BioBridges 2018

Regulatory Year in Review

Vit Perlik

Draft „Guidelines and Concept papers“

- **45 draft guidelines or concept papers**
  - 36 w/o veterinary and pharmacovigilance topics
  - mainly related to clinical, product specific and ICH guidelines and quality

Document title	Language	Status	First published	Last updated
Concept paper on the need for revision of the guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus	(English only)	draft: consultation closed	28.07.2016	07.02.2018
Concept paper on the development of guidance on the non-clinical evaluation of radiopharmaceuticals - First version	(English only)	draft: consultation closed	01.08.2017	20.02.2018
Draft qualification opinion on Proactive in chronic obstructive pulmonary disease (COPD)	(English only)	draft: consultation closed	20.12.2017	
Draft procedure for the review and revision of European Union herbal monographs and European Union list entries	(English only)	draft: consultation open	27.10.2017	31.10.2017
Reflection paper on the use of extrapolation in the development of medicines for paediatrics	(English only)	draft: consultation open	13.10.2017	
Draft guideline on implementation of risk assessment requirements to control elemental impurities in veterinary medicinal products	(English only)	draft: consultation open	16.10.2017	
Draft guideline on clinical investigation of recombinant and 4 human plasma-derived factor VIII products	(English only)	draft: consultation open	30.10.2017	
Draft guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products	(English only)	draft: consultation open	30.10.2017	
Draft guideline on the clinical evaluation of medicinal products indicated for the prophylaxis or treatment of respiratory syncytial virus (RSV) disease	(English only)	draft: consultation open	30.10.2017	
Concept paper on the development of a reflection paper on new analytical methods/technologies in the quality control of herbal medicinal products	(English only)	draft: consultation open	31.10.2017	
Concept paper on the need for a paediatric addendum of the guideline on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease	(English only)	draft: consultation open	31.10.2017	
Draft guideline on conduct of pharmacokinetic studies in target animal species - Revision 1	(English only)	draft: consultation open	21.11.2017	
Concept paper for the revision of the guideline on the summary of product characteristics for anthelmintics	(English only)	draft: consultation open	15.12.2017	
Draft ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management - Step 2b - Annexes - First version	(English only)	draft: consultation open	18.12.2017	
Draft ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management - Step 2b - First version	(English only)	draft: consultation open	18.12.2017	
Draft guideline on core summary of products characteristics (SmPC) and package leaflet for technetium (99mTc) macrosalb	(English only)	draft: consultation open	24.01.2018	
Concept paper for the revision of the guideline on safety and residue data requirements for pharmaceutical veterinary medicinal products intended for minor use or minor species (MUMS)/limited market	(English only)	draft: consultation open	26.01.2018	
Draft VICH GL57 on studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing species: marker residue depletion studies to establish product withdrawal periods in aquatic species	(English only)	draft: consultation open	26.01.2018	

Draft „Guidelines and Concept papers“

- Cont.
- 45 draft guidelines or concept papers
  - 36 w/o veterinary and pharmacovigilance topics
  - mainly related to clinical, product specific and ICH guidelines and quality

