M9 BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS

Guidance for Industry
Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2023
ICH - Multidisciplinary

This document has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

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To facilitate the implementation of the M9 Guideline, the EWG has developed a series of Q&As:

M9 Q&As
Document History

Code	History	Date
M9 Q&As	Adoption by the Regulatory Members of the ICH Assembly under Step 4	20 November 2019

FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

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1. INTRODUCTION - SCOPE[1]

#	Date of Approval	Questions	Answers
1.1	**Nov. 2019**	Are drug substances that exhibit non-linear pharmacokinetics eligible for a Biopharmaceutic Classification System (BCS)-based biowaiver?	Drug substances that exhibit non-linear pharmacokinetics are eligible for a BCS-based biowaiver if they meet the solubility and permeability criteria for BCS I or III classification.
1.2	**Nov. 2019**	Why does the guideline allow for regional differences in applications for BCS-based biowaivers for generic products?	The guideline focuses on BCS-based biowaiver principles to be applied for bioequivalence purposes provided they are supported by a sound scientific rationale. The provision in the guideline that accommodates exceptions to existing regulations that do not permit BCS-based biowaivers for generic product applications, at this time, does not disqualify implementation of these harmonized technical requirements to demonstrate BCS based biowaivers for other product applications unless explicitly stated.
1.3	**Nov. 2019**	For fixed-dose combination products, can one of the drug substances qualify for a BCS-based biowaiver, while the other does not?	All drug substances in a fixed-dose combination product must fulfill the criteria for either BCS Class I or III to qualify for a biowaiver. If one of the drug substances is not a BCS Class I or III drug substance, the possibility that the FDC formulation may influence in vivo performance cannot be excluded.

[1] This guidance was developed within the Expert Working Groups (Efficacy and Safety) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (formerly the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Assembly at Step 4 of the ICH process, February 2022. At Step 4 of the process, the final draft is recommended for adoption to the regulatory bodies of the ICH regions. Docket No. FDA-2018-D-3614.

1.4	**Nov. 2019**	Why are drugs with a narrow therapeutic index excluded from eligibility for a BCS-based biowaiver, especially if rate and extent of absorption of BCS Class I and III drug substances are a directly attributed function of solubility and permeability?	Drugs with a narrow therapeutic index can be defined as those drugs where small differences in dose or blood concentration may lead to dose and blood concentration dependent, serious therapeutic failures or adverse drug reactions. They are characterized by a steep drug dose-response relationship within the usual dose range or a narrow span between effective drug concentrations and concentrations associated with serious toxicity. Thus, doses must be titrated and monitored carefully. Although there is no international list of narrow therapeutic index drugs, the demonstration of in vivo bioequivalence for these drugs is generally subject to specific requirements such as tightened acceptance criteria (e.g., Cmax and/or AUC: 90–111%) and particular study design features in some regions. BCS-based biowaiver principles are not designed to take into account more stringent criteria for a biowaiver. Therefore, the BCS-based biowaiver approach is not considered a suitable surrogate for the establishment of bioequivalence of narrow therapeutic index drugs.

2. BIOPHARMACEUTICS CLASSIFICATION OF THE DRUG SUBSTANCE

#	Date of Approval	Questions	Answers
2.1	**Nov. 2019**	Is a BCS-based biowaiver applicable if the test and reference products contain different salt forms of the same drug substance?	A BCS-based biowaiver may be applicable if the test and reference products contain different (simple) salts, provided that both belong to BCS Class I (high solubility and high permeability). This biowaiver approach is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of a drug substance from that of the reference product, since these differences may lead to differences in bioavailability that may not be deducible by means of experiments used to support a BCS-based biowaiver. In addition to the scientific aspects, the legal basis for submission and regulatory requirements should be considered.
2.2	**Nov. 2019**	How is weight change associated with a different salt accounted for when assessing solubility?	The BCS classifies a specific drug substance. The dose of the specific active moiety needs to be identical irrespective of the salt forms. Hence, there is no relevance for weight change.
2.3	**Nov. 2019**	Why is a BCS-based biowaiver applicable only when a pro-drug is absorbed as the pro-drug?	The BCS is based on solubility and permeability criteria for a specific drug substance. The classification cannot be conferred to different compounds, e.g., a parent drug and a metabolite. Moreover, the solubility criterion considers oral intake with a defined amount of aqueous liquid which is not relevant for a metabolite unless it is formed immediately following intake and prior to absorption. BCS classification should refer to the drug substance in the drug product since *in vitro* dissolution of the same moiety is utilized to demonstrate product similarity.

