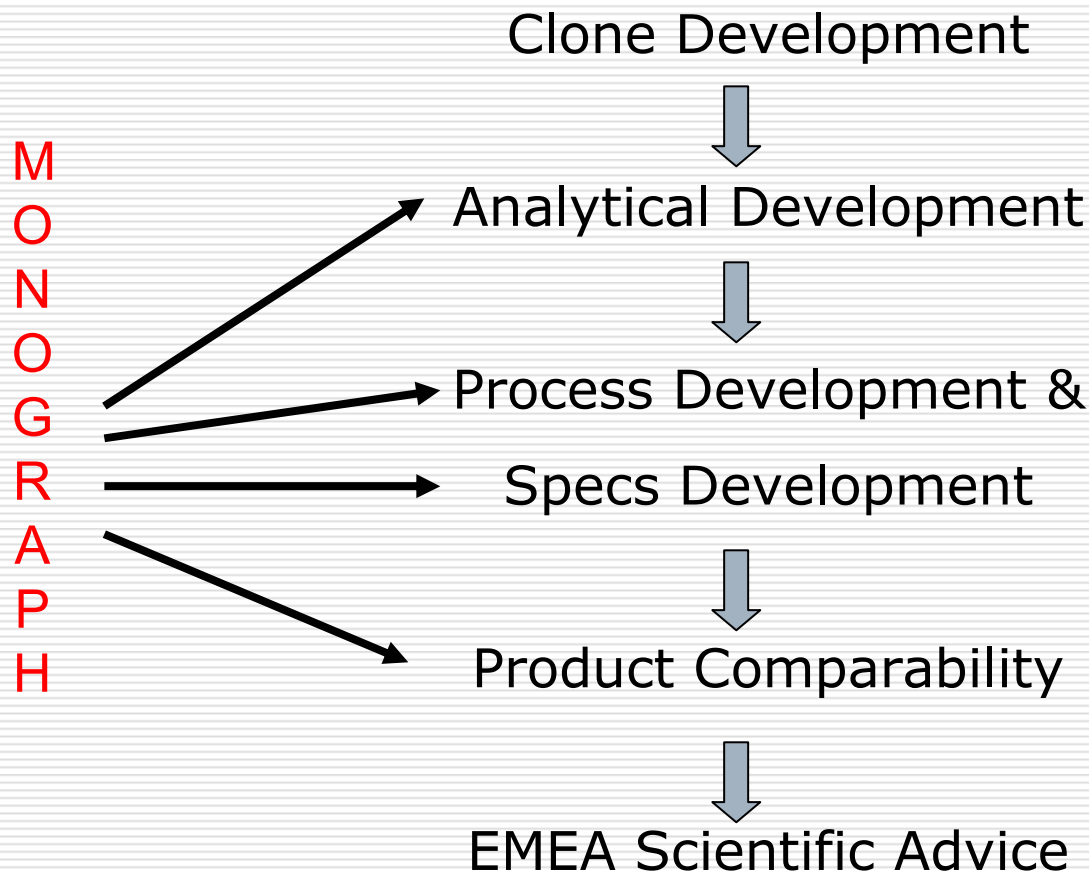
Differences demand special attention

By manufacturer & also In monograph

- ❑ Methods to detect the subtle differences in structural characteristics
- ❑ Methods to address all kinds of impurities also during shelf life
- ❑ Robust Bioassay methods with less variations to address the biological activity
- ❑ Methods predicting immunological issues

