The Challenges of Legal Basis Selection of a Complex Development.

Dr. Parvinder Punia – Pharmexon Consulting

This Presentation Represents the Opinions of the Author…

- ✓ Background is from a PhD in UK
- ✓ Then joined the Agency life – MHRA and INFARMED (EMA committees)
- ✓ After which I was Global Head of RA in Industry….
- ✓ Finally as a Consultant – now with a team of ex-Assessors serving the Industry with the immense background and expertise of their experience as Regulators, Committee Members and Authors of Guidelines

I also like to ride my bike and its why you see a slightly disfigured speaker today!

Deciding the Legal Basis ?

The current purpose is not to decide on the 8.3 – this presentation will focus on 10.1 and 10.3

- Article 10.1 – simply explained is the simple generic – matches criteria of bioequivalence needs, simple Quality development. Clear reference product available and recognised.
- Article 10a - Well- established use – more complex qualification criteria – 10 years of established medical knowledge, safety, lack of reference product, no true known reference known. Biologicals are out of scope. This article has its own issues -not for discussion today!
- Biosimilar – 10.4 – clear reference product of biological origin – where the 10.1 does not apply
- 10b – new fixed dose combinations – new combination of known actives in a single dosage form.

Definition of Article 10.1

- Same active substance,
- Same amount of active substance (strength),
- Same pharmaceutical form, and
- Bioequivalence has been demonstrated by appropriate bioavailability studies (where necessary).

No need to provide additional non-clinical tests or clinical trials

Article 10.3

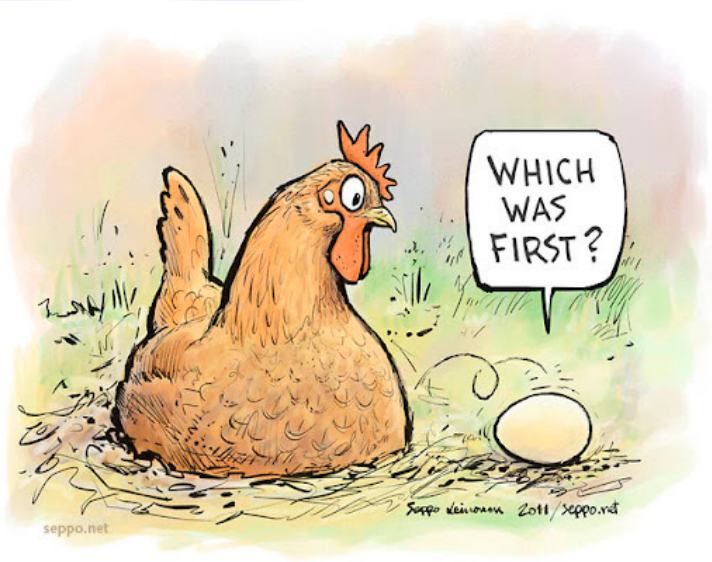
This is a more complex legal basis to define against the standard requirements.

- Definition is clear for most types of developments:
- The strict definition of a generic medicinal product is not met,
- Where bioequivalence cannot be demonstrated through bioavailability studies, or, in case of changes in active substance(s), therapeutic indications, strength, pharmaceutical form, or route of administration compared to the reference medicinal product.

10.1 versus 10.3 – Can the Applicant Choose Freely?

- Product development and choice of legal basis are interrelated?
- At which point does the Sponsor decide on the legal basis?
- How can product specific guidelines help us?
- What about the grey area development?

