EMA *versus* US-FDA regulatory requirements regarding bioequivalence of orally administered generics

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Guidelines

are guidelines

are guidelines.

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List of Abbreviations

Abbreviation	Explanation
21CFR	Code of Federal Regulations, Title 21 (USA)
A_e	Cumulative urinary excretion
ANDA	Abbreviated New Drug Application
API	Active pharmaceutical ingredient
App	Apparatus
Art.	Article
AUC	Area under the curve
AUCτ	AUC during a dosage interval at steady-state
BA	Bioavailability
BCS	Biopharmaceutics classification system
BE	Bioequivalence
bid	*bis in diem* / twice daily
C_{av}	Average concentration during a dosing interval
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum plasma concentration
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human
C_{mean}	Mean plasma concentration
C_{min}	Minimum plasma concentration
C_t	Concentration at time t
CV	Coefficient of variation
$C\tau_{,ss}$	Concentration at the end of the dosing interval at steady-state
DR	Delayed-release
e.g.	*exemplum gratum* / for example
EMA	European Medicines Agency
ER	Extended-release
EU	European Union
f	Female subjects

Abbreviation	**Explanation**
Fed BE guidance	Guidance for Industry. Food-effect bioavailability and fed bioequivalence studies.
General considerations	Guidance for Industry. Bioavailability and bioequivalence studies for orally administered drug products - General considerations.
HCl	Hydrochloric acid
i.e.	*id est* / that means
i.v.	Intravenous
IMI	Innovative Medicines Initiative
IND	Investigational New Drug Application
IR	Immediate-release
IR guideline	CPMP/EWP/QWP/1401/988Rev.1/Corr**
k_a	Absorption rate constant
LALAs	Locally applied locally acting drugs
m	Male subjects
MAPP	Manual of Policies and Procedures
mg	Milligrams
mL	Milliliters
MPA	Medicinal Products Agency (Sweden)
MR	Modified-release
MR Corr*	CPMP/EWP/280/96 Corr*
MR Corr1	CPMP/EWP/280/96 Corr1
N/A	Not applicable
NCE	New chemical entity
NTI	Narrow therapeutic index drug
OGD	Office of Generic Drugs (USA)
OrBiTo	Oral Biopharmaceutics Tools
$_{partial}$AUC	Partial area under the curve
PD	Pharmacodynamic
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetic
Ref	Literature reference

Abbreviation	**Explanation**
RLD	Reference listed drug (USA)
R_{max}	Maximal rate of urinary excretion
SAEs	Serious adverse events
SAS transport	Technical term for a special data format
SmPC	Summary of Product Characteristics
$_{SS}$	At steady-state
SUPAC	Scale-up and Post Approval Change Expert Working Group of the CMC Coordinating Committee of CDER at US-FDA
$t_{1/2}$	Half-life
t_{max}	Time until maximum plasma concentration is reached
The Draft	Draft Guidance for Industry. Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA.
US	United States (of America)
US-FDA	United States Food and Drug Administration
USA	United States of America
USP	United States Pharmacopoeia
λ_z	Terminal elimination rate constant

1 Introduction

1.1 Aims and objectives

This master thesis aims to compare the regulatory requirements for bioequivalence studies in the European Union and the United States of America that need to be fulfilled in order to successfully submit a generic application according to Directive 2001/83/EC [2], Article 10.1, or an Abbreviated New Drug Application according to 21CFR 314.94 [3], respectively. Due to the broad variety of regulations in this area, it is focused on chemical active ingredients, administered as oral immediate- and modified-release formulations including those locally acting in the gastro-intestinal environment. The goal is to point out similarities and differences in the requirements of the European Medicines Agency and the United States Food and Drug Administration in order to evaluate the possibilities for harmonization of the required studies for registration in both regions.

2 Basics

2.1 Immediate-release and modified-release

Immediate-release (IR) formulations are designed to make the active ingredient available to the body without relevant impact of the dosage form. There are several definitions of "immediately" in this context. From a pharmaceutical perspective, the European Pharmacopoeia (Ph.Eur.) [4] states that IR formulations should normally achieve *in vitro* dissolution of at least 80% of the drug substance within not more than 45 minutes. According to the United States Pharmacopoeia (USP) [5,6], in general more than 85% of the drug substance should be released within 30 to 45 minutes. In the framework of BCS (Biopharmaceutics Classification System)-based biowaiver (a surrogate for *in vivo* bioequivalence), very rapid dissolution is defined as 85% of the labeled content is dissolved within 15 minutes, and rapid dissolution would reach the same amount within a maximum time of 30 minutes [7]. But also, formulations containing a drug substance with e.g., a long half-life, limited solubility, or slow absorption of the drug substance are still considered as IR formulations, if they do not contain any excipients that are added in order to intentionally alter drug release [8].

The term modified-release (MR) formulation comprises different types of formulations: a) delayed-release (DR) formulations and b) prolonged-release formulations, also called extended- (ER), sustained-, or controlled-release formulations. Delayed-release formulations are usually gastro-resistant (enteric) and are designed to allow protected passage through the stomach in order to release the drug substance in the intestines. Prolonged-release formulations, on the other hand, are designed to release the drug substance continuously over several hours in order to maintain a constant plasma level of the drug substance over time, usually to reduce the dosing frequency compared to the respective IR formulation. [9,10,11] From a pharmaceutical perspective, delayed-release according to Ph.Eur. [4] and USP [5,6] should be shown by testing dissolution in different media, within 1 to 2 hours at pH 1 and within a pre-defined time at pH 6.8, preferably. The USP [5,6] sets a time limit of at most 45 minutes for the second step, whereas the Ph.Eur. does not define a time limit for this step. Prolonged release, on the other hand, according to both the Ph.Eur. and the USP should be shown choosing three or more points in time to check for potential dose dumping at usually 20-30% release, characterize the dissolution profile around 50%, and check for near completeness of release at 80%. [4,5,6] In contrast, acceleration of release, e.g. as sometimes intended with orally dispersible tablets, is not termed "modified-release" but such products belong to immediate-release formulations. [8]

More complex approaches are biphasic and pulsatile-release formulations. In biphasic formulations, both immediate-release and prolonged-release are combined in order to generate an immediate onset of the drug effects combined with the advantages of a prolonged-release formulation. Pulsatile-release formulations on the other hand generate a "burst of drug release at specific time intervals". [12] Both are only mentioned here for completeness since they belong to MR dosage forms, but are not subject of this paper.

A special case of oral formulations is a subgroup of the so-called locally applied locally acting drugs (LALAs). The term LALAs includes a wide range of administration forms like nasal, ocular, rectal, pulmonary, dermal, and oral administration. In the context of this paper, the focus will be on orally administered

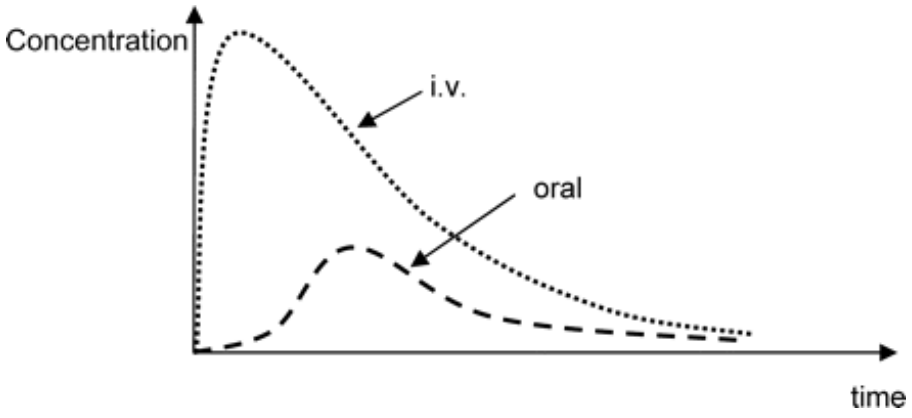
LALAs acting in the gastrointestinal tract. Of these drugs, if any, only a very limited amount of the drug substance is absorbed, so that the drug substance does not enter the blood circulation in relevant amounts. On the contrary, systemic action would even be regarded as an undesired effect for this group of products. [13]

