Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PKWP – BE/PK position on specific questions

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BioBridges 26 – 27 September 2018, Prague

Disclaimer

The views expressed in this presentation are those of the speaker, and are not necessarily those of MHRA or EMA.

Overview

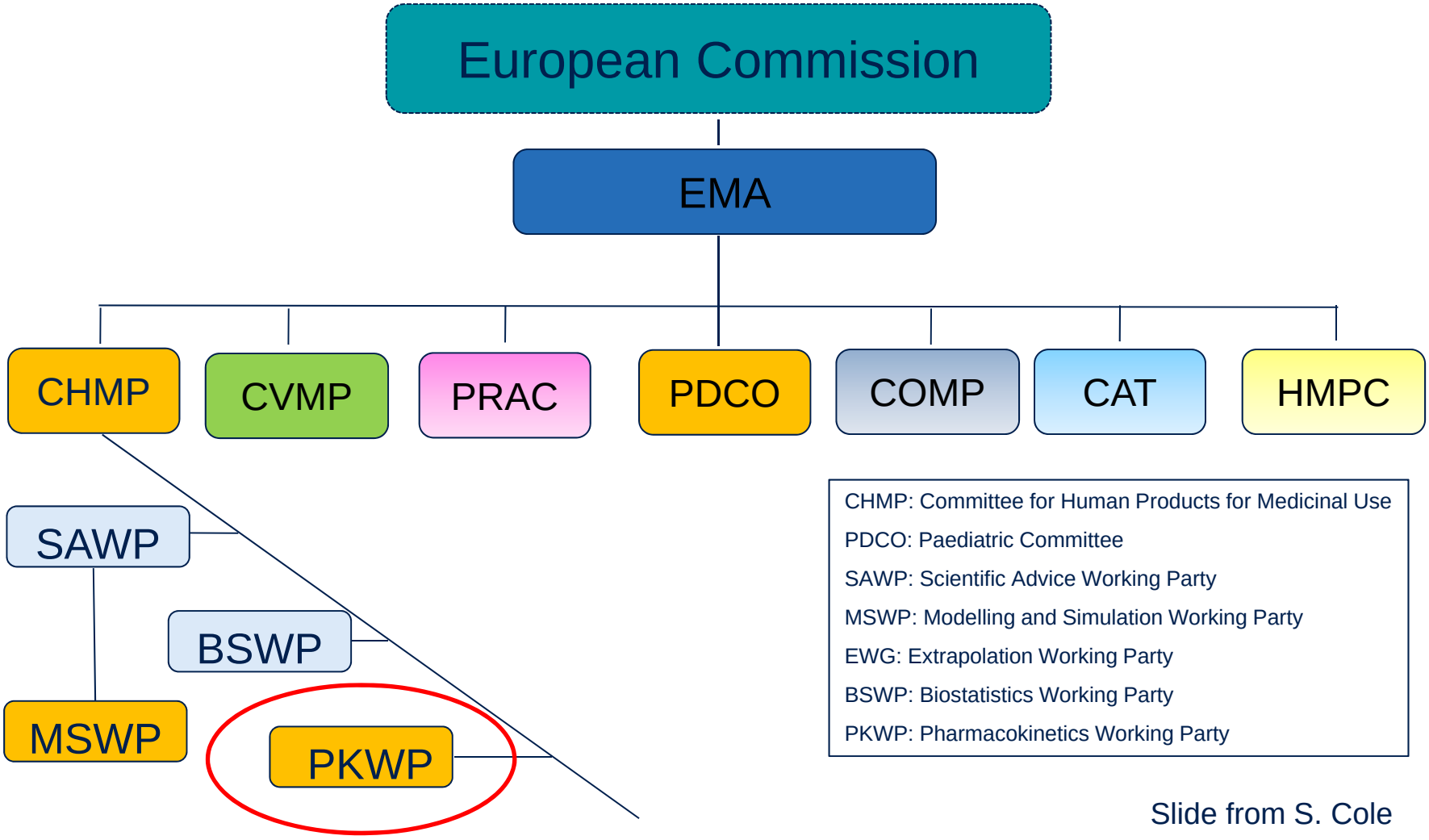
European Regulatory System

Pharmacokinetics Working Party (PKWP)

Product Specific Bioequivalence Guideline (PSBEGL)

Collaboration between PKWP and other WPs

The European Regulatory System



CHMP: Committee for Human Products for Medicinal Use
PDCO: Paediatric Committee
SAWP: Scientific Advice Working Party
MSWP: Modelling and Simulation Working Party
EWG: Extrapolation Working Party
BSWP: Biostatistics Working Party
PKWP: Pharmacokinetics Working Party

Slide from S. Cole

The PKWP 2017-18

Role	Name	Agency
Co-ordinator	Kevin Blake	EMA
Chair	Jan Welink	Netherlands
Vice-chair	Henrike Potthast	Germany
	Ridha Belaiba	France
	Eva-Gil Berglund	Sweden
	Susan Cole	UK
Experts	Sotiris Michaleas	Greece
	Janet Mifsud	Malta
	Jan Neuhauser	Austria
	Carolien Versantvoort	Netherlands
Plus additional observers		

