Challenges in demonstrating API sameness for drug products with complex APIs

Francis-Xavier Barretto

Chief Scientific Officer

Swati Spentose Pvt. Ltd.

SWATI SPENTOSE PVT. LTD.

Overview

- What are complex generics, examples
- Broad strategies to demonstrate equivalence in API sameness for complex generics
- Importance in understanding where molecular diversity comes from
- Factors to keep in mind before embarking on sameness
- Case study
- Other challenges

Complex APIs

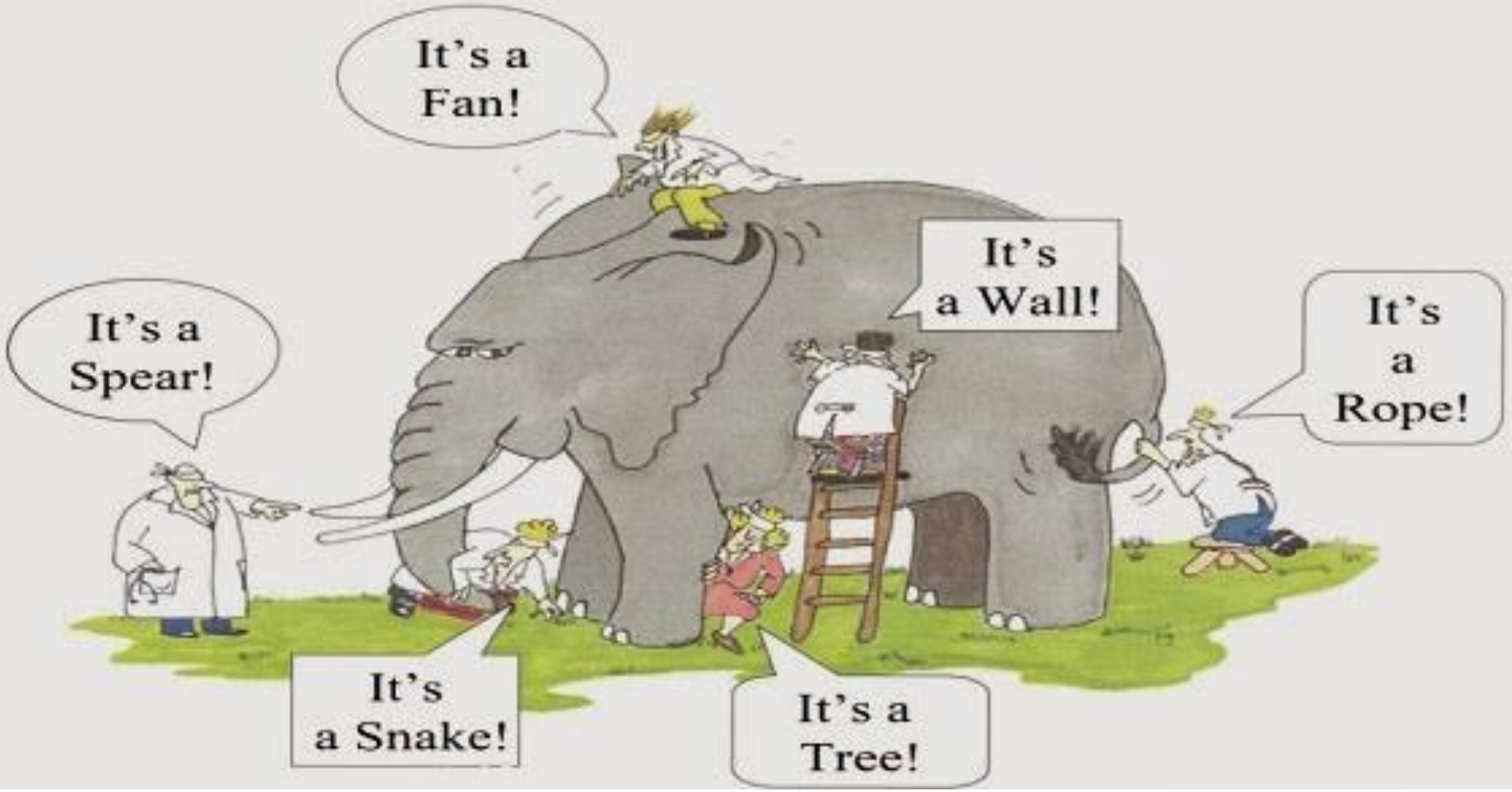
A complex API is often a mixture of different components and can contain a distribution of molecular weight. Any product whose labeling indicates that it is a mixture of active components or whose chemical structure formula includes repeating structure units or a range of molecular weights is considered complex.

Enoxaparin sodium, pentosan polysulfate sodium, glatiramer acetate

A naturally derived product containing a mixture of components is also often classified as a complex API.