2.2 Bioavailability and bioequivalence

Bioavailability (BA) is defined as the amount of drug that becomes systemically available (extent) and the rate of absorption from its pharmaceutical form into the blood stream. It is usually described by a plasma concentration/time curve that is influenced by the kinetics of the drug. In turn, the kinetics can be influenced by the formulation of a drug product and its route of administration, but also by parameters like food intake, beverages (e.g. alcohol or grapefruit juice) or simply physiological particularities. For drugs that are absorbed into the bloodstream the concentration of the drug substance is measured in the plasma, but in special cases it could also be measured in the serum, in the whole blood or in the urine of a subject. In the last case, the cumulative urinary excretion (A_e) is determined instead of the area under the concentration/time curve (AUC).

A difference is made between absolute and relative bioavailability. Absolute BA describes the systemic availability of a drug compared to intravenous (i.v.) application (which is *per definitionem* 100%), see **Figure 1** below:

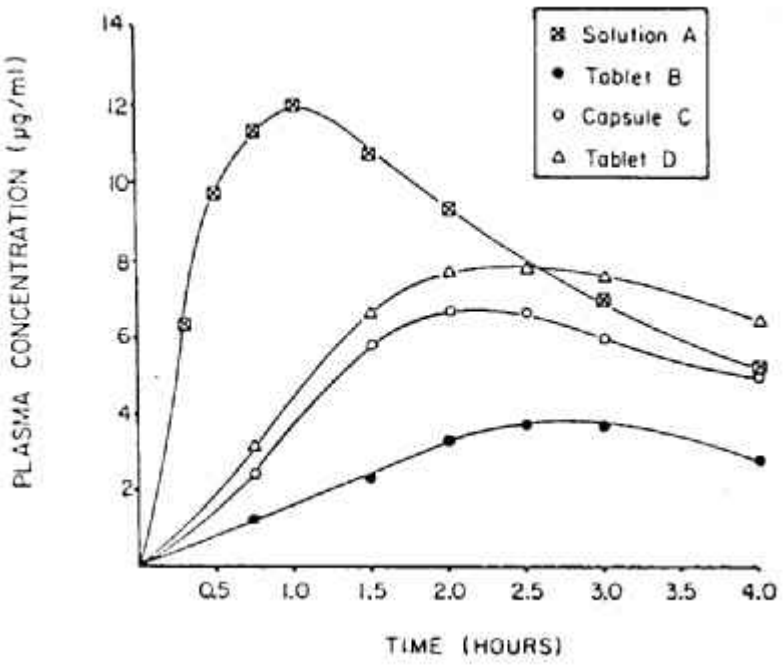
Figure 1: Example for absolute bioavailability [14]



Relative BA is a comparison of the bioavailability between different types of formulation, e.g. oral solid form *versus* oral solution as a reference [15], see **Figure 2** below. In this context, the reference could be a different dosage form of

the same drug substance, e.g. tablet B versus oral solution A, as well as a different formulation of the drug in the same dosage form (tablet B versus capsule C or tablet D).

Figure 2: Example for relative bioavailability [16]



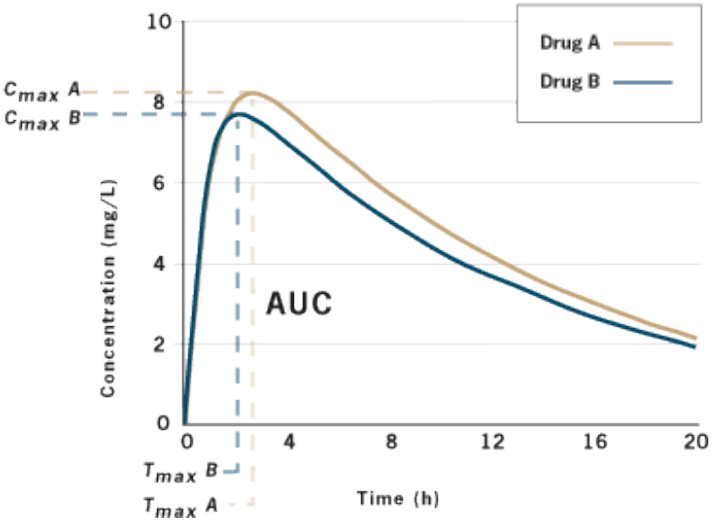
While bioavailability must be examined for new drug applications, generics must show bioequivalence (BE) to a reference product in both the European Union (EU) [2] and the United States of America (USA) [17]. In this context, the test product needs to contain qualitatively and quantitatively the same active pharmaceutical ingredient (API) in the same pharmaceutical form as the reference product. According to Directive 2001/83/EC [2] Art. 10.2, in the EU the expression "same" for drug substances includes "different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives" of the drug substance. Whereas, according to 21CFR Part 320 A [18], the definition of "same" in the USA only explicitly includes different salts or esters of the same therapeutic moiety. In this context, the US-FDA differentiates between pharmaceutical equivalents (same salt or ester) and pharmaceutical alternatives (different salt or ester). In the EU, also different oral pharmaceutical forms like tablets, coated tablets and capsules are defined to be the "same", as long as they are all immediate-release formulations [2]. In the USA, there is no explicit definition available for the "same" pharmaceutical form, but Reference Listed Drugs (RLDs) are identified in the US-FDA's Orange Book. Once

an RLD is identified, it should be used as the reference product for all BE studies with this drug substance. [19] If no RLD is listed, the choice of the reference product should be agreed with the US-FDA prior to study start. BE needs to be tested against both the EU reference and the US reference, as the EU reference has to be sourced within the EU.

Bioequivalence refers to the direct experimental comparison of the relative bioavailability of a test product and a reference. For generics, the reference is a formerly approved drug product based on a "full dossier", including appropriate preclinical and clinical studies ("reference product"). Bioequivalence may also need to be established during the life cycle of a drug product, e.g. in case of a change in formulation, in accordance with the EU Variation guidelines [20], Section B.II.a.3. For an innovator product, relevant variations require the new formulation to be compared against the previous formulation. Relevant variations for generics on the other hand require again bioequivalence testing *versus* the innovator product, not *versus* the previous generic formulation. If two drug products with the same qualitative and quantitative active ingredient (but not necessarily with similar excipients) are shown to be bioequivalent with a 90% confidence interval (CI) and an acceptance range of 80-125%, it is assumed that their *in vivo* performance concerning safety and efficacy is comparable, as well. [15]

Relevant parameters for the evaluation of BA as well as BE are the total exposure or extent of bioavailability, determined by the area under the curve (AUC), the peak exposure or maximum plasma concentration (C_{max}), and the time at which C_{max} is reached (t_{max}). The AUC is usually calculated from the time of administration (t=0) to the last measuring point (AUC_{0-t}) and extrapolated to t=∞ ($AUC_{0-\infty}$). Extrapolation of up to 20% of the $AUC_{0-\infty}$ is accepted by both the US-FDA and the EMA. That means that the sampling schedule should allow the AUC_{0-t} to cover 80% of the $AUC_{0-\infty}$. [15] In order to establish bioequivalence, the plasma concentration/time curves of the reference (Drug A) and the test product (Drug B) are compared by means of AUC and C_{max}, see **Figure 3** below.