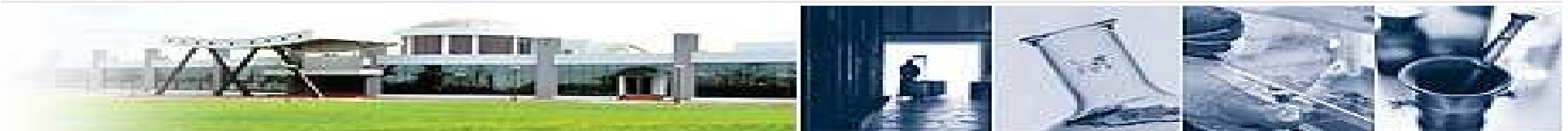


Use of Monograph in Biosimilar development

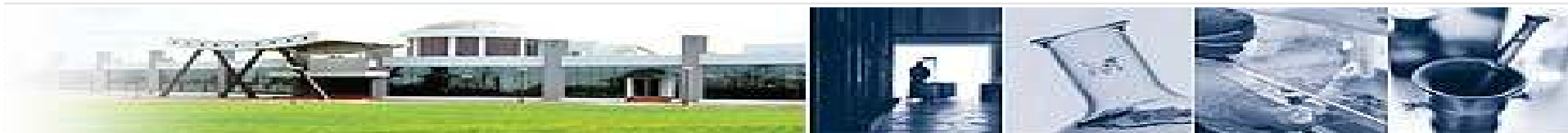
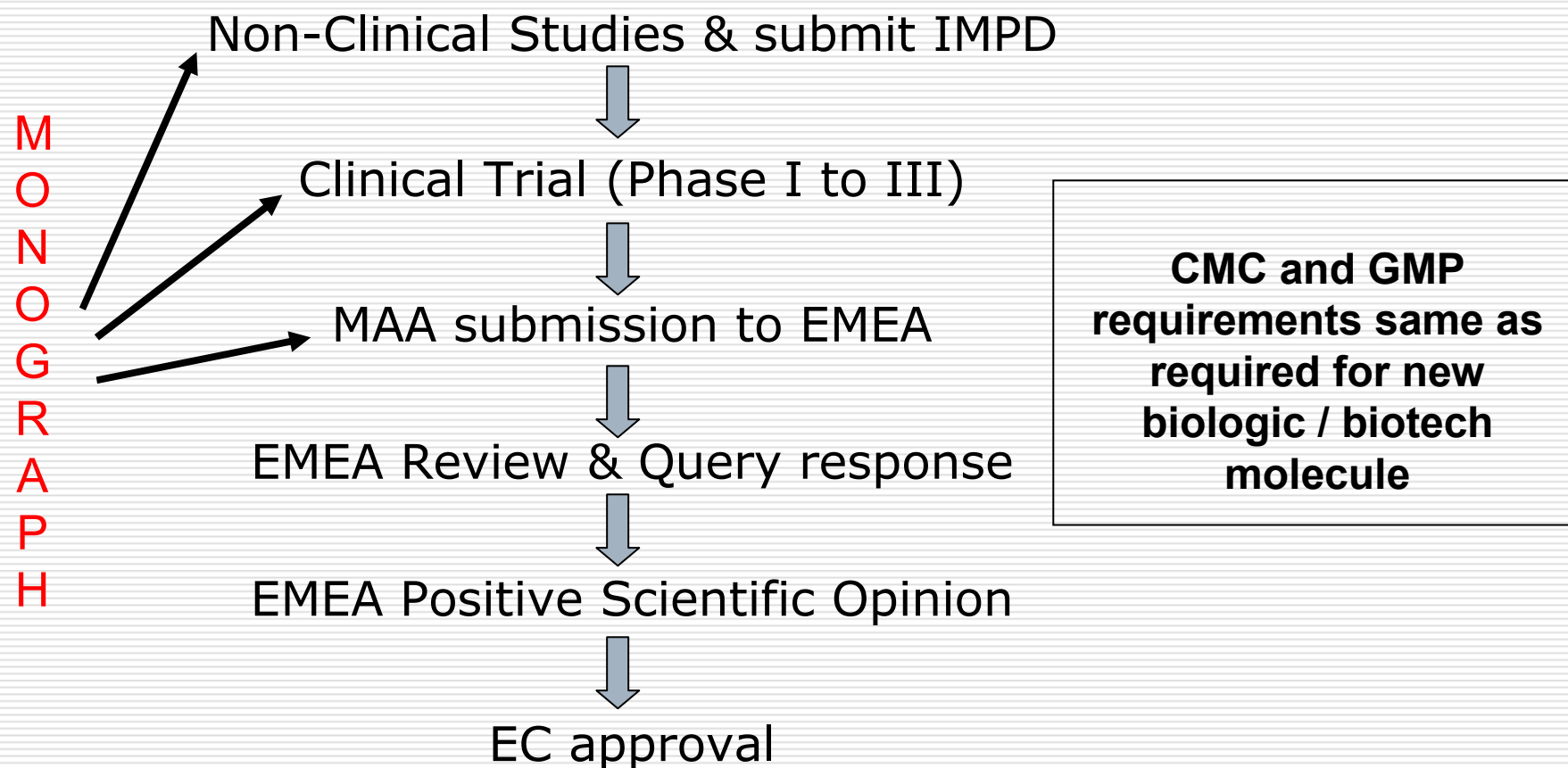


