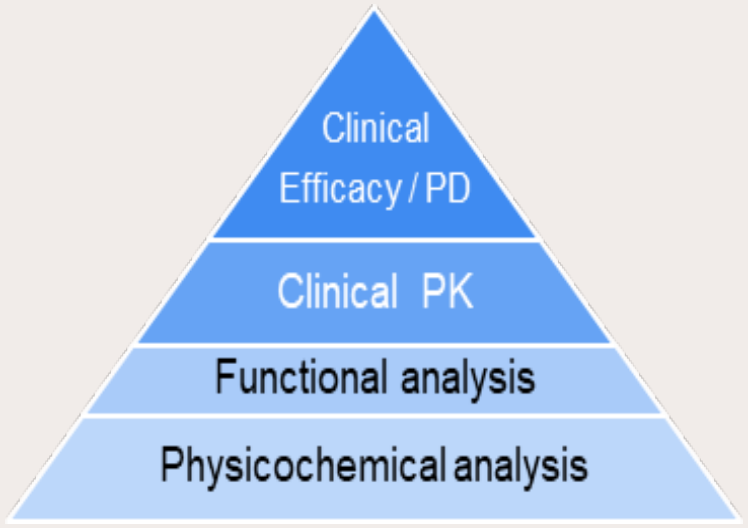
Martin Schiestl
Global Head Regulatory Policy
GRx+Biosims Conference
21 – 23 October, Bethesda

Ustekinumab case support adequacy of immunogenicity confirmation in a Streamlined Biosimilar Development

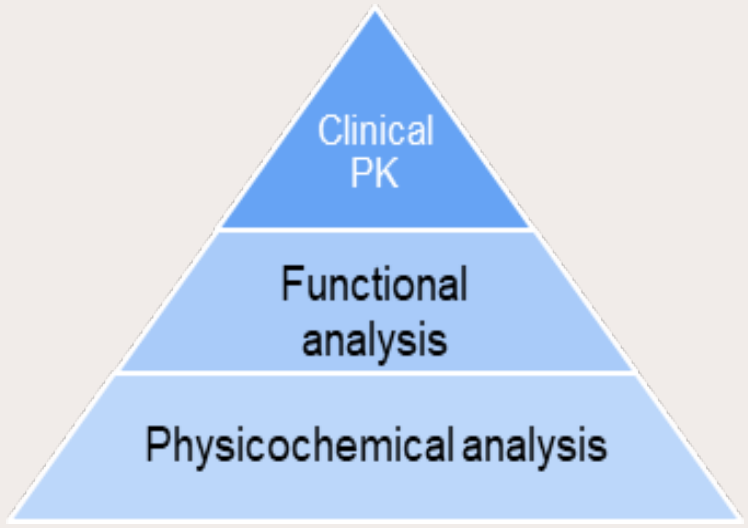
SANDOZ

Definition of a streamlined biosimilar development

- Streamlined Biosimilar Development as used in this slide deck means a future development and approval of biosimilars based on analytical (physicochemical and functional studies) and clinical pharmacokinetic (PK) comparison without the need for clinical comparative efficacy studies (CES), whether using pharmacodynamic (PD) marker or traditional clinical efficacy endpoints.



Today's default



Streamlined biosimilar development
Anticipated default

SANDOZ

How to ensure same immunogenicity in a streamlined biosimilar development?