Draft agomelatine oral tablet 25 mg product-specific bioequivalence guidance	(English only)	draft: consultation open	31.01.2018	
Draft cholic acid capsules 50 mg and 250 mg product-specific bioequivalence guidance	(English only)	draft: consultation open	31.01.2018	
Draft ledipasvir/sofosbuvir film-coated tablet 90 mg/400 mg product-specific bioequivalence guidance	(English only)	draft: consultation open	31.01.2018	
Draft posaconazole gastro-resistant tablet 100 mg product-specific bioequivalence guidance	(English only)	draft: consultation open	31.01.2018	
Draft vismodegib hard capsule 150 mg product-specific bioequivalence guidance	(English only)	draft: consultation open	31.01.2018	
Draft guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products - Revision 1	(English only)	draft: consultation open	01.02.2018	
Guideline on quality aspects included in the product information for vaccines for human use	(English only)	draft: consultation open	01.02.2018	
Questions and answers on Bovine Spongiform Encephalopathies (BSE) and vaccines - Revision 1	(English only)	draft: consultation open	01.02.2018	
Questions and answers on the Haemagglutination Inhibition (HI) test for qualification of influenza vaccine (inactivated) seed preparations	(English only)	draft: consultation open	01.02.2018	
Reflection paper on investigation of pharmacokinetics and pharmacodynamics in the obese population	(English only)	draft: consultation open	01.02.2018	
Draft guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus - Revision 2	(English only)	draft: consultation open	07.02.2018	
Public consultation concerning a request for CVMP opinion under Article 30(3) of Regulation (EC) No 726/2004 on the risk for the consumer resulting from the use of diethanolamine as an excipient in veterinary medicinal products for food-producing species (EMEA/V/A/127)	(English only)	draft: consultation open	16.03.2018	
Public consultation concerning the European Union template for good manufacturing practice (GMP) non-compliance statement	(English only)	draft: consultation open	03.04.2018	
Draft addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements - First version	(English only)	draft: consultation open	06.04.2018	
NEW Draft guideline on manufacture of the veterinary finished dosage form - Revision 1	(English only)	draft: consultation open	23.04.2018	
NEW Draft guideline on clinical evaluation of vaccines - Revision 1	(English only)	draft: consultation open	26.04.2018	
Volume 3b guidelines: Medicinal products for human use: Safety, environment and information: Excipients in the label and package leaflet of medicinal products for human use	(English only)		09.10.2017	01.03.2018
Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'	Select a language to view the document		09.10.2017	
Guideline on good pharmacovigilance practices (GVP): Module IX — Signal management with tracked changes (Rev. 1)	(English only)		12.10.2017	
Guideline on good pharmacovigilance practices (GVP): Module VIII — Post-authorisation safety studies with tracked changes (Rev. 3)	(English only)		12.10.2017	
Guideline on good pharmacovigilance practices (GVP): Module XV — Safety communication with tracked changes (Rev. 1)	(English only)		12.10.2017	
Guideline on good pharmacovigilance practices: Module IX Addendum I — Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions with tracked changes	(English only)		12.10.2017	
Overview of comments received on 'Draft Guideline on manufacture of the finished dosage form' (EMA/CHMP/QWP/245074) - Revision 1	(English only)		17.11.2017	
Overview of comments received on 'Paracetamol oral use, immediate release formulations product-specific bioequivalence guidance' (EMA/CHMP/356877/2017) - First version	(English only)		01.02.2018	
Overview of comments received on 'Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg product-specific bioequivalence guidance' (EMA/CHMP/315234/2014/Rev.1) - First version	(English only)		01.02.2018	
Overview of comments received on 'Rilpivirine film-coated tablets 25 mg product-specific bioequivalence guidance' (EMA/CHMP/356878/2017) - First version	(English only)		01.02.2018	
Overview of comments on 'Points to consider on frailty: Evaluation instruments for baseline characterisation of clinical trial populations' (EMA/CHMP/778709/2015) - First version	(English only)		22.02.2018	

Updated "Guidelines“

- **10 updated guidelines**
  - 1 w/o veterinary and pharmacovigilance topics
  - related to clinical development

Document title	Language	Status	First published	Last updated
Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis	(English only)	adopted	27.03.2015	11.10.2017
Guideline on good pharmacovigilance practices (GVP) - Module VIII – Post-authorisation safety studies (Rev. 3)	(English only)	adopted	25.06.2012	12.10.2017
Guideline on good pharmacovigilance practices (GVP): Module IX – Signal management (Rev. 1)	(English only)	adopted	25.06.2012	12.10.2017
Guideline on good pharmacovigilance practices: Annex I - Definitions (Rev. 4)	(English only)	adopted	25.06.2012	12.10.2017
Guideline on good pharmacovigilance practices: Module XV – Safety communication (Rev. 1)	(English only)	adopted	24.01.2013	12.10.2017
Guideline on good pharmacovigilance practices: Annex V – Abbreviations (Rev. 1)	(English only)	adopted	25.04.2013	12.10.2017
Guideline on good pharmacovigilance practices (GVP): Module VII – Periodic safety update report - Explanatory note	(English only)	adopted	06.04.2017	13.11.2017
Recommendation to marketing authorisation holders, highlighting recent measures in the veterinary field to promote reduction, refinement and replacement (3Rs) measures described in the European Pharmacopoeia - Applicable to veterinary vaccines from 01/01/2017	(English only)	adopted	24.01.2018	16.02.2018
Recommendation to marketing authorisation holders, highlighting recent measures in the veterinary field to promote replacement, reduction, and refinement (3Rs) measures described in the European Pharmacopoeia - Applicable to human vaccines from 01/01/2018	(English only)	adopted	24.01.2018	16.02.2018
Guidance on collection and provision of national data on antimicrobial use by animal species/categories	(English only)	adopted	24.03.2017	23.02.2018