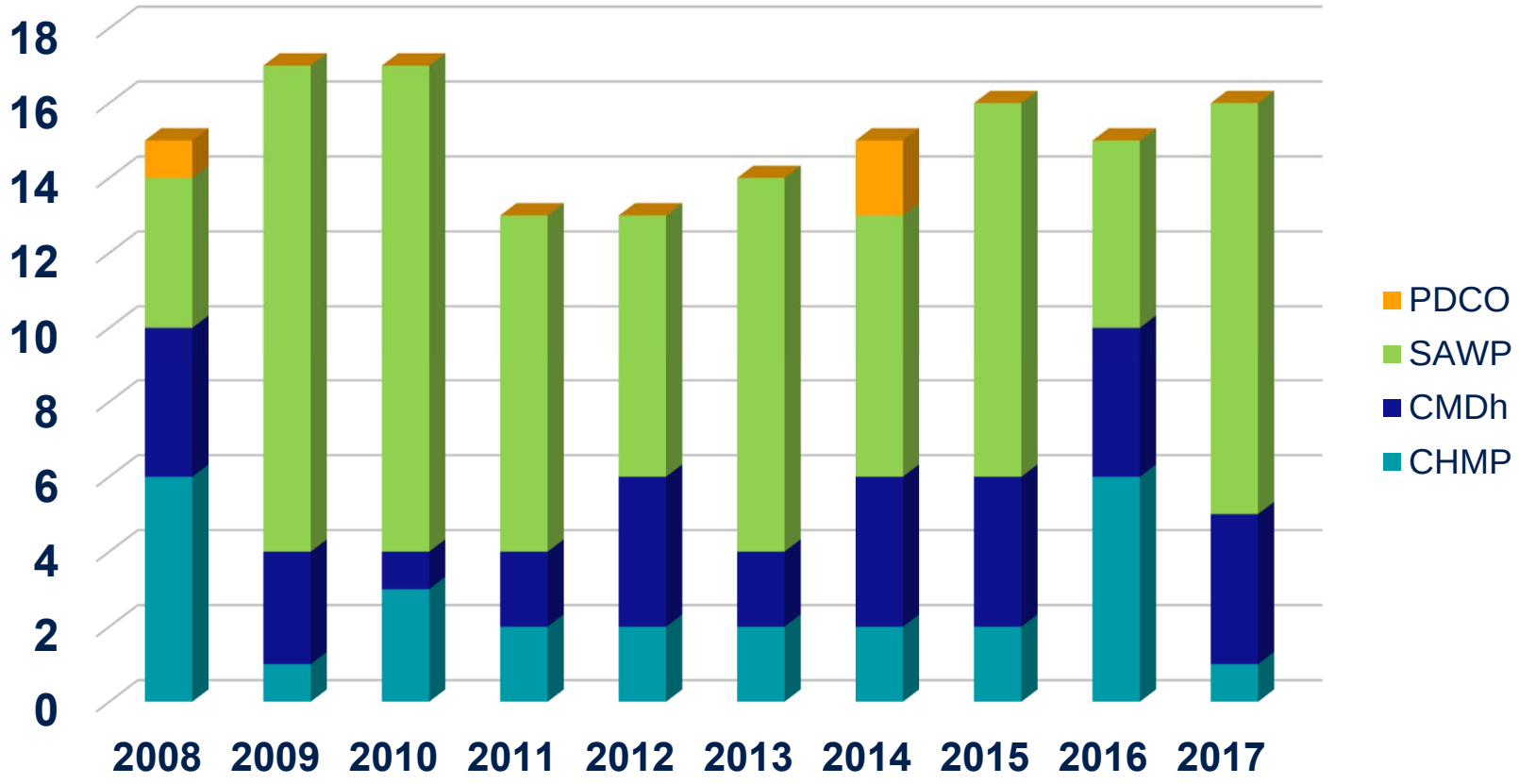
PKWP

Objective: to address specific questions in relation to PK evaluations and particularly the requirements and assessment of BE studies.

Main responsabilities:

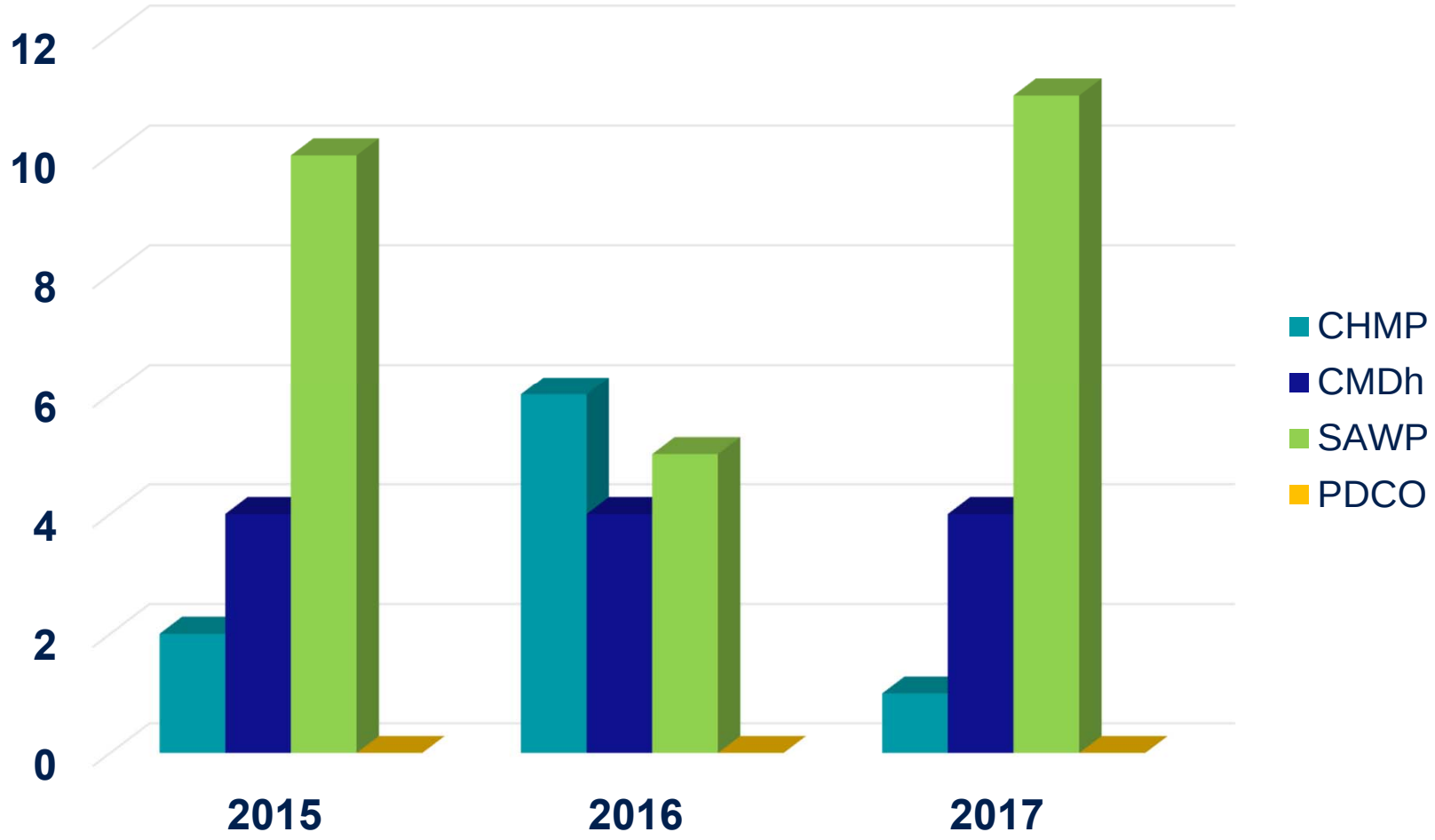
- preparing, reviewing and updating of guidelines and concept papers;
- contributing to SAWP activities upon request;
- contributing to product-related assessment following specific CHMP requests;
- preparing specific position papers and question-and-answer documents following specific CHMP requests;
- interacting with stakeholders under the supervision of the CHMP;
- European and international co-operation under the supervision of the CHMP;
- contributing to other committees' needs;
- training assessors.