This is a chicken and egg situation



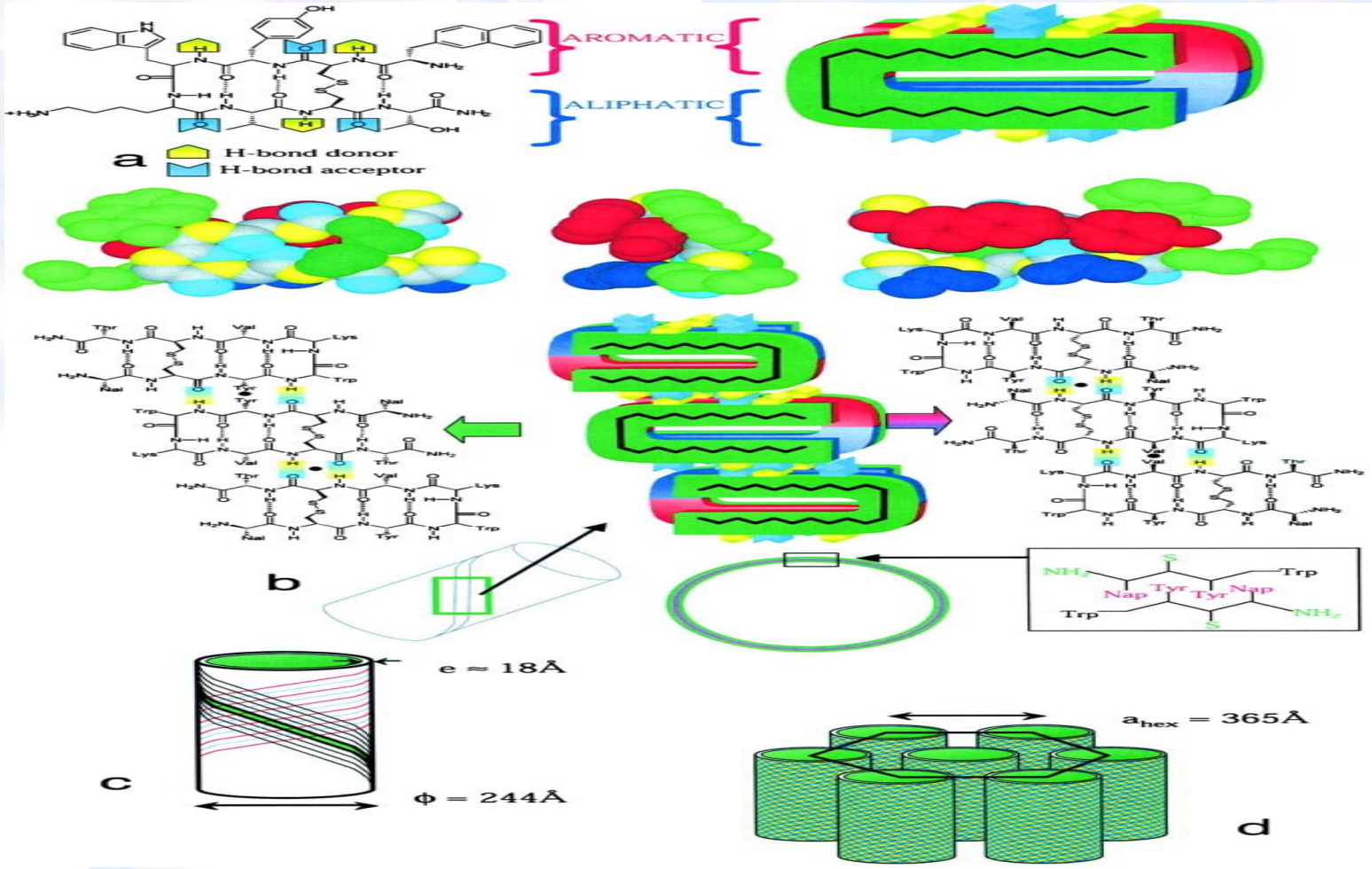
Product Specific Guidance – What Are They For?

- FDA: “Product-specific guidance (PSGs) provide recommendations for developing generic drugs and generating the evidence needed to support abbreviated new drug application (ANDA) approval, thereby helping to streamline generic drug product development by industry and ANDA assessment by FDA.”

- EMA: “ To further develop the regulatory framework for demonstration of bioequivalence, it is considered valuable to develop product-specific guidance based on the general principles. This should facilitate transparent, predictable and scientifically robust assessment in future marketing authorisation procedures.”

But not guidance for the regulatory pathway or legal basis…..should the PKWP consider it during their discussion?

Can Anyone Guess What This Is?