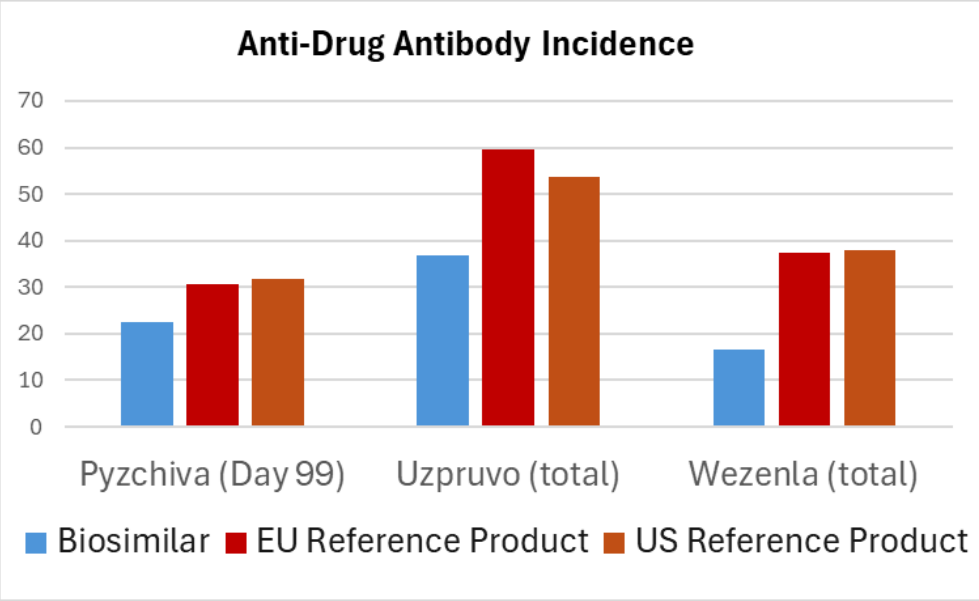
- Comparable immunogenicity is the result of [1,2]
  - Identicality of the amino acid sequence
  - Same T-cell epitopes, i.e. linear peptides formed by degradation of a protein
  - Today's analytical methods and quality standards adequately control risk factors that may increase unwanted product related immunogenicity
    - Keep impurities low, such as aggregates, non-human glycans etc.
- Clinical pharmacokinetic trial delivers confirmatory safety and immunogenicity data
- The Ustekinumab case study demonstrates the robustness of the immunogenicity confirmation by analytical and clinical PK data alone
  - adequacy of controlling risk factors such as non-human glycans, and the
  - sensitivity of a single dose PK study in healthy volunteers

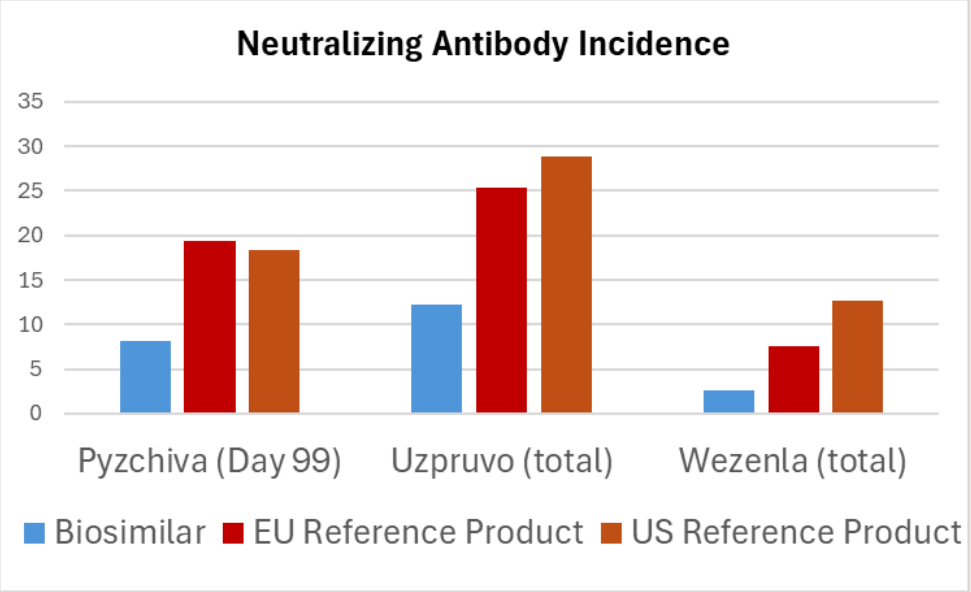
1. Kurki et al. BioDrugs 31, 83–91 (2017). https://doi.org/10.1007/s40259-017-0210-0
2. Kurki et al. Drugs 81, 1881–1896 (2021). https://doi.org/10.1007/s40265-021-01601-2