Figure 3: Example for bioequivalence [21]



If bioequivalence can be demonstrated within the above mentioned acceptance limits (80-125%), no further nonclinical and clinical studies need to be conducted for the test product, and full reference can be made to the studies conducted with the reference product instead. [2,3] Depending on the mode of action of a drug, additionally to AUC and C_{max}, the absorption rate can also be of importance for the determination of bioequivalence, especially for drugs where a fast onset of action is required. Additional pharmacokinetic (PK) characteristics are required e.g. for MR formulations.

It should be noted that a BE study can fail in both cases, if the bioavailability of the test product is lower than that of the reference or if it is higher. If the bioavailability of the test product is lower, the efficacy of the drug may be lower than required. If the bioavailability is higher, the safety profile is of concern, as more severe adverse reactions or a greater number of them could be the result. Such a product cannot be approved as a generic, but a hybrid application could be submitted instead in the EU in accordance with Directive 2001/83/EC [2], Article 10(4), including supplementary nonclinical and/or clinical data. Alternatively, a reformulation of the test product may need to be considered. [10,22]

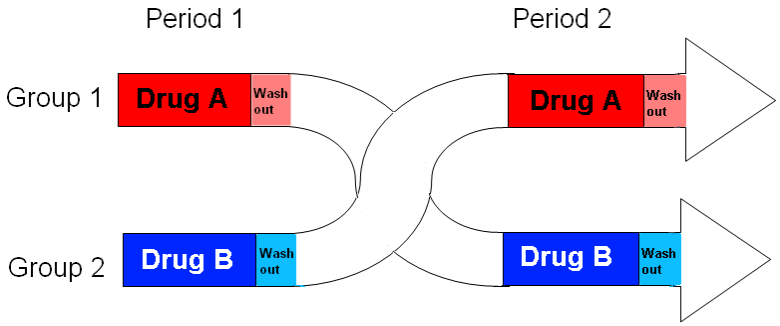
2.3 General approaches to establish bioequivalence

2.3.1 In vivo bioequivalence studies

2.3.1.1 Standard design

Typically, bioequivalence is investigated in healthy volunteers, in a highly standardized open two-arm single-dose crossover PK study at fasting state. With such a crossover study design, the inter-individual variability is eliminated and (almost) only intra-individual variability between test and reference product determines the outcome. In one arm, a single dose of the test product is administered and the plasma concentration of the drug is quantified over time. After a washout period, a single dose of the reference product is administered and again the plasma concentration of the drug is measured over time. In the other arm, the administration of the test and reference product are interchanged, see **Figure 4** below.

Figure 4: Example for crossover study design [23]



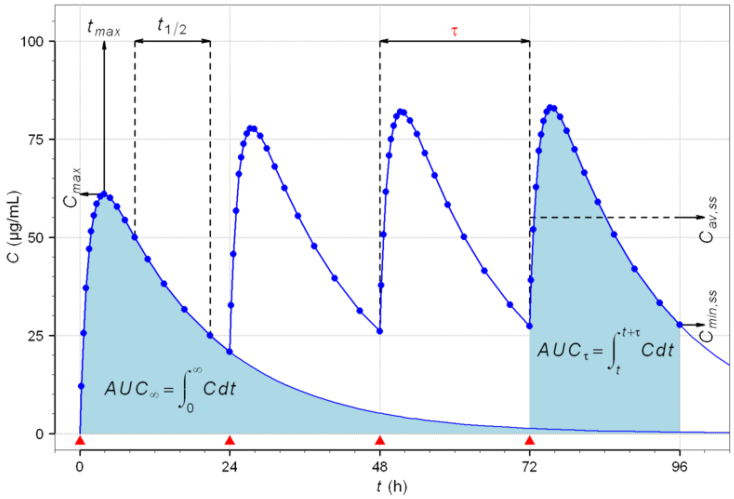
The washout period should be long enough to ensure that the drug substance and its metabolites (if applicable) are completely removed from the blood circulation prior to administration of the other product. [15]

2.3.1.2 Steady-state studies

In some cases, application to healthy volunteers is not possible and a single-dose application to patients would be unethical. In these cases, a steady-state BE study can be conducted in patients. Depending on region-specific requirements, this approach may also have to be followed for prolonged-release formulations additionally to single-dose studies. [15,24] Steady-state is reached by administering a drug repeatedly following a dose schedule that allows approximately for a dynamic equilibrium between intake and elimination [25]. An

example for a concentration/time curve at steady-state is shown in **Figure 5** below, in comparison with the single-dose curve of the same drug product:

Figure 5: AUC after single-dose administration and at steady state [26]



As can be seen in **Figure 5** above, the AUC within one dosing interval τ at steady state (AUCτ) normally equals the $AUC_{0-\infty}$ of a single-dose administration. [15,25] As shown by Zha and Endrenyi 1997 [27], the advantage of a steady-state study for drugs with highly variable pharmacokinetics is a lower coefficient of variation (CV) of C_{max} compared to single-dose administration, if the variability of the absorption rate constant (k_a) is substantially larger than that of the clearance. Hence, sample size may be lower in such studies as compared to equally statistically powered single-dose studies. The disadvantage is that in some cases the pharmacokinetics at steady-state are changed compared to single-dose administration due to enzyme induction. [15] Also, it is more likely to detect bio-inequivalence between drugs with single-dose studies especially for comparison of drugs with different absorption rates, as shown by Anttila et al 1979 [28].

2.3.1.3 Fasting versus fed-state studies

Usually, in BE studies the drug is administered to fasting subjects. For example, the subject receives a meal in the evening prior to the study day and the drug is administered on the next morning after 8-10 hours of fasting. Drinking water is allowed during this time until 1 hour before administration of the drug and again 1 hour after its administration. The next meal is then allowed to be taken 4 hours after administration. [7,10,15] But the intake of food may influence drug absorption

and thus bioavailability. So in cases where the reference drug explicitly needs to be taken with food according to its labeling, a fed-state study may be more appropriate. In this kind of studies, the study subjects receive a defined, standardized, usually high-fat high-calorie meal each prior to administration of the test product and its reference in order to simulate a worst-case scenario for administration of the drug product with food. [7]

2.3.1.4 Alternative approaches

If measuring PK parameters is not possible, pharmacodynamic (PD) methods can also be used for demonstrating bioequivalence, although PK studies are the preferred option. Finally, comparative clinical trials could be considered if all other approaches fail. Nevertheless, this is the least favorable option both from an industry point of view, due to expenses, as well as from an authority point of view, due to the lack of sensitivity for BE purposes. [10]

2.3.2 In vitro "bio"equivalence studies

In case of proportionality waivers, alternatively to *in vivo* BE studies, *in vitro* dissolution tests can be conducted. In such studies, the drug product is inserted into an apparatus (App) to allow determination of cumulative dissolution over time in an aqueous buffered medium at three different pH levels (pH 1.2, 4.5 and 6.8) and additionally using the method for batch release (quality control method), if applicable.

For special kinds of drug products, different approaches can be considered. For example for drug products containing calcium acetate as the active ingredient, *in vitro* binding to phosphate (equilibrium and kinetic binding studies) can be determined *in lieu* of dissolution/disintegration studies [29,30].

2.3.3 Waivers

Under specifically defined circumstances, both the EU and the USA accept biowaivers based on the Biopharmaceutics Classification System (BCS). In the USA, the drug product must be BCS Class I [31]; in the EU both BCS Class I and III products are accepted for BCS-based biowaivers [7]. The BCS-based biowaiver approach constitutes a surrogate for *in vivo* bioequivalence testing based on

physico-chemical drug substance characteristics and comparative *in vitro* dissolution of test and reference.