New "Guidelines“

- **46 updated guidelines**
  - 40 w/o veterinary and pharmacovigilance topics
  - related to clinical development, produt specific and quality guidelines, and labeling

Document title	Language	Status	First published	Last updated
Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure - Revision 2	(English only)	adopted	20.09.2017	
Guideline on clinical investigation of new medicinal products for the treatment of acute coronary syndrome - First version	(English only)	adopted	20.09.2017	
Guidance on the classification of veterinary medicinal products indicated for minor use minor species (MUMS) / limited market - Revision 1	(English only)	adopted	06.10.2017	
ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population - Revision 1 (addendum)	(English only)	adopted	06.10.2017	
ICH guideline E18 on genomic sampling and management of genomic data - First version	(English only)	adopted	06.10.2017	
Information for the package leaflet for fragrances containing allergens used as excipients in medicinal products for human use	(English only)	adopted	09.10.2017	
Information for the package leaflet regarding aspartame and phenylalanine used as excipients in medicinal products for human use	(English only)	adopted	09.10.2017	
Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use	(English only)	adopted	09.10.2017	
Information for the package leaflet regarding phosphates used as excipients in eye drops	(English only)	adopted	09.10.2017	
Questions and answers on benzalkonium chloride used as an excipient in medicinal products for human use	(English only)	adopted	09.10.2017	
Questions and answers on benzoic acid and benzoates used as excipients in medicinal products for human use	(English only)	adopted	09.10.2017	
Questions and answers on benzyl alcohol used as an excipient in medicinal products for human use	(English only)	adopted	09.10.2017	
Questions and answers on boric acid and borates used as excipients in medicinal products for human use	(English only)	adopted	09.10.2017	
Questions and answers on cyclodextrins used as excipients in medicinal products for human use	(English only)	adopted	09.10.2017	
Questions and answers on propylene glycol used as an excipient in medicinal products for human use	(English only)	adopted	09.10.2017	
Questions and answers on sodium laurilsulfate used as an excipient in medicinal products for human use	(English only)	adopted	09.10.2017	
Questions and answers on sodium used as an excipient in medicinal products for human use	(English only)	adopted	09.10.2017	
Questions and answers on wheat starch (containing gluten) used as an excipient in medicinal products for human use	(English only)	adopted	09.10.2017	
Guideline on good pharmacovigilance practices (GVP): Module IX Addendum I — Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions	(English only)	adopted	12.10.2017	
Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances - Veterinary	(English only)	adopted	23.10.2017	
Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials - Revision 1	(English only)	adopted	26.10.2017	
Guideline on the clinical investigation of medicinal products for the treatment of axial spondyloarthritis - Revision 1	(English only)	adopted	31.10.2017	
Guideline on the evaluation of anticancer medicinal products in man	(English only)	adopted	20.11.2017	