2.1 Solubility

#	Date of Approval	Questions	Answers
2.1.1	**Nov. 2019**	How should the pH be adjusted during the solubility experiment?	There are various acceptable methods to adjust the pH of the solution. When a pH adjustment is necessary, the sponsor should justify the chosen method. A deviation in pH of ±0.1 is considered acceptable.
2.1.2	**Nov. 2019**	How is the duration of the solubility measurement determined?	For an equilibrium solubility assessment, the duration over which the solubility is established should be supported by sufficient scientific justification based on the time required to reach equilibrium. In cases where equilibrium solubility cannot be determined, the duration of the solubility experiment should be supported by sufficient scientific justification based on the expected time for absorption in *vivo*.

2.1.3	**Nov. 2019**	How are common ion effects associated with certain buffers accounted for when testing solubility?	Common ion effects are not expected to affect solubility.
2.1.4	**Nov. 2019**	If there is significant variability among individual results, should the lowest solubility be based on the mean of the replicates at a given pH, or the lowest result obtained for a single replicate?	Typically, significant variability should not be observed in individual replicates for highly soluble drug substances. The determination of the lowest solubility should be based on the mean of the replicates.
2.1.5	**Nov. 2019**	Can literature data or alternative scientific justification for solubility be used as pivotal data to qualify a drug substance for a BCS-based biowaiver?	Experimental solubility data should be provided to establish the solubility of the drug substance. Literature data may be submitted to further support the solubility data.
2.1.6	**Nov. 2019**	Why does the guideline set a limit for degradation of a drug substance to not more than 10% when assessing solubility?	The 10% cutoff is set to ensure that the determination of solubility is not over estimated due to degradation of the drug substance. This limit is considered well achievable experimentally.

2.2 Permeability

#	Date of Approval	Questions	Answers
2.2.1	**Nov. 2019**	Why are permeability assessments restricted to Caco-2 cell lines? Can other fully validated cell-lines, e.g., MDCKII, LLC-PK1, be used to provide an estimate of permeability for BCS classification?	It is acknowledged that permeability can be estimated by other *in vitro* (other cell lines, such as MDCKII) or *in situ* (Loc-I-Gut)/*ex-vivo* (everted rat gut sac model) tools, however, as the assessment of permeability by *in vitro* approaches was not established at any other regulatory agency beyond the US FDA, it was agreed to rely initially on the method for which the most experience exists. In the future, when regulators have gained more experience with *in vitro* data, other cell-lines or animal *ex vivo* and *in situ* methods may be considered, but only with rigorous validation and standardization according to the principles as outlined in Annex I of the current draft guideline.
2.2.2	**Nov. 2019**	For certain drugs that demonstrate moderate permeability (50-84%) in validated Caco-2 cell line studies, but in practice are observed to be unstable in the GI tract and would otherwise be highly permeable, why are these drugs designated as low permeability?	As only highly permeable drugs will benefit from a BCS I classification (which gives additional flexibility for excipient changes and broader dissolution criteria (i.e., ≥85% within 30 minutes)), further differentiation of permeability classifications other than highly permeable (i.e., moderate or low permeability) is not relevant in the context of BCS-based biowaivers. For drugs with instability in the GI tract, it is not possible to demonstrate high permeability *in vivo*. In cases where high permeability cannot be conclusively demonstrated by one of the methods described in the guideline, a biowaiver can still be obtained by following the principles of a BCS III classification (i.e., restrictions on excipient changes and very rapid dissolution (i.e., ≥85% within 15 minutes).