Natural source (Crofelemer, conjugated estrogens)

Challenges in demonstrating API sameness



Challenges in understanding the product – before embarking on sameness

SWATI SPENTOSE PVT. LTD.

- What does the final product look like
- Understanding where molecular diversity comes from
- DP labelling, patents, pharmacopoeia, literature and practical experience
- Engagement with SME

Totality of evidence

- Starting material
- Process and process signatures
- Physicochemical comparison
- In-depth compositional analysis and structural signatures, secondary structures
- Additional product-specific studies (clinical, immunological) as agreed with FDA on case-to-case basis

Preparation for sameness

- Extraction of API from RLD
- Assurance of complete extraction of API from RLD
- Negative controls – critical tool in sameness evaluation

  To prove sensitivity of the analytical methods

  Ensure understanding and control of the manufacturing process.

Physicochemical properties

- Pharmacopoeia
- Substance specific tests:
  - MW, polydispersity
  - AA composition
  - Elemental analysis
  - Functional groups
  - Degrees of substitution
  - FT-IR, Raman spectroscopy
  - NMR (^{1}H, ^{13}C, Solid State)
  - Circular Dichroism
  - DSC, TGA
  - XRD, TEM, AFM (iron carbohydrate complexes)

High resolution methods for analysis

SWATI SPENTOSE PVT. LTD.

- To analyze
  - intact API
  - fragments and individual building blocks
- Can provide detailed insight into the molecular diversity, and with appropriate quantification, can establish equivalence
- Enzymatic digestions for peptide mapping, building block analysis
- 2D-NMR
- Capillary Zone Electrophoresis
- LC-MS
- RP-HPLC
- SAX-HPLC
- CTA-SAX

Evaluation of data – How?

SWATI SPENTOSE PVT. LTD.

- Aim of the analysis is important
- Quality Range based
- T-test
- Confidence interval based Equivalence test

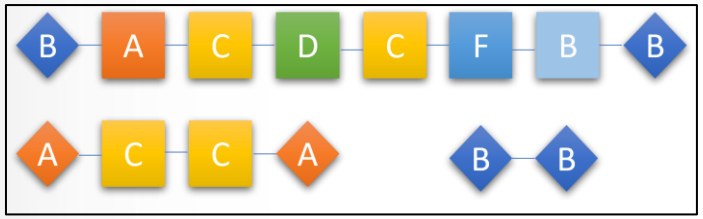
Chemometrics

SWATI SPENTOSE PVT. LTD.

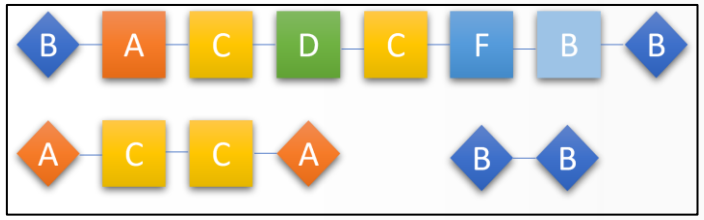
- Multivariate analysis
  - PCA – Enoxaparin sodium
  - Sparse PCA – Glatiramer acetate
- Data treatment?
- Essential to use PCA as support rather than necessity
- Good tool for QC, use in sameness is possible, but within boundaries

Case Studies

Surpassing challenges in Enoxaparin API sameness – Landmark framework



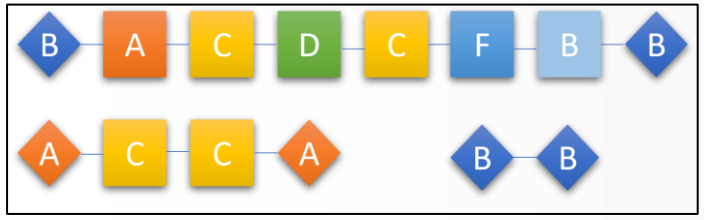
Innovator



Conclusion: Additional proof of sameness

Criterion 4: Equivalence in biological & biochemical assays
Criterion 5: Equivalence of in-vivo pharmacodynamic profile

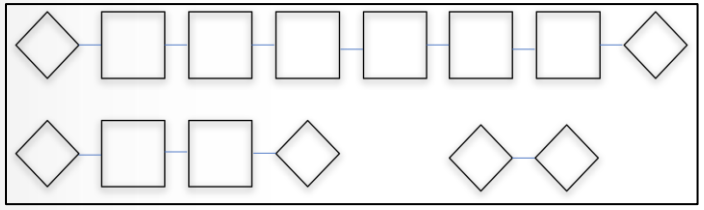
Generic product
Same or not same?