Quality by Design Approach

Manufacturing process is proactively designed to achieve a product equivalent to the reference product (quality, safety & efficacy)



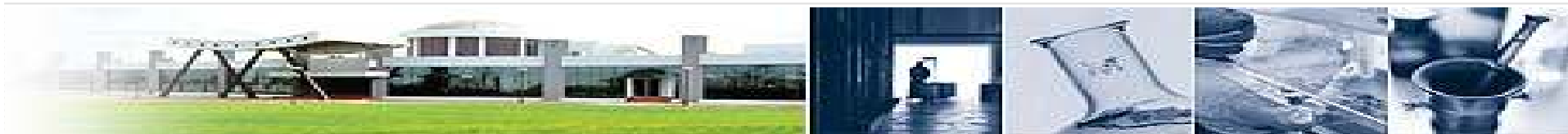
Use of Monograph in Biosimilar development



Analytical Development - Biosimilars

- ❑ Use of advanced analytical tools (clone to finished product)
- ❑ Extensive testing of Innovator product - Know your target
- ❑ Product related substances Vs related impurities
- ❑ Thorough characterization of molecule & Biosimilarity (EMA/CHMP/BWP/49348/2005)
- ❑ Identification of differences and impurity characterization
- ❑ Qualification, Validation, method comparability

Methods – Specifications – Reference Standards



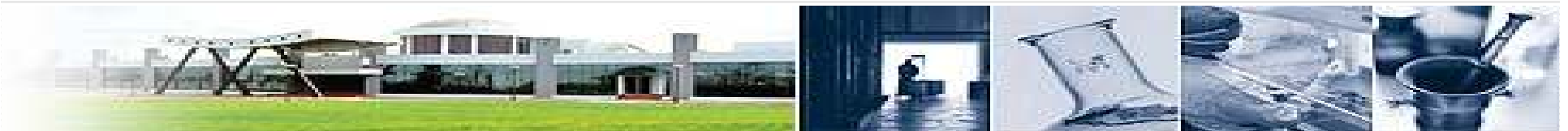
Regulatory expectations: Biosimilars

- ❑ Biosimilar manufacturer targets
 - ❑ Develop Methods
 - ❑ Design Specs to meet the regulatory expectation
 - ❑ Design Process to meet the specs

- ❑ Dilemma: Use Innovator product for development or use Monograph

- ❑ Monograph - release methods

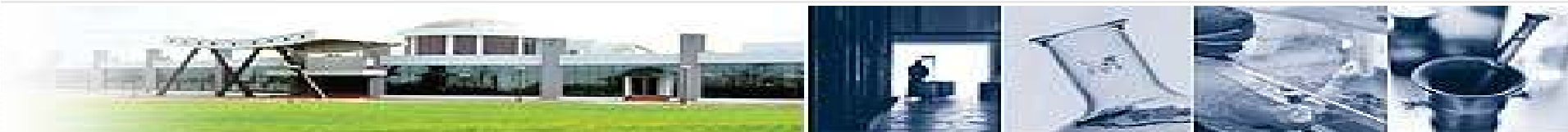
- ❑ Regulatory agency require comparability
Biosimilar product = innovator product



Differences In Global Regulatory Req.

Document / Studies	LR	SR	R
Product Characterization: Structural Analysis, Impurities, Biological assays, Comparability with innovator product	Yes Basic	Yes	All
Bulk and Finished Products Testing: Specs, Certificate of Analysis, Method of Analysis, Method Validation, Ref. Std., Justification of Specifications, Batch analysis	Yes	Yes Yes	All
Clone Details: Information of Clone and Cell Banks, Cell bank characterization, Viral Testing	No	Yes Basic	All
Stability: Report, Data, Protocol, Trend Analysis, Forced degradation studies	Yes Basic	Yes	All

LR - Less Regulated, SR – Semi Regulated, R - Regulated



Agency Vs Compendial requirement

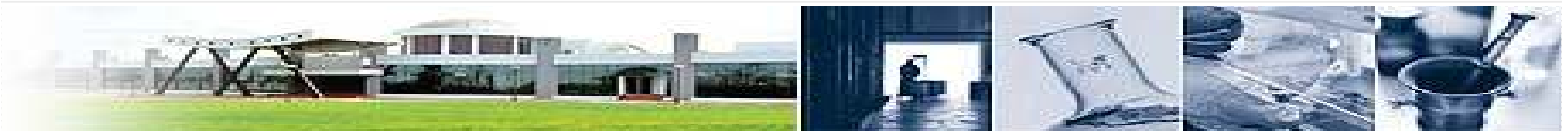
Regulatory agency demands are stringent than compendial requirements