SANDOZ

A clinical PK study in healthy volunteers can be a sensitive tool in comparing unwanted immunogenicity

- Single dose PK studies in healthy volunteers revealed a numerically lower immunogenicity of Ustekinumab biosimilars compared to the reference product
  - Anti-drug antibody values depend on the assay sensitivity of the respective study





Reference: EPAR Pyzchiva, EPAR Uzpruvo, EPAR Wezenla

SANDOZ

Non-human glycans are known risk factors for unwanted immunogenicity

- Non-human glycans: α-1,3-gal and N-glycolylneuraminic acid (NGNA)
- Ustekinumab biosimilars contain less non-human glycans (see next slide)
- Impact of manufacturing cell-line:
  - SP2/0 cell lines produce typically higher amounts of non-human glycans than CHO cell lines [1]
- Immunogenicity risk of α-1,3-gal structures is supported by evidence
  - α-1,3-gal present on the Fab portion of cetuximab is associated with causing anaphylaxis in some patients [1, 2]
  - α-1,3-gal Fc glycans (especially when bivalent) can also bind to anti-α-1,3-gal antibodies and should be therefore considered as a critical quality attribute [2]
  - Immunogenicity against α-1,3-gal is associated with allergy against red meat [3]
    - Risk factor are bites from the lone star tick which cause high-titer IgE Ab to α-1,3-gal

1. Hatfield et al., mAbs 2023; 15:1, https://doi.org/10.1080/19420862.2023.2239405
2. Chung et al., N Engl J Med 2008; 358:1109-1117
3. Berg et al., Ann Allergy Asthma Immunol 2014; 112:97-101

SANDOZ

Biosimilar Ustekinumabs contain less non-human glycans

- Public data show lower levels of non-human glycans in the Ustekinumab biosimilars compared with the reference product [1,2,3]
  - Other risk factors for unwanted immunogenicity are comparable
  - Lower Non-human glycan contents correlate with lower ADA levels in PK study

EPAR	Biosimilar α-1,3 gal	Reference product α-1,3 gal	Biosimilar NGNA	Reference product NGNA	Host Cell Line
Pyzchiva [1]	“lower”	“higher”	Not detected	Detected	CHO
Uzpruvo [2]	“much lower levels”	higher	Similar levels	Similar levels	SP2/0
Wezenla [3]	“does not contain α-1,3 gal”	1.7 – 4.9 %	Not detected	Detected	CHO

Remark: One biosimilar is, as the reference product, produced in SP2/0 cells, which corroborates hypothesis of causal relationship of immunogenicity and non-human glycans by exclusion of other cell-line dependent factors.

1. EPAR Pyzchiva, accessed 20 Sep 2024
2. EPAR Uzpruvo, accessed 20 Sep 2024
3. EPAR Wezenla, accessed 20 Sep 20204

NGNA: N-glycolylneuraminic acid; ADA: Anti-drug antibody

SANDOZ

Conclusions

- Ustekinumab case study demonstrates that confirmation of comparable immunogenicity can be robustly assessed by comparative analytical and clinical PK data alone
  - Retrospectively, the comparative efficacy studies for Ustekinumab biosimilars in patients would not have been needed for a differentiated evaluation of immunogenicity

- Risk factors for unwanted immunogenicity can be assessed and controlled by analytical methods
  - Analytical data enable the conclusion of comparable immunogenicity already

- A single dose PK study in healthy volunteers can be a sensitive tool to confirm comparable immunogenicity in the clinical setting

SANDOZ