Lanreotide

- Lanreotide is a synthetic analogue of somatostatin, a naturally occurring inhibitory hormone which blocks the release of several other hormones, including growth hormone, thyroid-stimulating hormone (TSH), insulin and glucagon. Lanreotide binds to the same receptors as somatostatin, although with higher affinity to peripheral receptors, and has similar activity.
- However, while somatostatin is quickly broken down in the body (within minutes),[7] lanreotide has a much longer half-life, and produces far more prolonged effects

Lanreotide – Case Examination

Citations from PAR:

- The application was made with reference to article 10(1) of Directive 2001/83/EC, as amended, i.e. a generic application.
- The reference product is Somatuline Autogel solution for injection in a prefilled syringe by Ipsen Pharma GmbH registered since 18-04-2005 in Germany. In Denmark the reference product is approved under the product name Ipstyl Autogel
- As part of the development of the product a quality sameness study was carried out. Batches of Myrelez were compared with batches of the reference product using a range of orthogonal techniques, NMR, different HRMS methods, and infra-red based techniques and in-vitro dissolution covering identity of the active substance, assay for peptide and acetate contents, molecular conformation of lanreotide in drug product, higher-order structure and other product-related properties and in-vitro dissolution.
- A quality sameness study has been provided as the pivotal study in support of the generic application for a solution for injection in a prefilled syringe and a single-dose bioequivalence study is presented as supportive data

Lanreotide – Case Examination

- Bioequivalence study
- The applicant presents single dose parallel design comparative bioavailability study with the proposed Lanreotide 120 mg solution for subcutaneous injection in a prefilled syringe using the marketed product, Somatuline Autogel® (lanreotide) 120 mg solution for subcutaneous injection in a prefilled syringe as reference product.
- The bio-equivalence study was an open-label, randomized, one-treatment, one-period, two-arm parallel single-dose bioavailability study. A 120 mg solution for subcutaneous injection in a prefilled syringe of either the test product, Myrelez (lanreotide) or the reference product, Somatuline Autogel® (lanreotide), was administered once.
- The study included 140 subjects (70 in each treatment group). 137 subjects were included in the statistical analysis of lanreotide.
- The primary variables for the assessment of bioequivalence were AUC0-t, Cmax and Cτ for lanreotide. AUC0-∞ and various partial Cmax and AUCs were evaluated as secondary variables.

Lanreotide – Bioequivalence Results

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) Treatment	AUC0-t xg/ml/h	AUC0-∞ xg/ml/h	Cmax xg/ml	Cτ Pg/ml	tmax h
Test	3710345.6 (±1084915.4)	4373842.3 (±1152184.7)	9567.7 (±8677.9)	1670.1 (±633.4)	10.00 (4.00–672.00)
Reference	3449672.3 (±1015257.8)	4064815.4 (±984000.1)	9781.6 (±18192.1)	1637.9 (±664.7)	12.00 (4.00–672.00)
*Ratio (90% CI)	107.34 (98.29 - 117.23)	106.79 (98.41 - 115.89)	108.09 (86.91-134.43%)	102.23 (89.38-116.92)	-

AUC0-t Area under the plasma concentration curve from administration to last observed concentration at time t.

AUC0-∞ Area under the plasma concentration curve extrapolated to infinite time.

Cmax Maximum plasma concentration

Cτ Plasma concentration at the end of the dosing interval

tmax Time until Cmax is reached

Conclusion on bioequivalence studies:

The results for the parameters AUC0-t, AUC0-∞ and Cτ lie within the normal bioequivalence acceptance limits of 80.00-125.00%, whereas the results for Cmax (86.91-134.43%) were outside the upper limit of the acceptance range. The bioequivalence study was considered inconclusive due to the very high inter-subject variability for lanreotide observed in the parallel design study and hence underpower of the study

Scientific Advice Schedule

(EMEA/H/SA/3188/1/2015/II) regarding the possibility of a biowaiver based on equivalent properties and structural characterisation of the applied product as compared to the reference product.

- In the 2015 Scientific Advice it was confirmed that the development approach was generally acceptable, with some uncertainties expressed over the biowaiver, namely that the PK study waiver will largely depend on the quality and results of in vitro tests.

In follow-up Scientific Advice (EMEA/H/SA/3188/1/FU/1/2018/I) the applicant was seeking advice on waiving a multiple-dose study.

- In the follow-up Scientific Advice, it was agreed that steady-state studies could be waived provided that the single-dose study was sufficiently descriptive of the PK performance of the generic lanreotide. Single-dose study design was not discussed in great detail, and a recommendation to follow the Modified Release Guideline was made.