New "Guidelines“

- Cont.
- 46 updated guidelines
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Guideline on the clinical development of medicinal products for the treatment of Autism Spectrum Disorder (ASD)	(English only)	adopted	21.11.2017
Questions and answers on allogenic mesenchymal stem cell-based products for veterinary use: specific questions on tumorigenicity	(English only)	adopted	21.11.2017
Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products	(English only)	adopted	28.11.2017
Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials - Revision 1	(English only)	adopted	28.11.2017
Results of juvenile animal studies (JAS) and impact on anti-cancer medicine development and use in children	(English only)	adopted	30.11.2017
Questions and answers on monoclonal antibodies for veterinary use	(English only)	adopted	11.12.2017
Guideline on implementation of risk assessment requirements to control elemental impurities in veterinary medicinal products	(English only)	adopted	13.12.2017
ICH Guideline S3A: Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies - Questions and answers - Step 5 - First version	(English only)	adopted	15.12.2017
ICH guideline E17 on general principles for planning and design of multi-regional clinical trials - Step 5 - First version	(English only)	adopted	18.12.2017
Guideline on clinical investigation of medicinal products for the treatment of rheumatoid arthritis	(English only)	adopted	10.01.2018
Guideline on the chemistry of active substances for veterinary medicinal products	(English only)	adopted	19.01.2018
Guidance for individual laboratories for transfer of quality control methods validated in collaborative trials with a view to implementing 3Rs	(English only)	adopted	24.01.2018
Dolutegravir film-coated tablets 10 mg, 25 mg and 50 mg product-specific bioequivalence guidance - First version	(English only)	adopted	01.02.2018
Dronedarone film-coated tablets 400 mg product-specific bioequivalence guidance - First version	(English only)	adopted	01.02.2018
Paracetamol oral use immediate release formulations product-specific bioequivalence guidance - First version	(English only)	adopted	01.02.2018
Rilpivirine film-coated tablets 25 mg product-specific bioequivalence guidance - First version	(English only)	adopted	01.02.2018
Tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg product-specific bioequivalence guidance - Revision 1	(English only)	adopted	01.02.2018
Reflection paper on physical frailty: instruments for baseline characterisation of older populations in clinical trials - First version	(English only)	adopted	22.02.2018
Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease - Revision 2	(English only)	adopted	28.02.2018
2003 European Commission guideline on 'Excipients in the label and package leaflet of medicinal products for human use'	(English only)	adopted	01.03.2018
Guideline on good pharmacogenomic practice - First version	(English only)	adopted	19.03.2018
Guideline on core SmPC and Package Leaflet for sodium iodide (131I) for therapeutic use	(English only)	adopted	22.03.2018
NEW Guideline on assessing the environmental and human health risks of veterinary medicinal products in groundwater	(English only)	adopted	30.04.2018

Product Specific Guidelines - Draft

- **Ibuprofen 200 - 800 mg oral use, immediate release formulations product-specific bioequivalence guidance**
  - end of consultation 31 October 2017

  What was suggested:

  - Single dose, cross over, fasting study in healthy volunteers using highest strength (linear PK 200 – 800 mg)
  - Analyte: Parent compound using enantioselective analytical method
  - Enantiomers have different PD and PK and the rate of absorption has been shown to affect the ratio of enantiomers
  - Pharmacokinetic variables: Cmax, AUC(0-t) and Tmax for S enantiomer

- Different formulations available (suspensions to rapidly dissolving tbl, cps)
- Majority of generic products registered using non- enantioselective analytical method
- ? Shall be removed from the market? What will happen during the MA renewals?

Pharmacokinetic Study ibuprofen sodium vs ibuprofen acid

- Single dose, cross-over, fasting PK study in healthy volunteers

Results

- No difference in AUC inf
- Different rate of absorption
- Different Tmax

Conclusion

- Ibuprofen sodium and lysinate faster rate of absorption compared to acid

Pharmacokinetic Parameter	Treatment			Treatment Comparison		
	A	B	C	A/C	B/C	B/A
AUC (0 - ∞) (µg.h/ml)						
Mean	127.1	132.9	135.9	0.936	0.978	1.045
90% CI for ratio				0.888 - 0.985	0.928 - 1.030	0.992 - 1.101
C_{max} (µg/ml)						
Mean	47.0	51.7	36.4	1.289	1.416	1.098
90% CI for ratio				1.204 - 1.380	1.323 - 1.516	1.026 - 1.176
t_{max} (h)						
Mean	0.583 (35 min)	0.500 (30 min)	1.250 (75 min)	-0.584	-0.667	-0.083
90% CI for ratio				-1.042 - -0.500	-1.084 - -0.500	-0.167 - -0.041
Half-life (h)						
Mean	1.986	1.958	1.984			

Treatment A = 2 x Dolormin tablets (lysine ibuprofen, each tablet equivalent to 200 mg ibuprofen)

Treatment B = 2 x sodium ibuprofen tablets (each tablet equivalent to 200 mg ibuprofen)

Treatment C = 2 x Nurofen ibuprofen 200 mg tablets

MHRA, 2008, NUROFEN EXPRESS 256MGPL, PL 00063/0372-4, 0411-2

Clinical Study
ibuprofen sodium vs ibuprofen acid

- Double blind, parallel, placebo-controlled, single dose RCT in patients with moderate to severe dental pain after tooth extraction
- Pain intensity – VAS and 4-point categorial scale