Furthermore, in case of product series of IR and MR formulations it may be possible to waive *in vivo* studies for some strengths, replacing the *in vivo* studies by certain *in vitro* dissolution tests as described in **Section 2.3.2** above. In this context, the US-FDA uses the term "waiver request" [e.g., 32], whereas the EMA uses the term "biowaiver of strengths" [7].

Additionally, the EMA published in Appendix II of the "Guideline on the investigation of bioequivalence" [7] a list of criteria where waivers are defined as acceptable depending on the formulation of the drug product. These include aqueous i.v. solutions in general, as well as aqueous oral solutions under defined circumstances. A similar approach is followed by the US-FDA, as can be seen in 21CFR 320.22 [17]. Drug products for which BE is self-evident, like all i.v. solutions and those generic drug products that are qualitatively and quantitatively completely identical to an approved drug, are in general eligible for waivers in the USA.

2.3.4 Latest development

In October 2012, a 5-year project called OrBiTo [33,34,35] has been started in the EU by a large group of experts from industry, universities, and the Swedish Medicinal Products Agency (MPA) within the frame of the Innovative Medicines Initiative (IMI) [35]. OrBiTo is the abbreviation for Oral Biopharmaceutics Tools, and the project aims for a better understanding of the behaviour of oral formulations in the gastrointestinal tract. In order to achieve this, a database is being generated where already existing data from *in vivo* studies are collected. Furthermore, the processes in the gastrointestinal tract are investigated in depth by combining physico-chemical measurements with *in vitro* and *in vivo* tests as well as *in silico* modeling. This is expected to lead to a refinement of existing tests and development of new, validated methods for the prediction of drug behaviour in the gastrointestinal tract, for which currently rather simplified, empirical models are available, limiting their use to a rather small group of drug substances belonging to BCS class I and parts of BCS class III. [34]

If the OrBiTo project is successful, facilitation of the prediction of drug behaviour especially for the challenging drug substances of BCS classes II and III and probably some active pharmaceutical ingredients (APIs) of BCS class IV as well as for MR formulations could be achieved by a combination of validated predictive *in vitro* and *in silico* tools. And with the help of these tools, finally a reduction in the number of *in vivo* BE studies could be achieved. [34]

3 Results

3.1 EMA regulatory view

The European Medicines Agency (EMA) has issued separate guidelines for immediate-release (IR) and modified-release (MR) formulations, which are summarized below.

3.1.1 Immediate-release

Guideline CPMP/EWP/QWP/1401/98Rev.1/Corr** [7] of 2010 is focused on chemical active ingredients in oral immediate release (IR) formulations with systemic action, and is therefore abbreviated as "the IR guideline" below. It describes design, conduct and evaluation of bioequivalence studies for IR formulations in great detail. The standard design for oral IR formulations as recommended in this guideline is a randomized, 2-period, 2-sequence single-dose crossover study with at least 12 healthy adult subjects and analysis of the drug substance concentration (parent) in blood plasma. It is recommended to determine the parent compound even if it is an inactive pro-drug, instead of the metabolites. Regarding the number of subjects and the design of the study, in general the linearity of the drug's pharmacokinetics, the need for fed-state and/or fasting studies and for enantioselective analysis are requested to be considered and a possibility of waivers for additional strengths is given. In the standard fasting study the study subjects are not allowed to drink water each for 1 hour before and after administration, and receive a standardized meal 4 hours after administration at the earliest. A couple of alternative study designs are given by the guideline as well, such as a) parallel design for drug substances with a "very long half-life" [7] ($t_{1/2}$), b) replicate designs in order to allow scaling based on within-subject variance of

the reference product, c) multiple dosing either in patients if single-dose in healthy volunteers is not possible and single-dose in patients is not feasible, or exceptionally if detection is only reliably possible at steady-state, d) fed instead of fasting (high-fat high-calorie meal), if intake with a meal is recommended in the Summary of Product Characteristics (SmPC) of the reference product, e) fed additionally to fasting for specific formulations like microemulsions or solid dispersions, f) analysis in urine instead of blood plasma (determination of the cumulative urinary excretion (A_e) and its maximal rate (R_{max}) instead of AUC and C_{max}). It is recommended to standardize the diet, fluid intake and exercise as well as the exact timing of the drug administration. Sampling times need to start before C_{max}, include frequent samples around t_{max}, and be long enough to reliably estimate 80% of $AUC_{0-\infty}$. Furthermore, at least 3-4 samples in the terminal log-linear phase are required to be taken, in order to allow for linear regression to accurately determine the terminal elimination rate constant (λ_z). Alternatively to the AUC_{0-t}, the truncated AUC_{0-72h} could be used for IR formulations, i.e. limiting the sampling time to a maximum of 72 hours.

The IR guideline [7] does explicitly mention the acceptability of a 3-period study in order to include both an EU reference and a US reference, and gives advice on the evaluation of such a study. Additional information is given regarding narrow therapeutic index drugs (NTIs), stating that here the AUC must be narrowed to 90.00-111.11% of the reference.

Furthermore, the IR guideline [7] explains the concept of waivers either for additional strengths or as BCS-based biowaiver with the goal to waive BE studies completely. Also, guidance is included on the conduct of dissolution studies either a) complementary to BE studies, or b) supporting the waiver for additional strengths, or c) included in BCS-based biowaivers. In general, dissolution is requested to be conducted at three different pH levels (pH 1.2, 4.5 and 6.8) plus the media used for quality control, if applicable.

The EMA's latest approach is to provide product-specific guidance on the design of bioequivalence studies. This was laid down in the "Concept paper on the development of product-specific guidance on demonstration of bioequivalence",

EMA/CHMP/423137/2013 [36] of 2013. Since October 2013, the EMA started to issue such guidances for public consultation, beginning with oral immediate-release formulations [37]. An overview of these guidances can be found in **Table 2 in Annex 1** and a discussion can be found in **Section 3.3.1** below as internal comparison, and in comparison with the corresponding US guidances in **Section 3.3.3** below. Within these product-specific guidance documents, the EMA does cover different dosage forms sometimes implicitly and sometimes explicitly. An example for an explicit coverage of different dosage forms is Oseltamivir, for which a study is requested for the capsule whereas in the same guidance document [38] a waiver is recommended for the solution under specified conditions. An example for an implicit coverage of capsules and tablets is Imatinib for which only a strength but no dosage form is mentioned in the guidance document [39]. As both capsules and tablets are treated in the EU as similar dosage forms, any distinction in the guidance document is *per se* obsolete in the view of European legislation. In **Table 2 (see Annex 1**), the different dosage forms are nevertheless shown in separate lines for ease of comparison, although the source is the same guidance document for the same drug substance.

3.1.2 Modified-release

Separate guidance for modified-release (MR) formulations can be found in guideline CPMP/EWP/280/96 Corr* [24] of 1999 (abbreviated as "MR Corr*" below). While the IR guideline [7] addresses also specific recommendations, MR Corr* [24] is less detailed. It addresses prolonged- as well as delayed-release formulations and new chemical entities (NCEs) as well as generics, although for NCEs it is only mentioned that a complete dossier must be provided. MR Corr* [24] does also include guidance on transdermal patches which are outside of the scope of this paper and will therefore not be discussed here. For new MR formulations for which an IR formulation is already approved, bioavailability studies are required. These are not in the focus of this paper either.