2.2.3	**Nov. 2019**	Comment on the sample size required to provide a reliable estimate of drug permeability.	An estimated number of replicates needed to correctly delineate the permeability classification is difficult to define as it depends on the individual assay variability. Inter-lab variability is considered high and potential sources of variability have been described (Volpe, J Pharm Sci) (97), 2008;(Lee et al, Eur J Pharm&Biopharm (114), 2017). However, inter-lab variability is substantially lower for BCS Class I compared to Class III drug substances (Lee et al.). For drug substances with a Papp > 10 x 10^{-6} cm/s, variability is reported to be moderate (5–20% ; Peng et al., Eur J Pharm Sci (56), 2014; Jin et al. J Pharmcol & Toxicol Methods (70), 2014). It is therefore unlikely that high variability would result in misclassification of high permeability. Therefore, the minimum number of three replicates defined for assays based on Caco-2 epithelial cell monolayers is considered justified.
2.2.4	**Nov. 2019**	If the Papp values obtained for low, moderate and high permeability drugs overlap, how are they statistically differentiated when comparing the individual values for drugs of each group?	In the context of this guidance a dichotomic outcome is the goal, i.e., the drug substance demonstrates high permeability or not. The in vivo permeability of the reference drug substances listed in Annex 1 has been confirmed in human studies, which demonstrate that the mean values are clearly differentiated into low, moderate and high permeability. Furthermore, numerous laboratories have successfully validated Caco-2 cell line systems for BCS classification using these reference drug substances, which necessitates differentiation between the high, moderate and low permeability drug substances *in vitro*. If the mean values for low, moderate and high drugs are overlapping when experimentally determined, this is likely an indication of an issue with the setup or performance of the Caco-2 cell line assay used. For demonstration of permeability classification of the test drug substance, the assay is standardized to these reference drug substances, and the test drug substance has to demonstrate an apparent permeability (Papp) equal or greater than the high permeability reference drug substance(s) to be classified as highly permeable. No further statistics need to be applied.

3. ELIGIBILITY OF A DRUG PRODUCT FOR A BCS-BASED BIOWAIVER

#	Date of Approval	Questions	Answers
3.1	**Nov. 2019**	Why are different dosage forms of test and reference products not eligible for BCS-based biowaivers?	Differences in formulations of the same drug substance can influence *in vivo* performance. Specific recommendations regarding the dosage forms and excipients have been considered in the context of this BCS-based biowaiver guideline to accommodate the impact of formulation differences on *in vivo* performance to

			mitigate the risk associated with incorrect conclusions of bioequivalence. However, the principles of the guideline may be applied to bridge different dosage forms during product development, if sufficiently justified, e.g., based on previous *in vivo* data.
3.2	**Nov. 2019**	Why are orodispersible tablets (ODT) not eligible for a BCS-based biowaiver if they are administered without water?	As residual gastric volume is well below 250 ml, the estimation of solubility of the drug substance in 250 ml of liquid media is not applicable to products that are taken without water. Defining the volume of media required to establish the solubility classification would be challenging for ODTs that are taken without water. Furthermore, the current dissolution methodology is of limited value for a product that is to be dispersed in the mouth without the intake of a glass of water. For such products, a bioequivalence study with the ODT dosed without water should be conducted.