Number of products requested by the origin over time



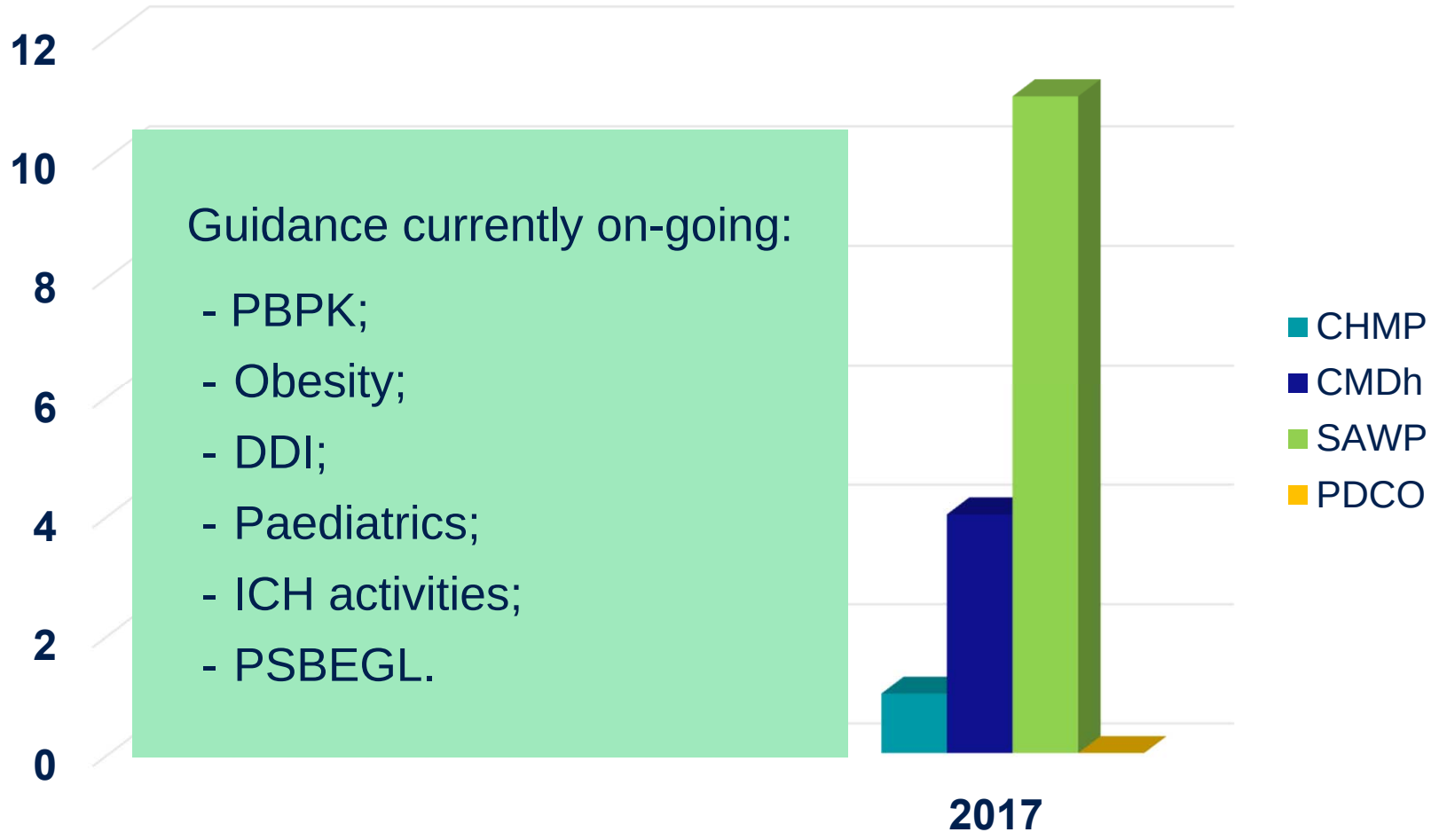
Data provided by PKWP

Number of products requested from 2015 to 2017



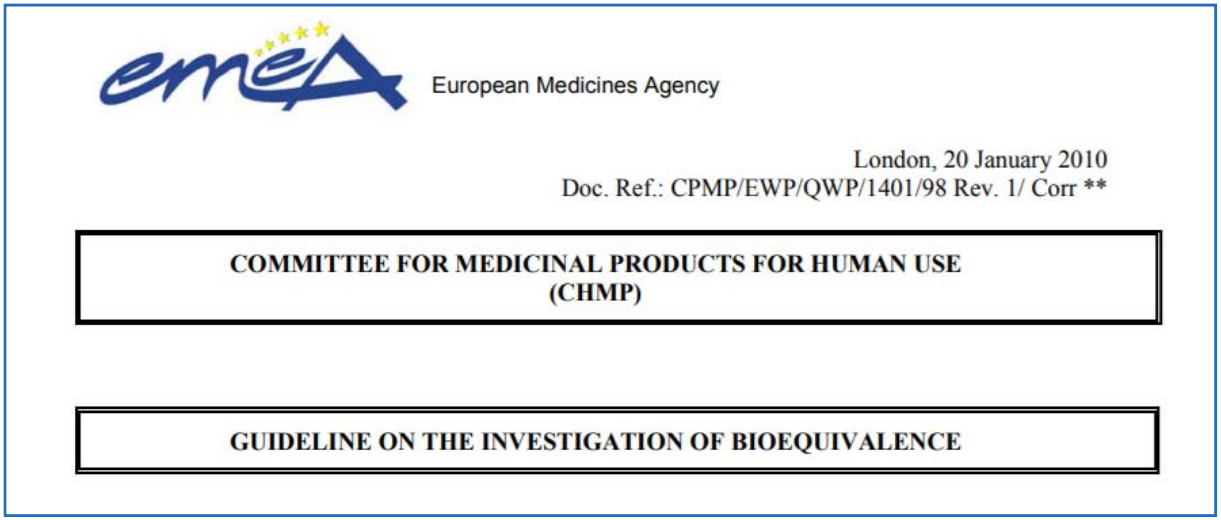
Data provided by PKWP

Number of products requested from 2015 to 2017



Data provided by PKWP

Bioequivalence guideline

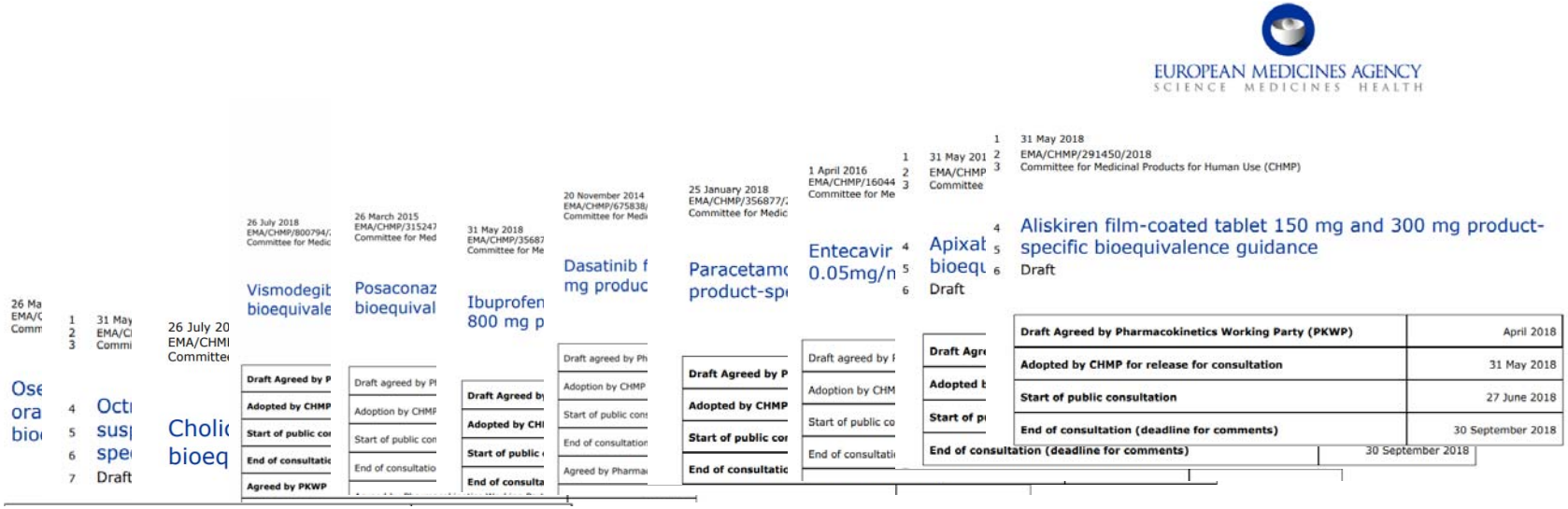


European Medicines Agency

London, 20 January 2010
Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE



http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

Bioequivalence

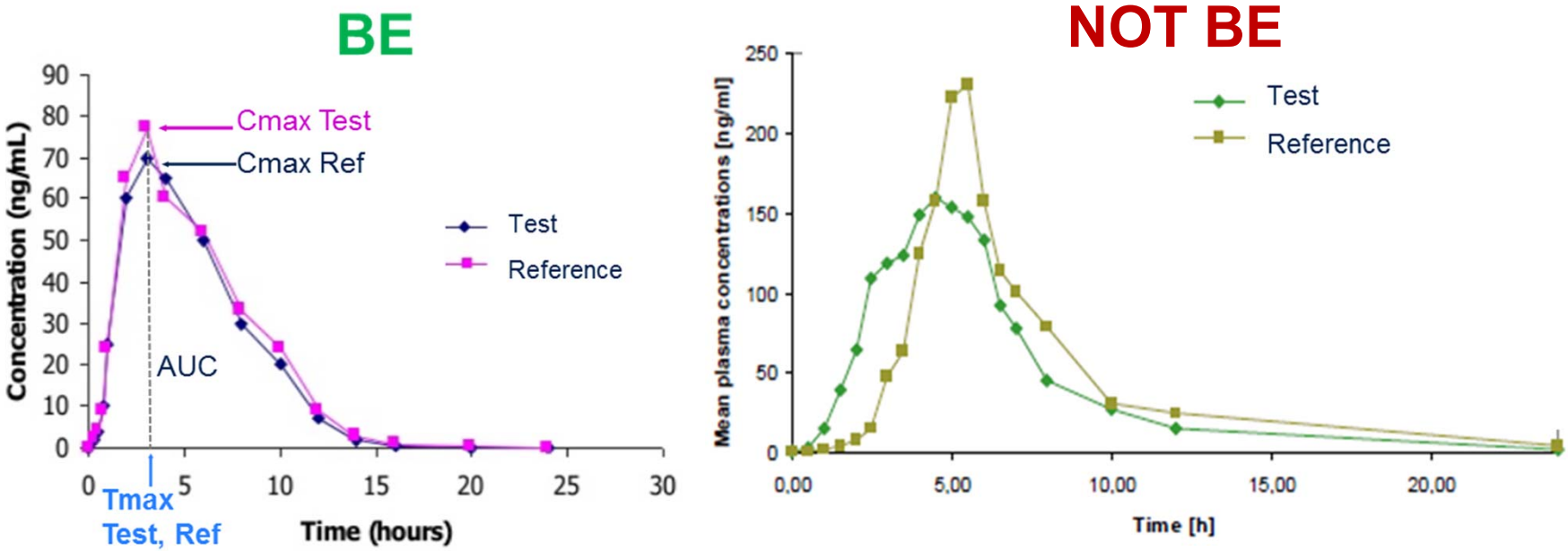
Definition

“Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits.”

Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

Bioequivalence

General criteria



BE established: 90% CI of mean T/R: 80.00 – 125.00% for Cmax and AUC

Narrow therapeutic index drugs: 90% CI of mean T/R: 90.00 – 111.11% for AUC (and Cmax, if clinically relevant)

Highly variable drugs: 90% CI of mean T/R: can be widened to a maximum of 69.84 – 143.19% for Cmax (NOT for AUC)

Questions & Answers:
Positions on specific questions addressed to the PKWP

1. Bioequivalence studies in children

2. Bioequivalence studies for generic products containing clopidogrel

3. Acceptance criteria for bioequivalence studies for losartan

4. Bioequivalence assessment of generics for tacrolimus

5. Requirements for demonstration of bioequivalence for ciclosporine generics