For MR formulations which differ from the reference product in the release controlling excipients, *in vitro* dissolution profiles of test and reference product are explicitly requested in MR Corr* [24] to be compared before the conduct of *in vivo* BE studies, in order to establish pharmaceutical essential similarity. Subsequently,

differentiation is made between prolonged-release and delayed-release formulations. While delayed-release formulations are recommended to be tested using the same approach as for IR formulations focussing on the delayed-release character of the formulation and with the request for conducting a fed-state study, for prolonged-release formulations the recommendations are more detailed. The focus here lies on the proper functioning of the release prolongation, making sure that an unexpected release ("dose dumping" [24]) is avoided and that the prolongation of release is working as expected. Equivalence of the test and reference must be shown at single-dose as well as steady-state, while food effects must be evaluated in a single-dose study only. Waivers are accepted for steady-state studies with additional strengths provided that the criteria for extrapolation of BE are met (like identical qualitative and proportional quantitative compositions, linear PK, etc.). But single-dose fasting studies must be conducted for each strength. Other than that, multiple unit formulations with multiple strengths must be investigated only in a single-dose fasting study on the highest strength, if their compositions are proportional containing "identical beads or pellets" [24] and provided that they have similar dissolution profiles. Apart from the AUC during a dosage interval at steady-state (AUCτ) and C_{max}, additionally the minimum plasma concentration (C_{min}) is to be assessed for prolonged-release formulations.

MR Corr* [24] is currently being revised to be replaced by CPMP/EWP/280/96 Corr1 [12] of 2013 (also called CPMP/EWP/280/96 Rev1 and abbreviated as "MR Corr1" below). MR Corr1 [12] is much more detailed than MR Corr* [24], not only in those aspects that concern this paper but also, for example, regarding BE studies for NCEs. Also, its scope has been widened to include multi-phasic formulations like biphasic- and pulsatile-release formulations, which are not in the focus of this paper. A new aspect in MR Corr1 [12] is furthermore the request for *in vitro* studies of drug substance release in high and low concentrations of alcohol.

While in MR Corr* [24] the request for additionally conducting a fed-state study for prolonged-release formulations can only be assumed and is confirmed in the respective Q&A document [40], MR Corr1 [12] elucidates that for all modified-release formulations both a fasting as well as a fed-state study need to be

conducted and the test product needs to be bioequivalent to the reference in both cases in order to apply for Art. 10(1) of Directive 2001/83/EC [2]. Furthermore it is clarified that single-dose and steady-state studies both should be generally conducted, if feasible. Possibilities for a combination of these studies in multiple periods and sequences as well as bracketing approaches are described separately in detail for prolonged- and delayed-release formulations. Other than for prolonged-release formulations, delayed-release formulations are not required to be conducted at steady-state. For single-dose studies the parameters AUC_{0-t}, $AUC_{0-\infty}$, residual area, C_{max}, $_{partial}AUC$ and t_{max} need to be determined whereas AUC_{0-72h} is explicitly excluded by the guideline as invalid parameter for modified-release formulations. For steady-state studies the parameters AUC_{τ}, $t_{max,SS}$, $C_{max,SS}$, $C_{\tau,SS}$ and fluctuation are required.

Although for delayed-release formulations steady-state studies are not requested in general in the guidelines summarized above, it could not automatically be assumed that they do not need to be conducted. For example, a steady-state study was requested by the Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) additionally to the provided single-dose fasting and fed studies in a referral for Omeprazole in February 2006 [40]. This was justified by the fact that the PK for Omeprazole is time dependent due to the increase of pH in time. With the draft MR Corr 1 [12], it is now clarified that steady-state studies are not required to be conducted for delayed-release formulations. So it can be expected, that the outcome of the Omeprazole referral would be different today.

3.1.3 Oral locally applied locally acting products in the gastrointestinal tract

Up to now, for oral locally applied locally acting products (LALAs) in the gastrointestinal tract, EMA has recommended clinical or pharmacodynamic studies in order to demonstrate bioequivalence, similar to other locally applied products like creams and ointments which were all summarized in the same document, CPMP/EWP/239/95 final "Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents" [13] of 1995. But as mentioned in **Section 2.3.1.4** above already, such approaches are difficult and not favorable in terms of reliability. Therefore, in 2013

EMA/CHMP/558326/2013, the "Concept paper on the development of a guideline on the demonstration of therapeutic equivalence for locally applied and locally acting products in the gastrointestinal tract" [41], was issued by the EMA to approach this difficult field. In this concept paper, the need is expressed to either systematically or product-specifically establish alternative *in vivo* and *in vitro* methods or models, in order to replace the current request for clinical or pharmacodynamic studies. It can be expected that the concept paper will lead to a new guideline where recommendations for dissolution testing and BE studies for this special group of LALAs are made.

3.2 US-FDA regulatory view

The US-FDA regulations regarding BE studies are divided into guidelines for post-approval changes (equivalent to the European Variations) and guidelines for generics. Currently, the Office of Generic Drugs (OGD) within the US-FDA is responsible for all guidances regarding BE studies for generics, whereas the Scale-Up and Post Approval Changes (SUPAC) Task Force within the Center for Drug Evaluation and Research (CDER) takes care of the recommendations for variations to approved products. As only the generics are subject of this paper, the regulations for BE studies for post-approval changes are not discussed here. It is worth noting that the US-FDA uses the term "Bio-INDs" for Investigational New Drug Applications (INDs) submitted for bioavailability or bioequivalence studies [42]. Anyway, other than the first part of the term ("bio") might imply, this term is not related to biologics or biosimilars.

3.2.1 General requirements

In the US Code of Federal Regulation, 21CFR Part 320 "Bioavailability and bioequivalence requirements" [17], at first the options for waiver of *in vivo* BE studies are listed, as already mentioned in **Section 2.3.3** above. Then the conditions for establishing bioequivalence are described in detail. A common study design in accordance with the US-FDA regulations would be a single-dose crossover fasting study in healthy volunteers. The washout phase should be at least three half-lives of the drug substance. Parallel designs, fed-state studies and other not explicitly detailed deviations from the standard design are allowed, if scientifically justified. Multiple-dose studies are only foreseen for bioavailability

studies, not for bioequivalence studies according to 21CFR Part 320 [17]. Additionally to the common understanding of bioequivalence defined by comparable absorption rates and extents, the US-FDA also explicitly accepts drug products with different absorption rates as bioequivalent if the differences are intentional, clinically insignificant, and reflected in the drug product's labeling. In contrast to the EU where a different labeling precludes a generic application, in the USA still an ANDA can be submitted for those products. In any case, *in vivo* or *in vitro* BE testing as well as a combination of both can be requested by the US-FDA. Therefore, close cooperation with the US-FDA regarding design, chosen reference, and analytical methods (both statistical and chemical) is highly recommendable in advance of conducting any BE study if no specific guidance is available (**see Section 3.2.4**).

The Guidance for Industry "Bioavailability and bioequivalence studies for orally administered drug products - General considerations" [10] of 2003, called "General considerations" for short below, summarizes and amends 21CFR Part 320 [17]. It is clarified that the drug content of the test product may only differ by up to 5 percent from the reference. Study subjects should be adults who are in sex, age, and race representative to the population intended to be treated. For the recommended fasting study, the study subjects are not allowed to drink water each for 1 hour before and after administration, they should receive a standardized meal 4 hours after administration at the earliest, and should refrain from drinking alcohol for 24 hours before administration and during the whole sampling time. Twelve to 18 samples per subject and dose are recommended to be taken within at least 3 times the terminal half-life of the measured substance, for an accurate determination of C_{max} and λ_z. Special focus is given to the sometimes problematic distinct determination of C_{max}. The guidance clarifies that sample collection within 5 to 15 min after dosing followed by two to five samples taken within the first hour is considered adequate even if the first sampling point coincidentally shows the highest concentration observed in the BE study. Additionally to C_{max} and λ_z, the following parameters usually need to be reported: AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, and $t_{1/2}$. Where applicable, food-effect studies are requested to be conducted as single-dose crossover studies as well.