3.1 Excipients

#	Date of Approval	Questions	Answers
3.1.1	**Nov. 2019**	*In silico* PBPK absorption modelling is widely used in industry to assess the risk of changes in formulation performance. Can a robust risk assessment be used to assess the potential impact (inclusion/ exclusion) of an excipient change beyond the recommended ranges?	Although it is recognized that *in silico* PBPK absorption modelling is used to assess the risk in product performance due to formulation changes, currently such models cannot comprehensively predict all potential differences in absorption due to critical excipients. Validation of *in silico* models for such purposes is further limited by a lack of mechanistic understanding for some observed excipient effects, including a lack of high-quality *in vivo* data for some excipient classes. Therefore, a risk assessment based on model predicted effects would not support a change in excipient beyond the recommended range. However, in some circumstances *in silico* PBPK modelling may provide useful supporting evidence as part of a wider excipient risk assessment, for example sensitivity analysis using an appropriately validated PBPK absorption model for excipients where the mechanism of effect is well understood.
3.1.2	**Nov. 2019**	Please clarify if the excipients listed under the heading "All excipients" in Table 1, are expected to affect absorption?	Table 1 provides criteria to demonstrate quantitative similarity for products containing BCS Class III drug substances. The excipient classes listed in the table are functional classes; however, within such a class an excipient can be an excipient which may affect absorption. In that case the difference in the % of the amount of this excipient compared to the reference should be within 10%.
3.1.3	**Nov. 2019**	What may be an 'appropriate justification' for a deviation of an acceptable difference in excipients as listed in Table 1?	Typically, a lot of data on the *in vivo* performance of a formulation is obtained during a product development program. Such data, e.g. formulations with different ranges of excipients showing no effect on drug absorption, including a

			thorough mechanistic assessment, may support changes in excipients beyond those mentioned in Table 1.
3.1.4	**Nov. 2019**	For BCS Class III drug substances, excipients are required to be qualitatively the same and quantitatively similar. What is the consideration on an excipient with the same type but different grade? Is this excipient considered as "qualitatively the same"?	If appropriate, a difference in grade of excipient should be assessed relative to the functional properties of the excipient in the formulation. For some excipient types, a change in excipient grade would not be expected to impact product performance. For others, a modification in grade can potentially impact drug product dissolution (e.g., changes in HPMC particle size distribution, viscosity and substitution; changes in specific surface area of stearate lubricants). The assessment of excipient comparability requires a case-by-case decision to conclusively demonstrate "qualitative similarity".
3.1.5	**Nov. 2019**	Why are limits not defined for allowable differences for sugar alcohol excipients?	Currently, sufficient data is not available to qualify thresholds of effect for these excipients. Furthermore, the impact of the changes caused by these excipients will vary depending on the properties of the drug substance (i.e., sensitivity of the pharmacokinetic profile to alterations in intestinal transit). Changes in the level of these excipients are therefore subject to the same restriction as other excipients that may affect absorption, i.e., within ± 10% of the amount of excipient in the reference product.
3.1.6	**Nov. 2019**	For BCS Class III drugs, all excipients should be qualitatively the same and quantitatively similar (except for film coating or capsule shell excipients, colorant, flavor agent, or preservatives) Can representative examples be provided that meet and do not meet these criteria?	Examples demonstrating excipient quantitative similarity can be found in Annex II of the guidance. Additionally, many of the recommendations for allowable excipient differences in Table 1, Section 3.1, of the guidance are expressed as percent difference relative to core weight (w/w). If a test product meets these recommendations, but there are large differences in absolute amounts of excipients (for example, if core weight is not similar between the test and reference products), additional justification may be requested.

3.2 *In vitro* Dissolution

#	Date of Approval	Questions	Answers
3.2.1	**Nov. 2019**	Can the use of sinkers be justified for situations other than for coning, i.e., sticking, floating etc.?	Yes, if appropriately justified, sinkers may be used to overcome issues noted during dissolution experiments. The same experimental conditions should be applied for the reference and test formulations.
3.2.2	**Nov. 2019**	What is the approach to compare dissolution profiles for BCS Class I products, where one meets the criteria for very rapid (≥85% for the mean percent dissolved in ≤15 minutes) and the other for rapid (≥85% for the mean percent	If one product exhibits dissolution at greater than 85% at 15 minutes but the other does not, sufficient sampling points should be taken to calculate f2 to demonstrate similarity.