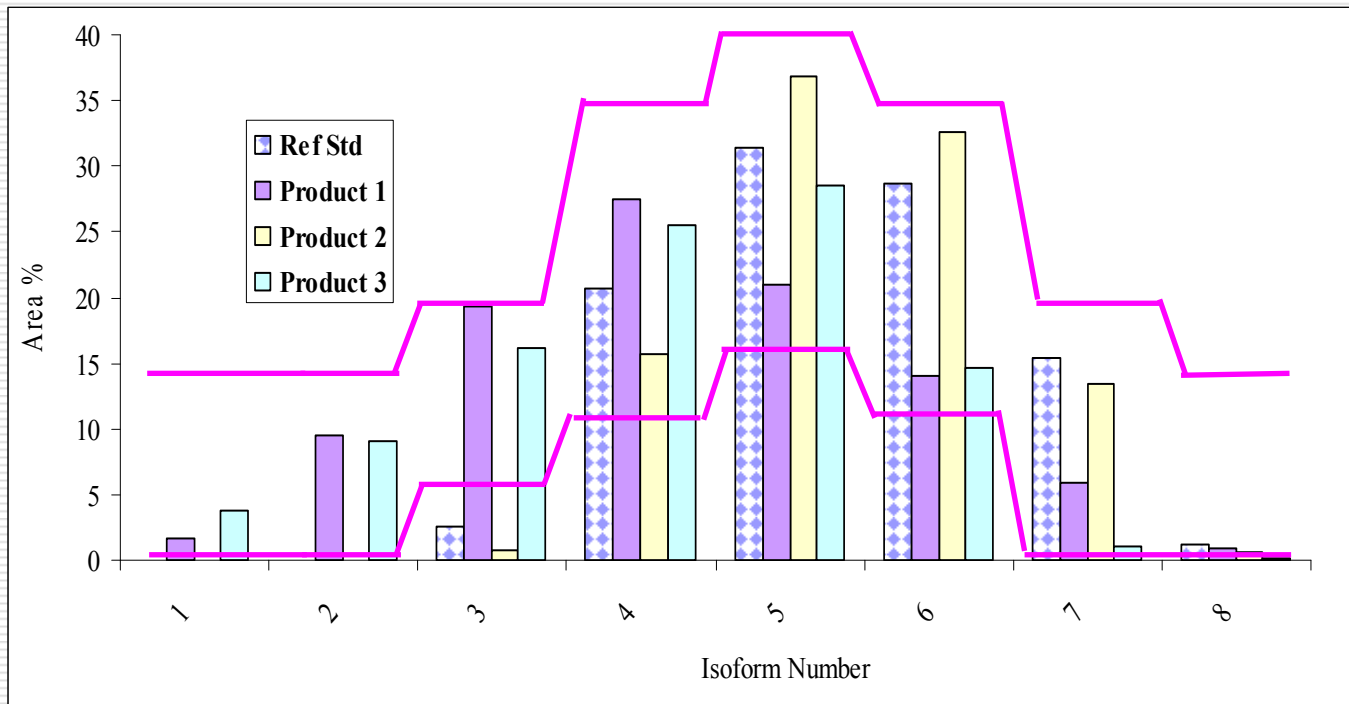
- ❖ Methods
- ❖ Specs

- ❖ Manufacturer can use monograph for analysis however **compliance to monograph is not sufficient**

- ❖ Does the monograph serve any purpose or is it just a minimum level to attain ?