In general, it is recommended to measure the parent drug rather than it's metabolite. Nevertheless, it is recognized that it may be useful to measure the metabolite if the drug levels of the parent in the blood circulation are too low for reliable detection or if the metabolite is more meaningful with regards to safety and/or efficacy. Thought should be given to the handling of enantiomeric drug substances. Measurement of the racemate by an achiral assay is recommended by the guidance unless the enantiomers differ in pharmacodynamic as well as in pharmacokinetic characteristics and primarily the minor enantiomer is active and the absorption of the enantiomers is nonlinear.

Principally allowed alternatives to the standard design, according to the General considerations [10] are steady-state studies, a replicate design, and inclusion of patients instead of healthy volunteers, if justified. For steady-state studies, AUC_{τ} instead of $AUC_{0\text{-}t}$, and additionally C_{min}, the average concentration during a dosing interval (C_{av}), the degree of fluctuation, and swing need to be reported. In separate sections, recommendations for the documentation of bioequivalence for IR and MR formulations are given.

While 21CFR Part 320 [17] generally requests a washout phase of at least three half-lives ($t_{1/2}$) for single-dose BE studies and at least five half-lives for multiple-dose BA studies, in the Attachment of the General considerations [10] a washout phase of more than five times the half-life of the measured substance is recommended in general. For drug substances with a long half-life, a parallel design can be used instead of the usual crossover design, and a suitable truncation of the AUC is allowed. Nevertheless, it is recommended to be cautious in truncating the AUC of drugs with high intrasubject-variability in distribution and clearance.

Additionally, the recommendations for different dosage forms are detailed in the General considerations [10]. For oral solutions, *in vivo* studies can be waived in accordance with 21CFR Part 320 [17]. For suspensions, *in vivo* and *in vitro* testing are recommended. Oral solid IR formulations should be tested using a single-dose fasting study and *in vitro* dissolution tests. Waivers can be submitted for lower strengths, based on *in vitro* dissolution profiles if contents are proportionally

similar. For MR formulations (extended- and delayed-release) both fasting and fed-state studies are required, and multiple-dose studies are explicitly discouraged even for products with nonlinear kinetics. Waivers for lower strengths can be submitted similar to solid oral IR formulations.

Special attention is also given to locally acting oral drugs (i.e., oral LALAs). Clinical studies with efficacy and safety endpoints and/or suitable *in vitro* studies are recommended for this kind of drugs, as well as additional fasting and fed-state studies for investigation of the degree of systemic exposure [10]. Based on the presentation from 2004, for narrow therapeutic index drugs (NTIs), the US-FDA seems to justify to keep the limit of 80-125% [43] unless specific guidance indicates otherwise [10]. But obviously, the discussion is ongoing at the US-FDA according to a more recent presentation from 2011 [44].

Furthermore, guidance is included on the conduct of *in vitro* dissolution studies. In general, dissolution needs to be conducted at three different pH levels (pH 1.2, 4.5 and 6.8), for MR formulations additionally in water. Different agitation speeds need to be tested, surfactants are allowed for poorly soluble substances.

3.2.2 Fed-state bioequivalence studies

The US-FDA's Guidance for Industry "Food-effect bioavailability and fed bioequivalence studies" [45] of 2002, called "Fed BE guidance" below for short, recommends that fed-state BE studies should be conducted additionally to fasting studies for all MR formulations, and for IR formulations that contain drug substances which are not BCS class I or where the labeling does indicate food effects or which are not explicitly requested to be taken on empty stomach. The recommended design for generics is a two-treatment, two-period, two-sequence fed-state crossover study in at least 12 healthy patients from the general population. The highest strength from the same batch as for the fasting study should be tested. Studies for lower strengths can be waived based on comparison of the dissolution profiles. A high-fat high-calorie meal is recommended during these studies and detailed description of the composition and administration of such a meal is given in the guidance document. Deviations from the recommended standard design are allowed, if scientifically justified (e.g., inclusion

of patients instead of healthy volunteers, administration of a lower strength due to safety concerns). Sample collection as well as the parameters to be reported and conditions for bioequivalence are similar to the fasting study. For MR formulations, the potential safety risk of dose dumping should be considered, due to a potentially more rapid release of drug when being co-administered with food. Furthermore, labeling recommendations are given in the Fed BE guidance [45]. Special thought is given to sprinkles and administration with special vehicles like beverages. Both should be used as described in the labeling of the RLD, if applicable.

3.2.3 Expected changes to current guidances

In December 2013, the Draft Guidance for Industry "Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA" [11], abbreviated below as "the Draft", was released for commenting and currently the comments are being reviewed and the finalization of the guidance is expected. This guidance will eventually revise and replace parts of the General considerations [10] and the Fed BE guidance [45] summarized above (**see Sections 3.2.1 and 3.2.2**). The most important changes are therefore described below. The product-specific recommendations described in **Section 3.2.4** further below will not be altered by the Draft [11]. Post-approval changes are additionally covered in the Draft [11] and reference is made to the respective SUPAC guidances. But as these are not part of this paper, they are disregarded here.

Additionally to the two-treatment, two-period, two-sequence single-dose crossover design mentioned in the Fed BE guidance [45], the same design is also requested for fasting studies in the Draft [11]. Alternatively it recommends a parallel design for products with long half-lives or a replicate design for highly variable drugs as described in the General considerations [10,11]. The advantages of single-dose studies over multiple-dose studies are stressed again in the Draft [11]. Still, steady-state studies are explicitly mentioned as the only alternative if patients need to be used as study population for safety reasons, while in the General considerations [10] only a reference to 21CFR Part 320 [17], Section 27 (a) is given, where other reasons for choosing steady-state studies are listed, like excessive inter-subject variability or low drug concentrations in the blood after

single-dose administration. A very detailed description of the general design of the corresponding fasting and fed-state studies is given in the Attachment of the Draft [11] in line with the recommendations in the General considerations [10] and the Fed BE guidance [45].

Similar to the Fed BE guidance [45] in general both fasting and fed state studies are recommended in the Draft [11] for all oral products, unless the labeling explicitly requests an empty stomach. In addition, the Draft also requests both studies to be conducted if the labeling explicitly requests intake with food. Anyway, it expressly excludes conducting a fasting study if serious adverse events (SAEs) must be expected on an empty stomach. [11]

While the title of the Draft [11] explicitly limits the guidance to pharmacokinetic BE studies, still general considerations are made regarding *in vitro* testing (*in vivo/in vitro* correlation, dissolution, drug release testing), pharmacodynamic endpoints and clinical endpoints, similar to the General considerations [10].

Other than in the General considerations [10], a fed-state BE study is requested additionally in the Draft [11] for oral solid IR formulations and for suspensions. This was so far only required in general for MR formulations [10] and for specific cases of IR formulations in the Fed BE guidance [45], as described above. Furthermore, it is more clearly expressed in the Draft [11] than in the General considerations [10], that suspensions are to be treated as any solid oral formulation.

While the General considerations [10] cover chewable tablets only regarding dissolution testing, demanding to test whole tablets, the Draft [11] mainly focuses on the *in vivo* requirements. It recommends chewable tablets in *in vivo* studies to be chewed, unless labeling alternatively permits swallowing them as whole, then they should be explicitly tested like this, in order to provide a worst-case scenario for the drug absorption.

Compared to the General considerations [10], it is clarified in the Draft [11], that "long half-life" means a half-life of more than 24 hours. This was previously not as explicitly defined, while the general recommendations are similar in both

documents. Also, the critical view on C_{max} as first measuring point was included into the Draft [11] similar to the General considerations [10].