Scientific Advice During The Procedure

(EMEA/H/SA/3188/1/FU/2/2020/II) was requested during the clock-stop period regarding the acceptability of basing the similarity between the applied product and the reference product on the quality sameness study and have the bioequivalence study as supportive data.

- **Waiver of a multiple-dose study was accepted based on the additional partial metrices calculated in the single-dose study.**
- **This could be justified based on the simple composition of product and the special properties of the active substance, responsible for the prolonged-release profile of the product. The formulation, consisting of a supersaturation of active substance in water/acetic acid, leads to the peptide self-assembling into nanotubules, forming a gel, which results in a prolonged-release profile.**
- If the Applicant want to follow a Biowaiver with the current BE study, an Article 10(3) would be more appropriate. If the Company want to follow a BE study, an Article 10(1) is better. CHMP advice has not been followed (except the one regarding the waiving of the Multiple dose study).

Was the legal basis discussed?

FDA Guideline - 2014

Option 1: biowaiver

A waiver of in vivo bioequivalence study will be granted if the test product demonstrates equivalent molecular, structural, and thermodynamic properties as the reference listed product. Lanreotide conformation, nanotube structure, and thermo stability at different temperature and dilution should be characterized. In addition, acceptable comparative in vitro drug release-rate tests of lanreotide acetate from the test and RLD formulations should be demonstrated. The comparative study should be conducted with at least three lots of both reference and test products.

Option 2: in vivo bioequivalence study

Type of study: Fasting
Design: Single-dose, randomized, parallel in vivo study
Strength: EQ 120mg base (Dose: EQ 120 mg base)
Subjects: Healthy males and females, general population
Additional Comments: The products should be administered as a deep subcutaneous injection at the superior external quadrant of the buttock.

Analytes to measure (in appropriate biological fluid): Lanreotide in plasma

Bioequivalence based on (90% CI): Lanreotide

EMA Guideline - 2022

15, December 2022 EMA/CHMP/559891/2021 Committee for Medicinal Products for Human Use (CHMP) Lanreotide acetate, prolonged-release solution for injection in prefilled syringe 60, 90 and 120 mg product specific bioequivalence guidance

	90% confidence interval: 80.00–125.00%
Waiver of bioequivalence study	A waiver of in vivo bioequivalence studies may be granted if the test product has the same quantitative composition as the reference product and demonstrates equivalent molecular, structural, and thermodynamic properties as the reference product using a range of orthogonal techniques. These studies could include: • Molecular structure characterisation (peptide sequence): HRMS (High Resolution Mass Spectrometry) and NMR • Molecular scale organisation: FTIR spectroscopy & FT-Raman spectroscopy • Supramolecular scale organisation (peptide folding): Freeze-fracture TEM, Small-Angle X-ray Scattering (SAXS) and Wide Angle X-ray Scattering (WAXS) or similar methods • Thermal stability: temperature-dependent SAXS.

	• Water behaviour: Differential scanning calorimetry (DSC) • Rheological property characterisation: Injectability measurements • In vitro dissolution study At least 5 batches of the test and reference product should be included in the comparability studies. *More batches may be needed in case of higher variability of the reference product results.* The selection of studies, choice of statistical methods and acceptance criteria should be justified.

Other Products – My Curiosity…

- Liraglutide 10.1 - DE/H/7650/001 – with BE study
- Liraglutide – DK as RMS – 10.1 –no PAR -??
- Teriperatide - Centrally Approved – EMEA/H/C/005793/0000 - 10.3 – comparison and BE study.
- Teriperatide – DCP- DE as RMS - analytical comparability – no BE study
- Teriperatide – 10.1 with – NL as RMS - BE study
- Teriperitide TEVA- 10.3 – DE as RMS - clinical and nonclinical;
- https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021318.pdf
- https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_206321.pdf

10.1 vs 10.3 – Product Specific Guidelines – Should They Help Us?

What Are The Challenges?

- Lack of knowledge of the molecule itself
- Freedom of the applicant to choose legal basis against the development
- Question for scientific advice – before BE study is performed? PILOT??
- Time?
- Lack of precedence
- Difference in SPC (not harmonised)
- Price and reimbursement – direct substitutions – some countries are sensitive to 10.3

Thank you!!!!

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Your success.

Q & A