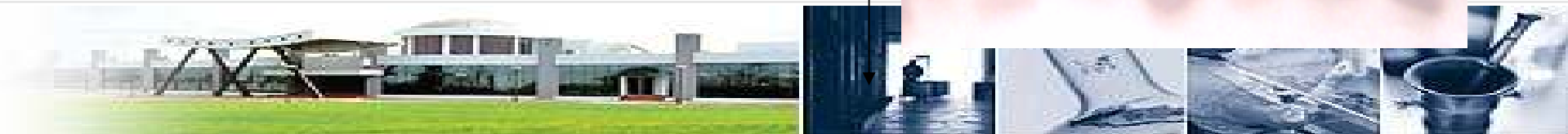
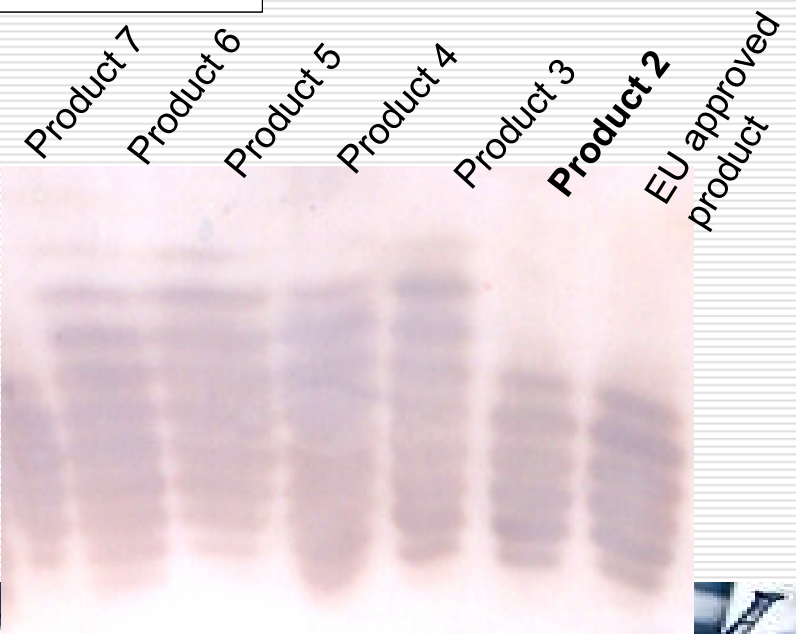
- ❖ Is compliance to monograph useful ?





• All products pass EP specifications

• Biosimilarity criterion may not be satisfied



Specs based on EP Vs Ref Std

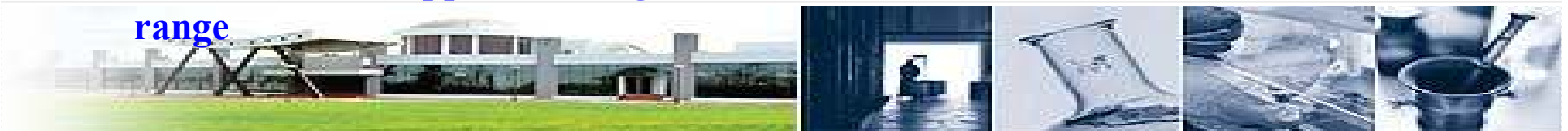
Isoform Number	EP range	EU Approved drug	Product 1	Product 2
1	0--15	0 - 0	1.64	0.0
2	0--15	0 - 0.3	9.53	0.0
3	5--20	2 - 3.5	19.37	0.77
4	10--35	19 - 22	27.46	15.77
5	15--40	29 - 33	21.02	36.80
6	10--35	28 - 30	14.09	32.67
7	0--20	14 - 16	5.94	13.44
8	0--15	0.5 - 3.0	0.92	0.55

- EP limits are wider and allow product heterogeneity

- Specifications based on normal values of Reference Product

Varying from the reference range

Close to the EU approved drug range

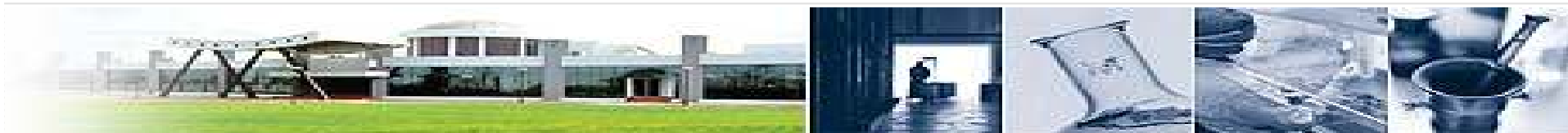


Pharmacopoeia Vs Regulatory expectation

Method	Pharmacopoeia	Regulatory expectations	In reality – Innovator's Quality
Size exclusion chromatography	< 2%	< 0.5%	0.1%
SDS PAGE	< 2%	< 0.5 %	0-0.1%
HCP	No method, no limit specified	10 to 100 ppm	1-5 ppm
DNA		10 ng / dose	1-100 pg/dose
Endotoxin	< 20 EU/ mg	< 2EU/ mg	< 0.2 EU / mg

What is basis of Pharmacopoeia limits?