Results

- No difference in efficacy as evaluated by SPIDR (6h)
- Similar for ITT and PP set

Sum of Pain Relief Intensity Differences (SPRID) Through 6 Hours (ITT and PP Populations)

	Treatment Group				
	Sodium Ibuprofen	Ibuprofen Acid	Acetaminophen	Placebo	p-value [a]
N (ITT population)	80	80	80	81	< 0.001
Mean (SD) (a higher value is favourable)	3.46 (1.59)	3.49 (1.54)	2.25 (1.77)	0.73 (1.40)	
Pairwise comparison	Estimate	SE	97.5% CI for estimate	p-value	
Sodium Ibuprofen versus Ibuprofen Acid	-0.03	0.25	-0.58, 0.53	0.91	
Sodium Ibuprofen versus Acetaminophen	1.22	0.25	0.67, 1.77	< 0.001	
Ibuprofen Acid versus Acetaminophen	1.25	0.25	0.69, 1.80	< 0.001	
N (PP population)	79	77	77	61	< 0.001
Mean (SD) (a higher value is favourable)	3.48 (1.60)	3.55 (1.50)	2.34 (1.74)	0.98 (1.53)	
Pairwise comparison	Estimate	SE	97.5% CI for estimate	p-value	
Sodium Ibuprofen versus Ibuprofen Acid	-0.07	0.25	-0.63, 0.50	0.79	
Sodium Ibuprofen versus Acetaminophen	1.13	0.25	0.57, 1.70	< 0.001	
Ibuprofen Acid versus Acetaminophen	1.20	0.25	0.63, 1.77	< 0.001	

Treatment definitions: Sodium Ibuprofen = 2 x 256 mg sodium ibuprofen tablets (each tablet equivalent to 200 mg ibuprofen acid); Ibuprofen Acid = 2 x 200 mg ibuprofen acid tablets; Acetaminophen = 2 x 500 mg acetaminophen caplets.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; SD = standard deviation; SE = standard error.
[a] p-value for treatment from an ANCOVA model with factors for treatment, study site, gender, and baseline pain intensity (categorical).
Source: Section 14.2, Tables 14.2.2.1 and 14.2.2.2.

MHRA, 2008, NUROFEN EXPRESS 256MGPL, PL 00063/0372-4, 0411-2

Clinical Study
ibuprofen arginate vs ibuprofen acid

- Double blind, parallel, placebo-controlled, single dose RCT in patients with moderate to severe dental pain after tooth extraction
- Pain intensity – VAS and categorial scale

Results

- No difference in efficacy as evaluated by SPID and TOTPAR (6h)

Table IV. Summary of analgesic efficacy.

	Ibuprofen Arginate		Ibuprofen		
	200 mg (n = 98)	400 mg (n = 98)	200 mg (n = 100)	400 mg (n = 100)	Placebo (n = 98)
SPID	5.7*	6.7*†	5.4*	6.7*†	1.2
TOTPAR	13.1*	15.0*†‡	12.6*	14.9*†	6.9
Peak pain relief	3.2*†	3.4*†	2.9*	3.2*	2.0
Global assessment	2.2*	2.5*†	2.1*	2.5*†	1.1

SPID = summary of pain intensity differences from baseline; TOTPAR = total pain relief from baseline.
*$P < 0.05$ versus placebo.
†$P < 0.05$ versus ibuprofen 200 mg.
‡$P < 0.05$ versus ibuprofen arginate 200 mg.