6. Requirements for demonstration of bioequivalence for mycophenolate mofetil generics

7. Recommendations on determination of absolute and relative bioavailability

8. Clarification on the recommended statistical method for the analysis of a bioequivalence study

9. Effect of sorbitol on the pharmacokinetics of highly permeable drug substances

10. Requirement to perform incurred sample reanalysis

11. Number of subjects in a two-stage bioequivalence study design

12. Bioequivalence studies for generic application of omega 3 fatty acid ethylesters in a soft gelatine capsule

13. Acceptability of an "additional strengths biowaiver" when bioequivalence to the reference product has been established with a BCS-based biowaiver

14. Question on a generic application for Quetiapine Lambda 200, 300, 400 mg prolonged release tablets

15. Ebastine: use of metabolite data to demonstrate bioequivalence between inactive prodrugs

16. IQ Consortium Induction Working Group Questions

17. Evaluation of orally inhaled medicinal products

18. Clarifications on the "Evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function" guideline

19. Suitability of a 3-period replicate design scheme for the demonstration of within-subject variability for Cmax

Product Specific Bioequivalence Guideline (PSBEGL)

To help applicants to meet the regulatory expectations in EU, mainly for generic applications, across all regulatory submission routes.

Contents

BCS Classification

where BCS biowaiver seems possible