Explicitly stressed in the Draft [11] is the influence of alcohol on MR formulations and the request for conducting specific *in vitro* studies in order to evaluate the potential impact of alcohol on the formulation. Even *in vivo* studies on this matter are to be considered in special cases according to the Draft [11]. Previously, only the need for abstinence during a BE study had been included in the General considerations [10] without further explanation, whereas it is linked in the Draft [11] to the risk for dose dumping that is also mentioned in the Fed BE guidance [45] in a more general context.

Special thought was given in the Draft [11] to endogenous substances. This point had not been raised at all in the General considerations [10] or in the Fed BE guidance [45] previously. In the Draft [11], determination of a baseline and control of the diet for compounds present in food are recommended.

For locally acting oral drugs (i.e., oral LALAs), other than in the General considerations [10] where only clinical and *in vitro* studies are discussed for this subgroup of LALAs, it is recognized in the Draft [11] that in some cases PK endpoints are feasible and the possibility to use PD endpoints is added. BE studies for this kind of drug are at least not negated in the first place by the Draft [11].

3.2.4 Product-specific recommendations

In accordance with its "Guidance for Industry - Bioequivalence recommendations for specific products" [46] of 2010, the US-FDA is issuing product-specific recommendations for bioequivalence studies since 2007 already. As of 27 February 2014, 1,127 guidance documents are available on the US-FDA homepage [47], separately for different routes of administration and dosage forms, and sorted by active ingredient. In these recommendations, the design of the bioequivalence studies expected by the US-FDA to be conducted by the generic industry is described. A few examples are given in **Table 1 (see Annex 1** below). Focus was given here to a number of products where an extended-release

formulation is available or where interesting differences were noted between different formulations containing the same drug substance.

In **Table 1 in Annex 1** below it becomes obvious that, in accordance with the Draft [11] described in **Section 3.2.3** above, two studies, one at fasting- and one at fed-state respectively, are usually recommended, with their designs, analytes to be measured, recommended data to be reported, and acceptable waivers (for additional strengths) described in detail. Exemptions are for example the IR formulation of Acetazolamide and the ER suspension of Azithromycin (see **Table 1 in Annex 1**), where in both cases only one fasting study and no fed-state study is recommended [48,49]. For Azithromycin ER this can be explained by the fact that the labeling recommends intake on an empty stomach [50]. For Acetazolamide IR such a connection with the labeling could not be confirmed. Comparing recommendations between different formulations for the same API, it is remarkable that for Acetazolamide IR [48] the fed-state study is not recommended, while it is recommended for the ER formulation [51], in line with the General considerations [10]. On the other hand, for Alprazolam [52,53,54] no differences in recommendations are made for the IR and ER formulations. Here, the standard set of two studies, one fasting and one fed, is recommended in line with the US-FDA's current thinking as reflected in the Draft [11]. Surprisingly, the product-specific recommendations for the IR formulations of Acetazolamide [48] and Alprazolam [52,53] were issued around the same time - Acetazolamide in July 2008, and Alprazolam in September 2008. Accordingly, a common approach could have been expected. Similarly, for Atovaquone tablet [55] a parallel design is listed as an alternative due to the prolonged half-life, whereas this alternative is missing in the recommendation for the suspension [56]. There is no obvious explanation for this difference, so it is not clear if this is an intentional or an unintentional deviation in the guidances. Comparing the different recommendations of the US-FDA as summarized in **Table 1 in Annex 1**, also a discrepancy regarding the requested pregnancy-state of the female subjects can be noted. It is described in three different ways: Sometimes not mentioned at all, e.g., for Alprazolam [52,53,54] and Azithromycin [49,57,58], in some cases only mentioned as "nonpregnant", e.g., for Acetazolamide ER [51] and Amoxicillin IR [59], in other cases specified as "not pregnant or lactating, using abstention or contraception",

e.g., for Acetazolamide IR [48] and Amoxicillin ER [60]. So, to be on the safe side, the strictest constraints should be followed in general when planning a BE study.

Dissolution testing is requested in general in a standardized form. Usually testing of 12 dosage units each of all strengths of test and reference is recommended, sometimes with additional requests regarding apparatus (App), medium or test objects (see Acetazolamide ER capsules [51] or Atovaquone [55,56]). Waivers for additional strengths are normally proposed based on comparable dissolution profiles. For both purposes, a Dissolution Methods Database is referred to, maintained by the US Office of Generic Drugs (OGD) and available via the Internet [61].

It is noteworthy that since July 15, 2009, the US-FDA explicitly requests all BE studies conducted for an ANDA with the same drug product to be submitted, not only the successful ones [22].

3.3 Comparison of the product-specific recommendations of EMA and US-FDA

In the past, the US-FDA issued a couple of general guidance documents for orally administered drugs regarding the proof of bioequivalence, as described in **Sections 3.2.1 and 3.2.2** above. Additionally, the US-FDA currently regularly issues product-specific guidances, as described in **Section 3.2.4**. Since October 2013, the EMA as well has issued product-specific bioequivalence guidances for a number of IR formulations as described in **Section 3.1.1** above, additionally to their general guidelines described in the same section. As the same drug substances are also covered in the US-FDA's product-specific guidances, **Table 2** (**see Annex 1** below) lists the recommendations for these drug substances from the EMA and the US-FDA. For ease of comparison the differences between the recommendations are highlighted in **bold print** in **Table 2 in Annex 1** and are further described below.

3.3.1 EMA internal comparison

In line with the general EMA guidelines described in **Section 3.1** above, it would be expected that for IR formulations the EMA usually requests solely one fasting

2-way single-dose crossover study in healthy subjects, and analysis of the parent drug in plasma with determination of AUC_{0-t} and C_{max}. Indeed, only six of the EMA's 16 currently available product-specific guidelines do completely comply with these expectations. These are Dasatinib [62], Miglustat [63], Oseltamivir capsule [38], Repaglinide [64] (testing this antidiabetic drug in healthy subjects requests concomitant glucose administration), Telithromycin [65], and Voriconazole [66]. The main deviation (in seven cases) is an explicit option to determine a truncated AUC_{0-72h} instead of AUC_{0-t}. This is the case for Carglumic acid [67], Erlotinib [68], Imatinib [39], Memantine [69], Posaconazole [70], Sorafenib [71], and Tadalafil [72]. In two cases a fed-state study is requested instead of a fasting study, these are Capecitabine [73], where additionally the inclusion of patients is recommended instead of healthy volunteers, and Posaconazole [70]. And in two cases both fasting and fed-state studies are recommended. These are Sirolimus tablet and oral solution [74] and Tadalafil [72]. The guidance for Sirolimus [74] additionally recommends the analysis of whole blood instead of plasma and narrows the AUC_{0-t} to 90-111% due to the fact that Sirolimus is currently considered a Narrow Therapeutic Index drug (NTI). Also, for one drug substance (Oseltamivir [38]) a waiver for an *in vivo* BE study of the oral solution is explicitly allowed under specified conditions, in line with the EMA's IR guideline [7], Appendix II, where it is stated that for aqueous solutions no *in vivo* studies are requested when the reference is a comparable aqueous solution.