What is your objective?



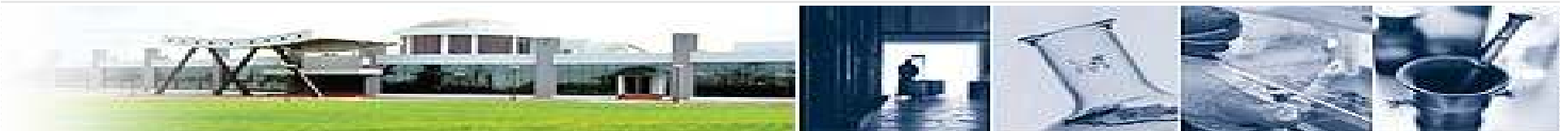
Dossier requirements for Biosimilars

Common Technical Document

- ❑ Module 1 – Normal requirements
- ❑ Module 2 – Normal requirements
- ❑ Module 3 Quality – Full dossier + Comparability
- ❑ Module 4 Non clinical – Reduced + Comparability
- ❑ Module 5 Clinical – Reduced + Comparability

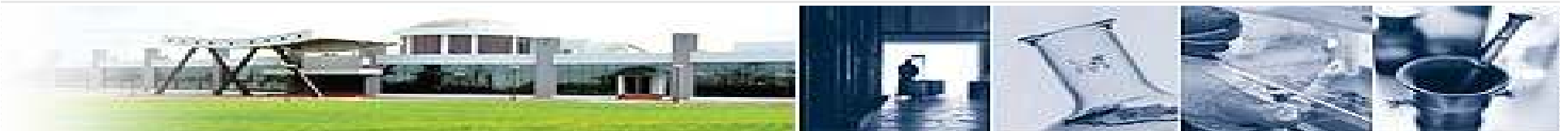
In Module 3, **45% sections** are related to analytical methods

So having Biosimilar monographs is very important



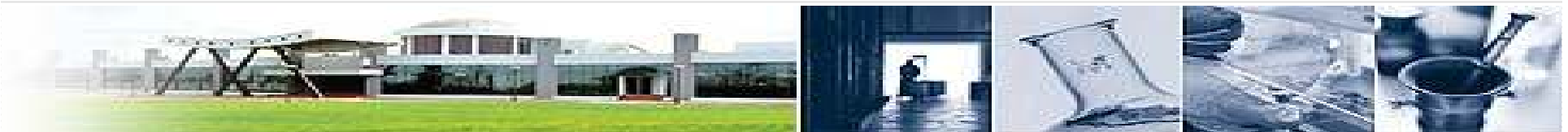
Current issues that industry faces

- ❑ Reference standard mixture of two different moieties (EPO)
- ❑ Reference standard not available or in limited amounts
- ❑ Limits given in monograph are much wider than actual quality of the pharmacopoeial standard
- ❑ Bioassay: Proprietary cell line of innovators – access to cell line not possible, assays not generic



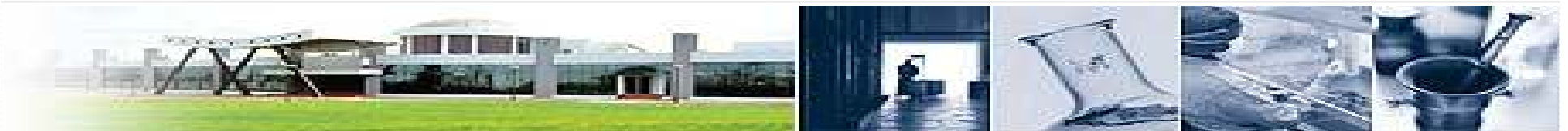
Current issues that industry faces

- ❑ Specifications relaxed than the regulatory expectations
- ❑ Data not published from the collaborative multi lab analysis in all cases before finalization of monograph
- ❑ Quality of pharmacopoeial standard considerably different from that of approved drugs: contradictory to biosimilar requirement (isoforms)
- ❑ No chapters / guidance for finished product