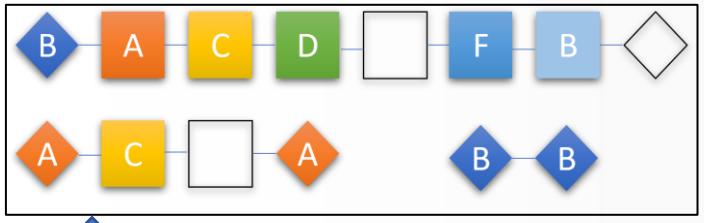
Conclusion: composition & sequences are the same

Criterion 1: Evaluation of physicochemical properties

Criterion 3: Equivalence of disaccharide building blocks, fragment mapping and sequence of oligosaccharide species



Conclusion: composition & sequences may differ



Conclusion: composition & sequences are similar

Criterion 2: Equivalence of heparin source and mode of depolymerization

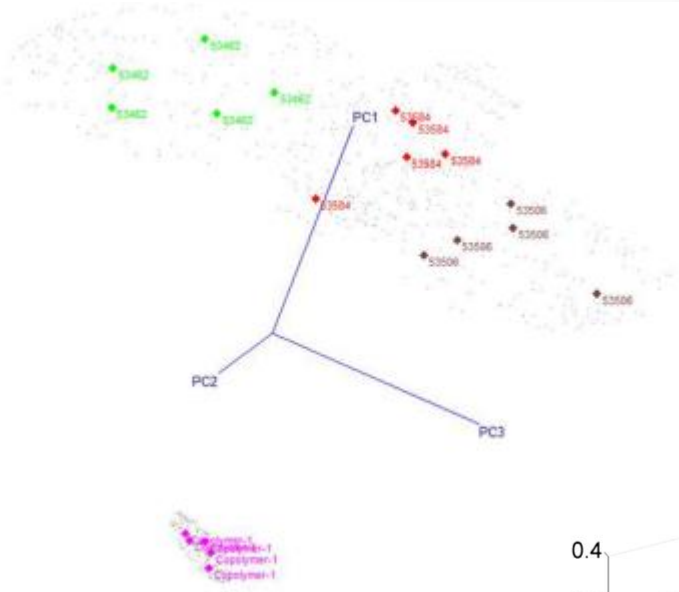
Challenges in PPS – Personal Experience

SWATI SPENTOSE PVT. LTD.

Source of naturally-occurring starting material – should be the same as that used to manufacture the drug substance.	Same starting source with all proof, documentation & ancillary information as requested by FDA
Physicochemical properties – molecular weight distribution, overall structural properties or characteristic fingerprints of the proposed PPS, including (but not limited to) the degree of sulfation, sodium content, Raman and IR spectra	Established this equivalence using tests recommended by FDA as well as in-house analysis
The monosaccharide building block composition and chain branching of the proposed PPS should be equivalent, including (but not limited to) xylose units, sulfation pattern, glucuronic acid groups, linkages, and anomeric configurations.	Used orthogonal tools, and have included tests like 2D-NMR and Capillary Zone Electrophoresis

Chemometrics – sparse PCA

- Here, a glatiramoid Copolymer 1 can be shown to be quite different to the innovator glatiramer.
- What can also be seen is that the 3 distinct spaces represent 3 batches of same product, therefore allowing to demonstrate batch to batch variability
- The actual composition between the 2 products is very similar, and differences seen are due to a small proportion of the total structure



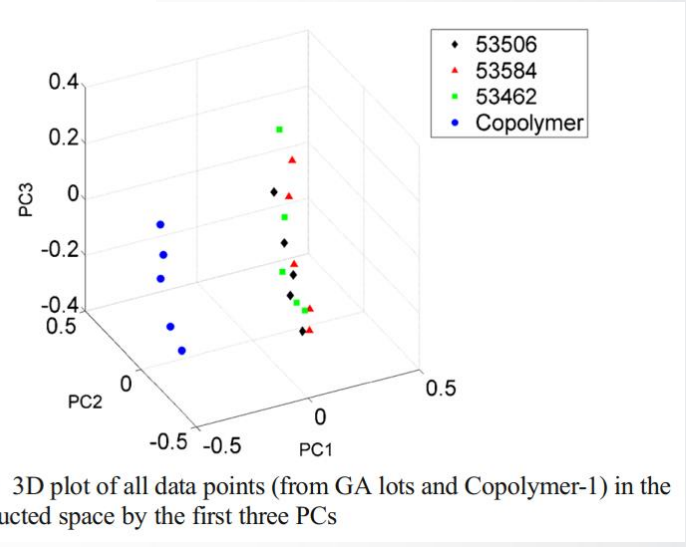


Fig. 8 3D plot of all data points (from GA lots and Copolymer-1) in the constructed space by the first three PCs