Black et al, 2002

Clinical Study - other studies

Reference	Medication	Design	N	pain model	Conclusion	Note
Mehlisch et al., 2002	Ibuprofen arginine 200/400; Ibuprofen acid 200/400; Placebo	double-blind; parallel	500	postoperative dental pain	significantly **faster onset** of analgesia in patients treated with arginate; **TOTPAR P<0.05 for 200 mg dose 400 mg**	any parameter of **general efficacy** superior for either dose of conventional ibuprofen when compared with arginate **(P>.05)**
Desjardins et al., 2002	Ibuprofen arginine 200/400; Ibuprofen acid 200/400; Placebo	double-blind, double-dummy; parallel	226	postoperative dental pain	significantly **faster onset** of analgesia with arginate 400 mg compared with ibuprofen acid **(both doses; P<.05)**	arginate **as safe and effective** an analgesic as ibuprofen; **overall analgesia comparable**
Seibel et al., 2004	Ibuprofen lysine 400 Ibuprofen acid 400 Placebo	double-blind; cross-over	24	**healthy using laser somatosensory evoked potential** (UV-irradiated skin)	lysinate **superior** to acid **with respect to onset** (primary; P=.0366) **and extent** (secondary efficacy variable; P=.0041);	
Schleier et al., 2007	Ibuprofen sodium .H2O 400 Ibuprofen acid 400 **(no placebo!)**	multicentre, double-blind, Parallel	396	postoperative dental pain	first sign of **pain relief earlier for sodium salt**; **increase in pain relief earlier**; overall analgesic efficacy (secondary) in terms of SPID, TOTPAR and remedication times in the two groups were similar	in summary, when compared to ibuprofen, sodium dihydrate formulation has a **faster onset** of pain relief; **as safe and effective**
Norholt et al., 2011	Ibuprofen sodium .H2O 400 Ibuprofen acid 400 **(no placebo!)**	double-blind, double-dummy; cross-over (split-mouth design)	144	postoperative dental pain	first sign of pain relief faster for sodium salt (by 6 minutes; P=0.004); no difference in **time to substantial pain relief (N.S.)**	sodium dihydrate **as effective as conventional ibuprofen**

FDA – Product-Specific Guidances

- **Draft Guidance on Ibuprofen, Mar 2015**
- Applicable also to other dosage forms (suspension, tablets)

Active Ingredient: Ibuprofen

Dosage Form; Route: Capsule; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: EQ 200 mg free acid and potassium salt
   Subjects: Healthy males, nonpregnant females, general population
   Additional comments: None

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: EQ 200 mg free acid and potassium salt
   Subjects: Healthy males, nonpregnant females, general population
   Additional comments: None

Analytes to measure: Ibuprofen in plasma

Bioequivalence based on (90% CI): Ibuprofen

Product Specific Guidelines - Comments

Submission of comments on 'Ibuprofen 200 - 800 mg oral use, immediate release formulations product-specific bioequivalence guidance' (EMA/CHMP/356876/2017)

Comments from:

Name of organisation or individual
Cadore INV s.r.o., Czech Republic and Zentiva, k.s., Czech Republic

Product Specific Guidelines – Adopted (effective 01/12/2018)

	Other design aspects: Additional studies may be necessary depending on the formulation in accordance with the Guideline on the Investigation of Bioequivalence (for example orodispersible tablets).
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, C_{max} and T_{max}.
	90% confidence interval: 80.00 – 125.00% for AUC_{0-t} and C_{max}. Comparable median and range for T_{max}.

* 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.

** This tentative BCS classification of the drug substance serves to define whether *in vivo* studies seems to be mandatory (BCS class II and IV) or, on the contrary (BCS Class I and III), the Applicant may choose between two options: *in vivo* approach or *in vitro* approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. *in vitro* dissolution being less than 85 % within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2018
EMA/CHMP/356876/2017
Committee for Medicinal Products for Human Use (CHMP)

Ibuprofen oral use immediate release formulations 200 - 800 mg product-specific bioequivalence guidance

Draft Agreed by Pharmacokinetics Working Party (PKWP)	April 2017
Adopted by CHMP for release for consultation	20 July 2017
Start of public consultation	3 August 2017
End of consultation (deadline for comments)	31 October 2017
Agreed by Pharmacokinetics Working Party (PKWP)	April 2018
Adopted by CHMP	31 May 2018
Date of coming into effect	1 December 2018

Keywords	***Bioequivalence, generics, ibuprofen***

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Product Specific Guidelines - Draft

- **Paracetamol oral use, immediate release formulations product-specific bioequivalence guidance**
  - end of consultation 31 October 2017

What was suggested:

- BCS Class I biowaiver possible, Paracetamol is high solubility compound with >85% absorption

or

- Single dose, cross over, fasting study in healthy volunteers (paracetamol is highly soluble and shows linear PK, in principle any strength may be used)
- Analyte: Parent compound
- Pharmacokinetic variables: Cmax, AUC(0-t) and Tmax

Product Specific Guidelines – Adopted (effective 01/08/2018)