Design

i.e. administration schedule, study participants, fasting/fed conditions, strength, and N. of studies.

Analyte

i.e. parent/metabolite, compartment (plasma/blood/urine), and need for an enantioselective method.

Criteria

i.e. main pharmacokinetic variables and width of confidence intervals.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000625.jsp&mid=WC0b01ac0580848f74

PSBEGL

Before public consultation

CMDh
- Compiles list of NAS to be reviewed according to the set criteria (time of MAA, envisaged number of applications, potential for large number of CMDh referrals)
- Proposed volume: 5 new NAS every 6 months

MS rapporteur
- The EMA lead requests completion of template Part A to the CHMP rapporteur of the originator product (1 month deadline. Part A remains an internal document and is never published.)
- The CHMP rapporteur of the originator product fills in Part A of the draft guidance

PKWP
- PKWP names a PKWP rapporteur (if possible, same country as CHMP Rapp)
- PKWP reviews part A of the draft guidance and fills in Part B with the available information
- Discussion with CHMP Rapp who filled Part A if there are open questions
- Draft is finalized at PKWP level

CMDh / CHMP
- The finalized draft is presented to CHMP (for adoption) and CMDh (for information)
- CHMP/ORGAM confirmed they will only discuss the GLs when they are final (ie after public consultation). At this stage they are likely adopted silently.