Other challenges

RLD availability

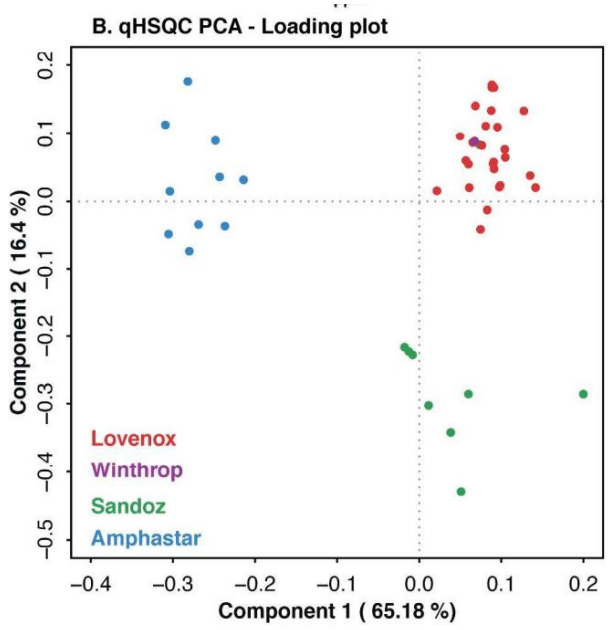
- Difficult to understand whether API used in different batches is from the same lot, hence need to expand library
- Chemometrics is dependent on large number of RLD samples to build a library
- May not be possible to find enough RLD for plethora of studies – considering that disease may be orphan
- High cost of RLD

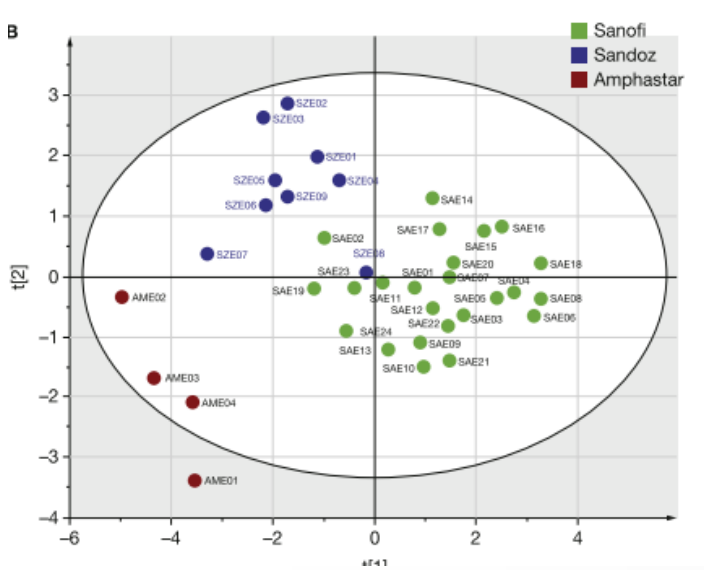
Similar products (similar activity but different APIs)

- FDA learns with you – FDA funded research, company experimental data, literature
- Broad areas of similarity, but critical to know where this area begins and ends
- Concepts may be applicable, but methods may not be transferrable
- Critical to engage with FDA so that best decisions can be taken - PSG

Chemometrics

- Where do we stand now?
- Loading plot of different enoxaparins approved by FDA
- Are there significant differences between the innovator and the generics?





Some questions that have to be evaluated by all stakeholders

SWATI SPENTOSE PVT. LTD.

- When is the work enough?
- State-of-the-art is ever evolving, is perfection demanded?
- RoI? – time to market vs. regulatory uncertainty

Engagement with FDA

SWATI SPENTOSE PVT. LTD.

- Controlled correspondence
- Pre-ANDA meeting
- The goal is to resolve or get clarity in criteria for API sameness as early as possible in the development phase, in order to increase chances of a favorable ANDA review

When it comes to complex generics,
history is written by people who attend meetings.

It is complex, not complicated. Make it simple.

References

- MAPP 5240.10 https://www.fda.gov/media/157675/download
- Lee *et al.* "Scientific considerations in the review and approval of generic enoxaparin in the United States." *Nat Biotechnol* 31, 220–226 (2013)
- Rogstad *et.al* "Modern analytics for synthetically derived complex drug substances: NMR, AFFF–MALS, and MS tests for glatiramer acetate" Anal Bioanal Chem (2015) 407:8647–8659
- Guerrini *et. al.* "Differentiation of Generic Enoxaparins Marketed in the United States by Employing NMR and Multivariate Analysis" Anal. Chem. (2015), 87, 16, 8275–8283
- Mourier *et. al.* "Analytical and statistical comparability of generic enoxaparins from the US market with the originator product." J Pharm Biomed Anal. (2015), 115:431-42.
- https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020193.pdf

THANK YOU

Francis-Xavier Barretto

Chief Scientific Officer

Swati Spentose Pvt. Ltd.

francis@spentose.com