		dissolved in ≤30 minutes) *in vitro* characteristics?	
3.2.3	**Nov. 2019**	For dissolution profile comparisons not enough sampling points may be valid for the calculation of f2 due to a high variability at the earlier time points. How can this be addressed?	For BCS Class I drug substances, high variability in dissolution is not expected and alternate statistical methodologies, e.g., boot strapping, to demonstrate similarity is therefore not considered applicable. In cases where high variability occurs due to coning, alternative methods (e.g., the use of sinkers or other appropriately justified approaches) may be considered to overcome issues such as coning, if scientifically justified.
3.2.4	**Nov. 2019**	For dissolution profile comparisons, in some cases, different time-points may result in different f2 values, although the time-points may meet the criteria and conditions listed in the guideline. For example, time-points of 10, 20, 30min result in a f2<50, whereas time-points of 8, 20, 30min yield a f2>50. How can this situation be reconciled?	This situation should only occur in exceptional cases. The time points for the calculation of the f2 value have to be pre-specified. In general, all pre- specified sampling points should be used and justified.
3.2.5	**Nov. 2019**	When the dissolution profiles are different (rapid and very rapid) between test and reference products, do the same dissolution time points have to be used for a f2 calculation to demonstrate comparability?	The same time points should be used for the f2 calculation. See also response to 3.2.4.
3.2.6	**Nov. 2019**	Can a BCS-based biowaiver for one product strength be extended to other strengths in the product series?	No; a BCS-based biowaiver requires supporting data for each strength in a product series. *In vitro* comparison of the test product strengths to respective strengths of the reference product excludes possible drift that may occur when an additional waiver is made without comparison to the respective reference strength.
3.2.7	**Nov. 2019**	Are comparisons between the following dosage forms eligible for a BCS-based biowaiver? - Uncoated tablets versus film-coated tablets? - Tablets versus capsules?	- Uncoated tablets and non-functional film-coated tablets are considered to be the same dosage form; a comparison between these dosage forms would be eligible for a BCS-based biowaiver. - Tablets and capsules are not considered to be the same dosage form and in principle a BCS-based biowaiver may not be acceptable (see also response to 3.1).
3.2.8	**Nov. 2019**	What is the recommended agitation requirement for comparative dissolution assessments for suspension dosage forms?	For suspensions, a rotational speed of 50 rpm is recommended with the paddle apparatus. A lower rotation speed may be used but is not required.

ANNEX I: CACO-2 CELL PERMEABILITY ASSAY METHOD CONSIDERATIONS

#	Date of Approval	Questions	Answers
A.1	**Nov. 2019**	The guideline states that the BCS classification through *in vitro* permeability demonstration is limited to passively transported	In a comparison between 24 human jejunal permeabilities and Caco-2 permeabilities the *in vivo* and *in vitro* drug permeability measurements correlated well for passively absorbed drugs but