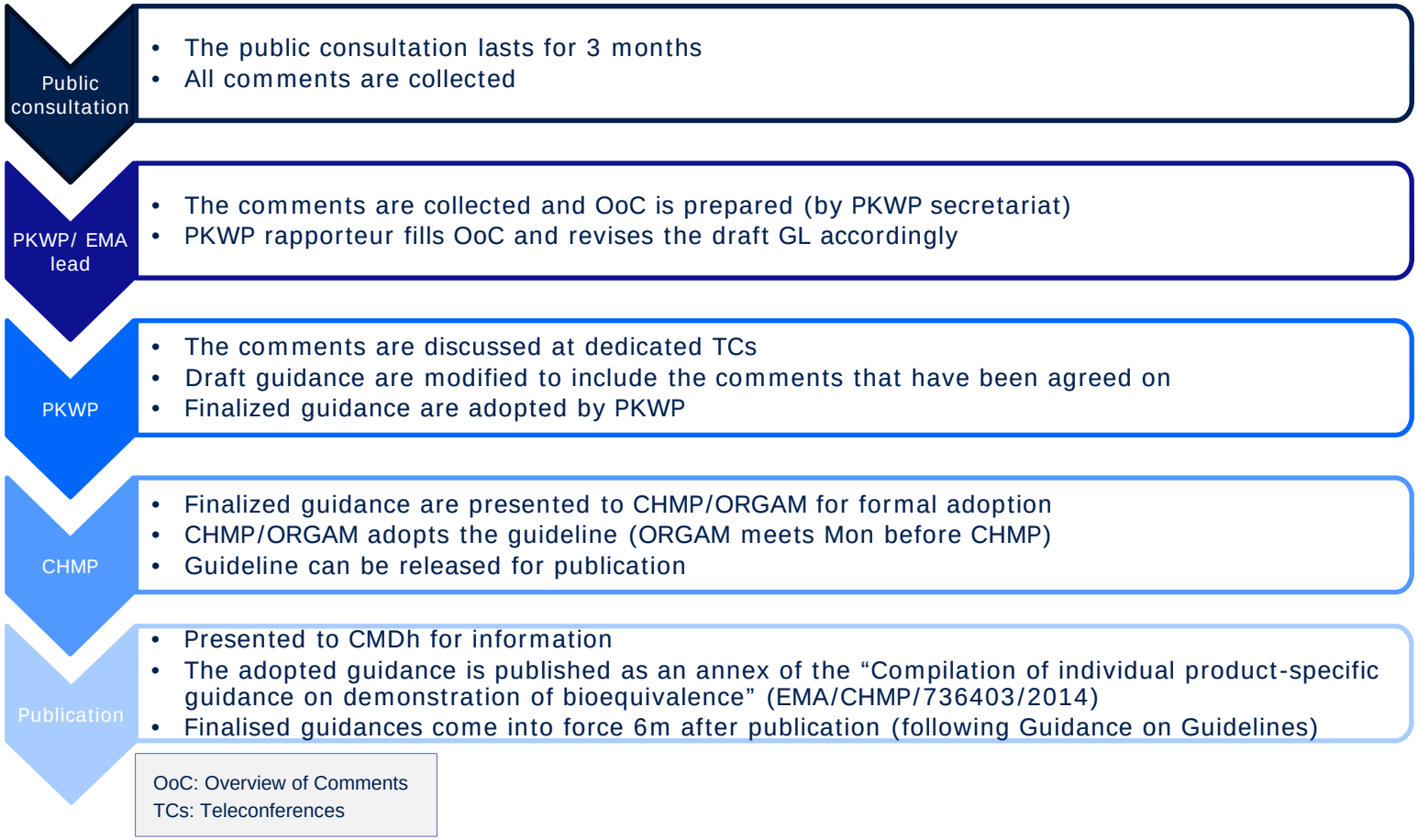
Originator
- Submission of the adopted draft guidance to the MAHs of the originator for information and comments related to confidential information in the guidance.

Public consultation
- The finalized draft guidance are published for a three month public consultation under http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000625.jsp&mid=WC0b01ac0580848f74

Slide from PKWP

PSBEGL

After public consultation



Slide from PKWP

Clin Pharmacol Ther. 2018 Sep; 104(3): 539–545.

PSBEGL

Update Sept 2017 to Sept 2018

PSBEGL

Update 2017/18

7th batch and revisions

Dabigatran etexilate hard capsule 75, 110 and 150 mg
Dimethyl fumarate gastro-resistant capsule 120 and 240 mg
Dolutegravil film-coated tablets 10, 25 and 50 mg
Dronedarone film-coated tablets 400 mg
Ibuprofen immediate release formulations 200 - 800 mg
Paracetamol immediate release formulations
Prasugrel film-coated tablets 5 and 10 mg
Rilpivirine film-coated tablets 25 mg
Tadalafil film-coated tablets 2.5, 5, 10 and 20 mg

Final GL for publication

Q4 2017 **Q2 2018** **Q3 2018**

PSBEGL

Update 2017/18

8th batch

Cholic acid capsules 50 and 250 mg
Posaconazole gastro-resistant tablet 100 mg
Ledipasvir/sofosbuvir film-coated tablet 90 mg/400 mg
Vismodegib hard capsule 150 mg
Agomelatine oral tablet 25 mg

GL for adoption for public consultation

Public consultation finished

Q4 2017 **Q2 2018** **Q3 2018**

PSBEGL

Update 2017/18

9th batch

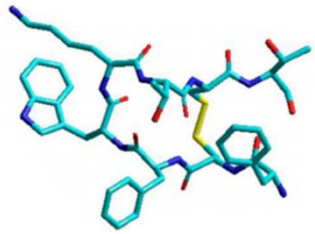
Aliskiren film-coated tablet 150 and 300 mg
Apixaban film-coated tablet 2.5 and 5 mg
Gefitinib film-coated tablet 250 mg
Lapatinib film-coated tablet 250 mg
Octreotide depot powder/solvent for suspension for injection 10, 20 or 30 mg
Pegylated liposomal doxorubicin HCl concentrate for solution 2 mg/ml