Additional general chapters required

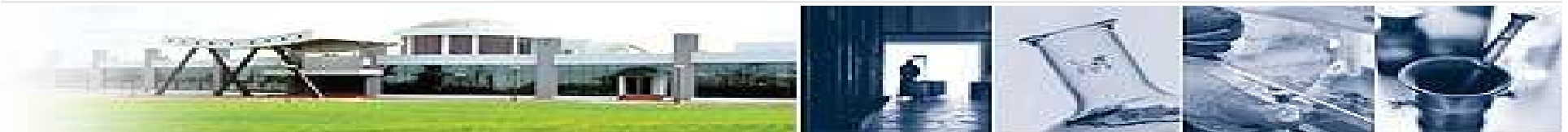
- ❑ Cell bank characterization methods
- ❑ Testing required for product characterization
- ❑ Methods used for structural characterization for product / process comparability & extent of structural studies needed
- ❑ Key issues to be addressed in microbial / mammalian based products
- ❑ Biologic Impurity identification and characterization guidance
- ❑ Post translational modification and characterization guidance



Additional general chapters required

- Process related impurities, recommended methods and specs
- Immunogenicity related methods
- Stability indicating methods
- Methods for Glycan characterization
- Guideline on devices used for Biotech products & studies req.

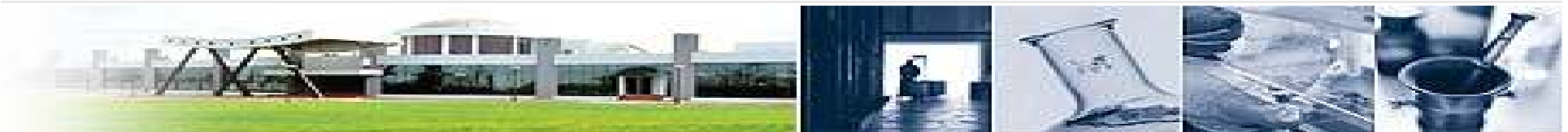
Without these chapters, there is
Lack of understanding, Lot of variation
and Low compliance



Ideal scenario for a Biosimilar company

Global monograph & Global reference standard

- Harmonize requirements
- Uniform standard for all testing - Quality
- Reduce redevelopment and revalidation requirements
- Reduce repetition of method comparability
- Reduce development cost
- Ensure same quality of drug to Patients
- Ease of regulatory agency review in quality section
- Speed to market

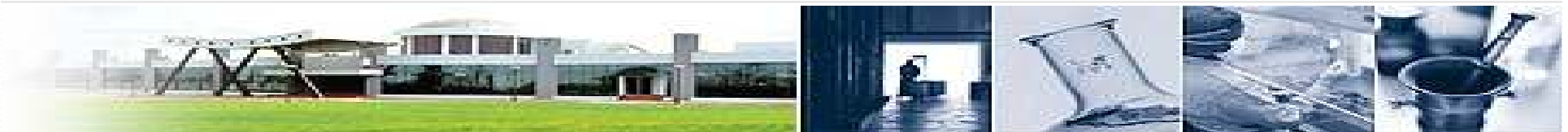


Ideal scenario for a Biosimilar company

Global reference medicinal product for
Comparability study for
Quality, Non-clinical and Clinical

&

Establishment of International
Central Testing laboratory for
Biosimilar testing & characterization



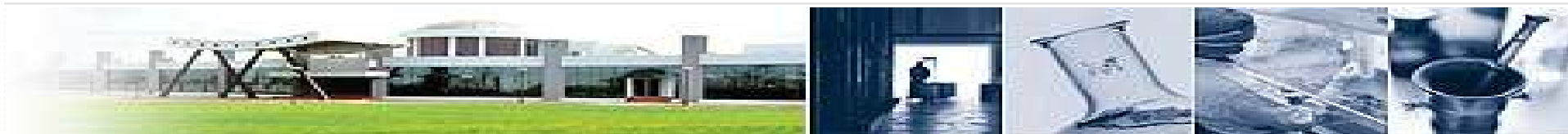
When can monographs benefit Biosimilar companies

- ❑ Methods and specs geared towards regulatory expectations
- ❑ Monograph specs should be based on the approved products
- ❑ One Reference Standard for both purity tests and bioassay (quality same as approved product)
- ❑ Reference standard available before the monograph is published
- ❑ Inclusion of methods based on inherent issues & structural issues of molecules