Paracetamol oral use immediate release formulations product-specific bioequivalence guidance

Disclaimer:

This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☒ **I** ☐ **III** ☐ **Neither of the two** **Background:** Paracetamol is considered a high solubility compound with >85% absorption.
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: Depends on the applied generic formulation; in principle any strength may be used. **Background:** Multiple product formulations are available; as paracetamol is highly soluble and shows linear

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21 July 2016
EMA/CHMP/474825/2016
Committee for Medicinal Products for Human Use (CHMP)

Paliperidone palmitate depot suspension for injection 25, 50, 75, 100 and 150 mg product-specific bioequivalence guidance

Draft

Draft agreed by Pharmacokinetics Working Party	June 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	1 August 2016
End of consultation (deadline for comments)	31 October 2016

Comments should be provided using this template. The completed comments form should be sent to PKWPsecretariat@ema.europa.eu

Keywords	***Bioequivalence, generics, paliperidone***

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Agreed by Pharmacokinetics Working Party	December 2016
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Date of coming into effect	1 September 2017

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Product Specific Guideline for Paliperidone

Draft guidance

Bioequivalence study design**	**Multiple dose:** any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths), patients **Background:** single-dose studies in healthy volunteers are not considered feasible.
	cross-over or parallel

Adopted guidance

Bioequivalence study design** *in case a BCS biowaiver is not feasible or applied*	**Single dose:** any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths), in healthy volunteers (if feasible) or in patients stabilized on other antipsychotic medication. **Multiple dose:** any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths) in patients.
	cross-over or parallel

Selected Draft "Guidelines"

- **Product specific guidelines – drafts for:**
  - **Aliskiren** – BE fasting and fed are necessary (food decreases BA);
  - **Apixaban** – solubility data to allow BCS class III classification;
  - **Gefitinib** – BE, plus in vitro studies to demonstrate similarity of tablets as dispersion in water or through nasogastric tube;
  - **Lapatinib** - BE fasting and fed are necessary (food increases BA);
  - **Octreotide**, suspension for injection - SD AUC(0-28d), AUC(28-56d), AUC(0-t), AUC(0-∞), Cmax and Ct (MD potentially waived) parallel design could be used;
  - **Pegylated liposomal doxorubicin** – one indication sufficient, proportional pharmacokinetics;

- End of consultation 30 September 2018 for all

Product Specific Guidelines - Draft

- **Pegylated liposomal doxorubicin hydrochloride concentrate for solution 2 mg/ml product-specific bioequivalence guidance**
  - end of consultation 30 September 2018

What is suggested:

Bioequivalence study design	**Single dose study:** Any dose (but no dose adjustments for toxicities during the study) in e.g. stable ovarian/breast cancer patients. **Background:** Dose proportional pharmacokinetics.
	Cross-over
	Other critical aspects: The single dose study may need to be conducted with standardized light meals rather than in the fasting state due to patient's needs.
Analyte	☐ **total drug** ☒ **encapsulated drug** ☒ **unencapsulated drug** ☐ **doxorubicinol (metabolite)**

Pegylated liposomal doxorubicin - Caelyx

- **SmPC Caelyx**
- *At lower doses (10 mg/m²-20 mg/m²) Caelyx displayed linear pharmacokinetics. Over the dose range of 10 mg/m²-60 mg/m² Caelyx displayed* ***non-linear pharmacokinetics***.

- **Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product** EMA/CHMP/806058/2009/Rev. 02
  - **Demonstration of bioequivalence at the highest and lowest doses**

- **Development of „generics“ nearly impossible due to mismatch between the doses and indications in patients**

FDA – Product-Specific Guidances

- Draft Guidance on Doxorubicin HCl, liposomal Recommended Feb 2010; Revised Nov 2013, Dec 2014, Apr 2017, Sept 2018

In Vivo Study:

Type of study: Fasting*
Design: Single-dose, two-way crossover in vivo
Strength: 50 mg/vial or 20 mg/vial
Dose: 50 mg/m2
Subjects: Ovarian cancer patients whose disease has progressed or recurred after platinum-based chemotherapy and who are already receiving or scheduled to start therapy on doxorubicin hydrochloride (liposomal).

Analytes to measure (in appropriate biological fluid): Free doxorubicin and liposome encapsulated doxorubicin.

Thank you for your attention!

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