Adoption for public consultation

Q4 2017 **Q2 2018** **Q3 2018**

PSBEGL

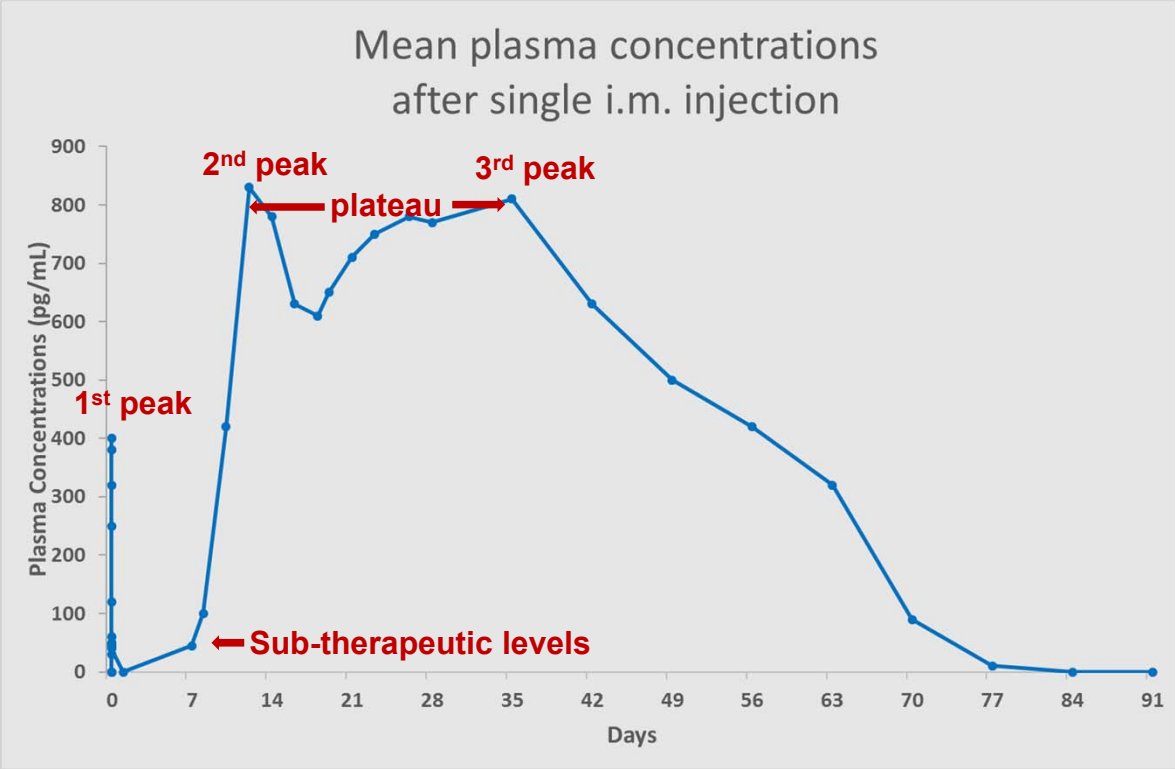
Octreotide acetate



- Synthetic long-acting analogue of the natural hormone somatostatin.
- Inhibits pathologically increased secretion of growth hormone (GH) and of peptides and serotonin produced within the gastro-entero-pancreatic (GEP) endocrine system.
- Intramuscular injection formulation containing biodegradable microspheres in which the drug substance is encapsulated. The drug substance is gradually and slowly released from the i.m. depot
- Sandostatin LAR® approved in EU as long-acting slow-release form since 1995 for treating various conditions including acromegaly, GEP endocrine tumours and certain neuroendocrine tumours (NET).

PSBEGL

Octreotide acetate



- 3-phase release
- 3 plasma peaks
- Initial burst followed by a sustained release phase and a 3rd complete release phase

PSBEGL (draft)

Octreotide acetate

Status: currently under public consultation – 9th batch

Requirements for bioequivalence demonstration (PKWP)*

Bioequivalence study design	**Single dose:** In healthy volunteers. **Background**: Taking into account the difficulties in performing a multiple dose study (e.g. 28 day dosing interval, multiple indications and limited target populations), as accumulation is not high and the single dose profile is captured over a prolonged period, a multiple dose study may be waived if the single dose PK is well characterized. Further analysis of the single dose data is therefore required to fully capture the pharmacokinetic profile.
	Parallel design **Background**: Due to the long half-life the crossover design may not be practically feasible, therefore a parallel design could be used.
	Strength: 30 mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** $AUC_{(0\text{-}28d)}$, $AUC_{(28\text{-}56d)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, C_{max} and C_t (concentration at the end of the dosing interval, i.e. day 28) **Secondary parameters:** $AUC_{(0\text{-}24h)}$, t_{lag}, $C_{max\ per\ partial\ AUC}$ and $C_{max\ initial\ release}$
	90% confidence interval: 80.00 – 125.00%

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}, $C_{T,ss}$ and partial AUC. If high intra-individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/06/WC500251059.pdf

PSBEGL (draft)

Octreotide acetate

Primary parameters:

$AUC_{(0\text{-}28d)}$

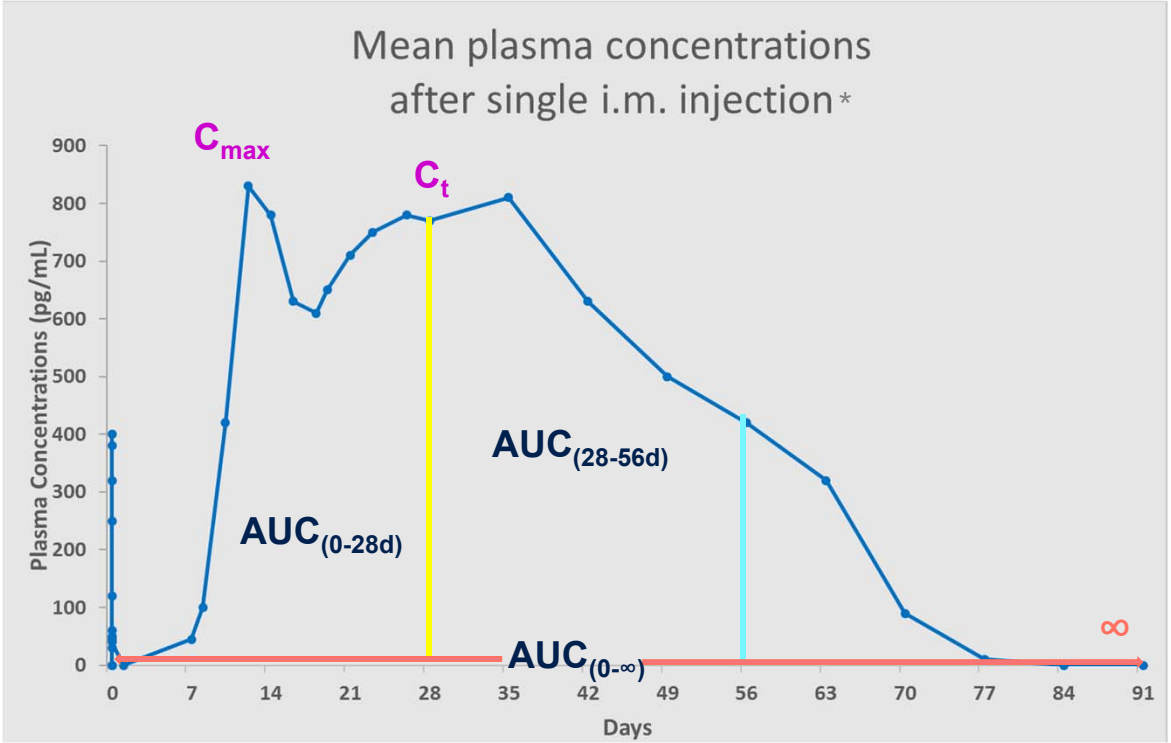
$AUC_{(28\text{-}56d)}$

$AUC_{(0\text{-}\infty)}$

C_{max}

C_t (day 28; dosing interval)

90% CI of mean T/R:
80.00 – 125.00%

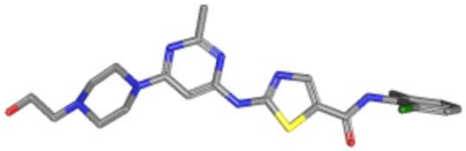


Secondary parameters: $AUC_{(0\text{-}24h)}$, t_{lag}, C_{max} per partial AUC, and C_{max} initial release

* Example of the typical PK profile observed after single i.m. injection of octreotide acetate

PSBEGL

Dasatinib



- Originator: Sprycel
- Tyrosine kinase inhibitor, indicated in chronic myelogenous leukaemia (CML), acute lymphoblastic leukaemia (ALL).
- Film-coated tablet; 20, 50, 70, 80, 100, 140 mg.
- Initial dose 100 mg QD in CML and 140 mg QD in ALL.
- BCS class II. Weak base; pH-dependant solubility → high solubility in the acidic stomach and low solubility in the small intestine.
- Linear PK
- High variability

PSBEGL

Dasatinib (2015)

Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** dasatinib may be considered a low solubility compound.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 140 mg **Background:** highest strength to be used for a drug with linear pharmacokinetics and low solubility.
	Number of studies: one single dose study
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t} and C_{max}
	90% confidence interval: 80.00 – 125.00%

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}. If high intra-individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.

Dasatinib

Single dose, randomized, crossover, replicate/not replicate, BE studies

Reference: dasatinib monohydrate form

Test: dasatinib anhydrous form

BE results		
	AUC	Cmax
fasting	✗ *	✓ **
fed	✓	✓

* high T/R-ratio and upper 90% CI above the upper limit

** within widened acceptance limits

Atypical AUC	Within subject variability	AUC BE fasting
IN	↑	✗
OUT	↓	✓

Note: the content of this slide represents a general evaluation based on findings observed in a number of regulatory procedures, scientific advices and published data

PKWP and BSWP

Mahalanobis distance (MD) in dissolution: state of the art

Is the MD an adequate measure for use in the assessment of dissolution similarity, in particular in cases where the f2 statistic is not suitable?

19th Sept 2018

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 July 2018
EMA/810713/2017
Human Medicines Research and Development Support

Question and answer on the adequacy of the Mahalanobis distance to assess the comparability of drug dissolution profiles

Draft agreed by Biostatistics Working Party	June 2018
Adopted by CHMP	26 July 2018

PKWP and BSWP

Mahalanobis distance (MD) in dissolution: state of the art

Is the MD an adequate measure for use in the assessment of dissolution similarity, in particular in cases where the f2 statistic is not suitable?

AIM: *to provide clarification about the suitability of the MD as a tool to assess the comparability of drug dissolution profiles and to a larger extent to emphasise the importance of confidence intervals to quantify the uncertainty around the point estimate of the chosen metric (e.g. the f2 factor or the MD).*

Mahalanobis distance (MD)

Question-and-answer

- MD is a measure of the distance between a point P and a distribution D, and takes into account the correlations in the data set;

- It is a multi-dimensional generalization of the idea of measuring how many standard deviations away P is from the mean of D.

- Dependent on variance and covariance estimates. In dissolution data sets, covariates generally correspond to dissolution % collected for different time-points. Under some assumption, the MD becomes smaller, indicating similar dissolution profiles, with increasing variability observed in the data;

Mahalanobis distance (MD)

Question-and-answer

Summary of the BSWP position

*"The **MD metric cannot be supported as a preferred methodological approach to decide upon similar dissolution**, even in situations where the f2 statistic should not be used in the way outlined in the CHMP bioequivalence guideline".*

PKWP and BSWP

Type 1 error in two-stage study: state of the art

PKWP in collaboration with the BSWP to finalise the ongoing discussion related to type 1 error control in two-stage designs in bioequivalence studies.

Discussions currently suspended.

Acknowledgements

- Kevin Blake - EMA
- Susan Cole - MHRA
- David Brown - MHRA

Thank You