		drugs. However 12 of the 40 model drugs (see Table 2) for method validation of Caco-2 cells are transported actively: Four of these 12 are efflux markers (digoxin, paclitaxel, quinidine and vinblastine), the other eight are transported actively (Furosemide = OAT3; Metformin OCT1 and OCT2; Amiloride=OCT2; Famotidine= OCT2; Acyclovir =OAT1 and OCT1, Theophylline =OAT2; and Enalapril = PepT1 and 2). Can the apparent contradiction be explained?	less well for actively transported drugs (Sun et al. Pharm Res (19) 2002). Caco-2 monolayers can be, thus, used to predict passive drug transport in humans, whereas prediction of transport by carrier mediated systems might be inaccurate, owing to an altered expression of carriers in this cell line (Di et al., Drug Discover Today (17) 2012). Accordingly, the reference drugs defining high permeability are rapidly (passively) permeating drugs such as naproxen, antipyrine and metoprolol with comparable permeability coefficients in Caco-2 cells and in human jejunum. Although some of the example model drugs may in some part undergo active transport, the permeabilities of these drug substances in Caco-2 monolayers have been shown to reliably correlate with *in vivo* permeability. Because carrier expression in cell lines may be different from *in vivo* conditions, this correlation is not universally observed for all actively transported drugs. Therefore, without meaningful *in vivo* data, *in vitro* data cannot be the sole means to determine the permeability classification of actively transported drugs. The final conclusion of a drug substance being classified as highly permeable by means of the Caco-2 cell monolayer assay would be feasible only for drug substances devoid of any active transport.
A.2	**Nov. 2019**	In situations where a drug substance is subject to efflux in Caco-2, but the apparent Km value is much lower than the relevant intestinal concentrations, efflux activity can be saturated at all concentrations and permeability is then only driven by passive diffusion. *In vitro* data could be used in such cases, especially if human clinically observed pharmacokinetics is linear. Can products with low Km qualify for a BCS-based biowaiver based on supportive data, e.g. human pharmacokinetics, Absorption- Distribution- Metabolism- Elimination (ADME) data?	Lack of efflux or saturation of efflux transporters cannot be differentiated if the applied physiologically-relevant concentrations (see Annex I e.g., 0.01, 0.1 and 1x highest strength dissolved in 250 ml medium) exceed a drug's Km value. In that case, a drug substance may qualify for high permeability if the apparent permeability, Papp, is ≥ the high permeability reference standard. Additionally, the Caco-2 assay must be validated demonstrating the bi-directional transport of known probes (Table 2) proving functional activity of efflux transporter(s). If *in vivo* data can be presented that demonstrate high permeability according to the guidance (i.e., ADME or absolute bioavailability), a high permeability classification may still be granted. For drug substances that do not qualify for a high permeability designation, it needs to be emphasized that a BCS Class III waiver option is also available if all other conditions according to the guidance are fulfilled.
A.3	**Nov.2019**	Since Caco-2 cells predict permeability of actively transported drugs why are these drugs excluded	See response A1; actively transported drugs are not excluded if the human *in vivo* data support the classification as highly permeable. The use of the Caco-2 cell assay only would be not adequate for

		from qualification for a BCS-based biowaiver?	this purpose (as transporter expression in Caco-2 systems may differ from *in vivo* expression).
A.4	**Nov.2019**	For some validated Caco-2 cell monolayer models, an efflux ratio greater than 2 might be more appropriate as the threshold for observed efflux. Can an efflux ratio threshold of greater than 2 be justified based on the model compounds/dataset from validation results?	In the of absence of any active transport whether uptake or efflux, the ratio between Papp apical (A) to basolateral (B) –absorptive- and B to A is expected to be 1 or close to 1. Any deviation from 1 would indicate some contribution of an active transport. An efflux ratio of greater than 2 has been adopted as indicative of the drug being a substrate for efflux transporter (Giacomini, et al. Nat Rev Drug Discov. 2010; 9:215-236).
A.5	**Nov. 2019**	Provide examples of references for the model drugs for permeability assay method validation.	Please refer to: o Volpe DA. Application of Method Suitability for Drug Permeability Classification. AAPS J. 2010;12(4):670-8." o Li C. et al. Development of *In Vitro* Pharmacokinetic Screens Using Caco-2, Human Hepatocyte, and Caco-2/Human Hepatocyte Hybrid Systems for the Prediction of Oral Bioavailability in Humans. Journal of Biomolecular Screening 2007; 12(8):1084-1091 o Peng Y. et al. Applications of a 7-day Caco-2 cell model in drug discovery and development. European Journal of Pharmaceutical Sciences 2014; 56: 120-130 o Kasim NA et al. Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. Molecular Pharmaceutics 2004; 1(1): 85-96 o Lennernäs, H. 'Intestinal permeability and its relevance for absorption and elimination', Xenobiotica 2007; 37(10): 1015 – 1051 o Thiel-Demby VE. Biopharmaceutics Classification System: Validation and Learnings of an *In Vitro* Permeability Assay. Molecular Pharmaceutics 2009; 6(1): 11-18 o Giacomini, et al. Nat Rev Drug Discov. 2010; 9:215-236 o FDA, United States *In Vitro* Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies Guidance for Industry (October 2017)[2]

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

4. ANNEX: Q&As linked to the respective Sections of ICH M9 Guideline

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