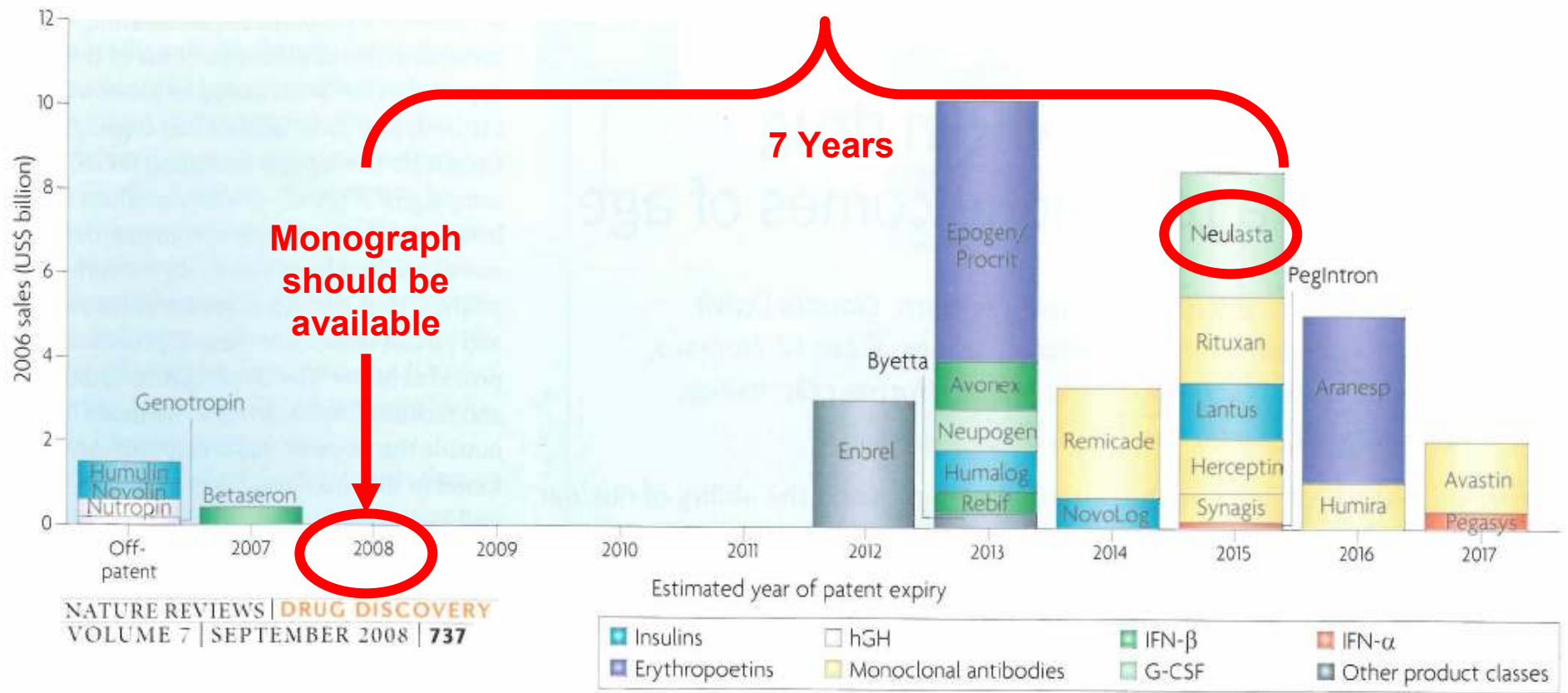


When can monographs benefit Biosimilar companies

- ❑ Amend and add new general chapters
- ❑ For columns and reagents should have multiple vendors
- ❑ Involve biosimilar manufacturer during monograph development
- ❑ Extensive collaborative analysis prior to finalization of monograph & reference standard
- ❑ Publish monograph 7 yrs prior to patent expiry as Biosimilar companies start work at that time



Patent expiry & Monograph availability



Monographs available and required by 2020

Currently available monographs for biotech (rDNA)

- o EPO - EP
- o IFN alpha 2b - EP
- o G-CSF - EP
- o hGH - EP and USP
- o Insulin - EP and USP
- o Factor IX - EP and USP

Indian Pharmacopoeia initiative - (EPO, G-CSF, IFN, Streptokinase)

General chapters in pharmacopoeia EP, USP and IP

Monograph required for major molecules expiring by 2020

- o Peg L-Asparaginase
- o Etanercept
- o Peg-filgrastim
- o Follicular stimulating factor
- o Peg-interferon alpha 2b
- o Follitropin
- o Interleukin 2
- o Exenatide
- o Darbepoietin
- o Various Mabs

- o **7 years before expiry is key**