3.3.2 US-FDA internal comparison

In line with the general guidelines described above, the US-FDA would be expected to usually request one fasting study similar to that requested by EMA plus one fed-state 2-way single-dose crossover study in healthy subjects, also with analysis of the parent drug in plasma. In the 19 product-specific US-FDA guidance documents for the 16 drug substances covered in the EMA's product-specific guidances, also only six of the recommendations do completely follow the expected pattern. These are Dasatinib [75], Miglustat [76], Posaconazole [77], Repaglinide [78], for which the drug should be administered together with glucose solution similar to the EMA's recommendation, Tadalafil [79], and Telithromycin [80]. In some of the remaining guidance documents, two or three deviations from the expectations are present at once. The main deviation (in five cases) is a

request for one fasting study only, these are Carglumic acid [81], Erlotinib [82], Sorafenib [83], Voriconazole tablet [84] and Voriconazole powder for suspension [85]. In two cases only a fed-state study is requested, these are Capecitabine [32] and Imatinib, for which a light breakfast is recommended instead of the usual high-fat high-calorie meal [86]. The recommendation for Capecitabine can be explained with the recommended administration in the labeling [87]. For Imatinib, merely administration "with a meal and a large glass of water" [88] is requested in the labeling, but the explicit request for a light breakfast in the product-specific guidance seems to be taking into account that cancer patients usually do not tolerate the standard high-fat high-calorie meal for fed-state studies. In the case of Memantine tablet [89] it is left to the applicant to either test in fasting- or fed-state and this guidance explicitly mentions the alternative of a BCS waiver for the formulation, as does the guidance for Capecitabine [32]. In three cases a study in treated patients is requested instead of healthy volunteers (Capecitabine [32], Imatinib [86] and Sunitinib [90]), for Sunitinib at steady-state conditions, whereas Capecitabine and Imatinib do not reach steady-state conditions at the requested dosing intervals, due to their short half-lives. Therefore, these studies can still be conducted as single-dose studies. For Oseltamivir the additional detection of the metabolite is recommended for both the capsule [91] and the powder for suspension [92]. The guidance for Carglumic acid only mentions the analysis "in appropriate biological fluid" [81], the guidance for Sirolimus [93] that of whole blood instead of plasma, the latter similar to the EMA, but in the US-FDA guidance determination of $AUC_{0\text{-}72h}$ is explicitly requested instead of $AUC_{0\text{-}t}$, while the necessity to narrow the AUC for NTIs is still under discussion at the US-FDA, as described in **Section 3.2.1** above.

3.3.3 EMA and US-FDA inter-regional comparison

Comparing the product-specific EMA and US-FDA guidances for each formulation, in seven cases the recommendations are similar, allowing for the same study design to be used for submissions in both the EU and the USA. These are Carglumic acid [67,81], Erlotinib [68,82], Memantine [69,89], Sorafenib [71,83], Tadalafil [72,79], Voriconazole tablet [66,84], and Voriconazole powder for suspension [66,85]. In five more cases, the same study design could be used for one study for both the EMA and the US-FDA, while the guidances request an

additional study for the US-FDA. These are Miglustat [63,76], Oseltamivir capsule [38,91], Posaconazole [70,77], Repaglinide [64,78], and Telithromycin [65,80]. While in four of these cases an additional fed-state study is required by the US-FDA, for Posaconazole [70,77] the fed-state study is the common design and an additional fasting study is requested by the US-FDA. This is in line with the EU labeling requesting administration of Posaconazole with food [94]. Regarding Capecitabine [32,73], both the EMA and the US-FDA request the inclusion of patients, but only the US-FDA explicitly requests treated patients stable on 500 mg Capecitabine twice daily (bid). Therefore, it should be possible to agree with the EMA that the same criteria can be applied to a BE study that would be accepted in the EU. In that case, for Capecitabine also only one study would need to be conducted for the EMA and the US-FDA. It should also be noted that the US-FDA guidances explicitly mention the specific salt of the drug substance to be used, e.g. for Erlotinib [82], Imatinib [86], Memantine [89], Oseltamivir [91], Sorafenib [83], and Sunitinib [90], so this would need to be considered as well in the drug development, where applicable. Only for four drug products the requirements are so different that a combined study design would not be feasible. These are Dasatinib [62,75], for which different strengths are recommended by the EMA and the US-FDA, Imatinib tablet [39,86], where the US-FDA requests patients to be tested in a fed-state study after light breakfast, while the EMA prefers a fasting study in healthy volunteers with truncated $AUC_{0\text{-}72h}$, Sirolimus tablet [74,93] for which the EMA requests testing of two strengths (5 mg and 0.5 mg) with analysis of the narrowed $AUC_{0\text{-}t}$, while the US-FDA requests 2 mg to be tested with a truncated, but not narrowed $AUC_{0\text{-}72h}$, and Sunitinib [90,95] where the US-FDA requests a steady-state study in patients in crossover or parallel design, while the EMA requests a single-dose fasting study in healthy volunteers. As Oseltamivir oral solution for which the EMA allows for a waiver under specified conditions [38], and Oseltamivir phosphate powder for suspension [92] for which the US-FDA requests two *in vivo* studies with similar designs to that of the capsule [91], are different formulations, a comparison of their product-specific EMA and FDA guidances is not reasonable. Also, for two drug products covered by the EMA's guidances no comparable formulation is approved or discussed in the US-FDA guidances, these are Imatinib capsule [39], and Sirolimus oral solution [74]. *Vice versa*, Memantine ER capsule [96] is not yet covered by the EMA.

While the EMA so far did not issue separate guidance documents for different dosage forms, but rather distinguishes between dosage forms within one guidance document, where necessary (see Oseltamivir capsule and solution [38], Sirolimus tablet and oral solution [74] and Voriconazole tablet and powder for suspension [66]), the US-FDA issues its product-specific guidances explicitly dedicated to a specific dosage form. Comparing the product-specific guidances of the US-FDA with the dosage forms approved in the USA containing these drug substances, for four dosage forms there is no product-specific guidance available so far from the US-FDA although the dosage forms are approved. These are Memantine oral solution [97], Posaconazole delayed-release tablet [98], Sirolimus oral solution [99], and Telithromycin capsule [100]. Regarding Sirolimus oral solution, the EMA's guidance is very similar to the general recommendations of the US-FDA, in recommending both a fasting and a fed-state study. Therefore, it would be worthwhile discussing with the US-FDA if the design resulting from the EMA's guidance could be applied here for the US BE study as well, allowing to analyze the whole blood instead of plasma and applying the narrowed AUC_{0-t} limits for NTIs (90-111%) that are still under discussion at the US-FDA [44]. This should be acceptable for the US-FDA, as the amount of Sirolimus in plasma is very low [101] so that the measurement in whole blood is more accurate, and applying narrower limits than requested is usually unproblematic with the agencies.

While the EMA currently focuses its product-specific guidances on IR formulations, the US-FDA has also issued product-specific guidances for several MR formulations. One of them, Memantine ER capsule [96], is part of **Table 2**, as for Memantine IR a product-specific EMA guideline was issued [69]. A few more of the US-FDA's MR guidances are exemplarily described in **Table 1** (**see Annex 1**) and compared with the respective US-FDA IR recommendations, where applicable. A summary of them has been given in **Section 3.2.4** above. It should be noted that the US-FDA does not request multiple-dose studies in these examples, in line with their general recommendations where multiple-dose studies for MR formulations are explicitly discouraged, whereas the EMA explicitly recommends additional multiple-dose studies for prolonged-release formulations, but not for delayed-release formulations in the respective guidelines [12,24], as

described in **Section 3.1.2** above. It is expected that this will also be reflected in EMA's corresponding product-specific MR guidelines. Also, both the US-FDA and the EMA in general request both fasted and fed-state studies for MR formulations (and the US-FDA also for IR formulations), whereas for Azithromycin ER [49] for example only a fasting study is required by the US-FDA, but both fasting and fed state studies are requested for the IR formulations [57,58].

4 Discussion

Summarizing the region-specific requirements described in **Sections 3.2.1 and 3.2.2** above, **Table 3** shows a simplified comparison of the general recommendations from the EMA and the US-FDA:

Table 3: Tabular summary of similarities and differences

EMA	**US-FDA**
IR formulations: 1 study: fasting, 2-way, single-dose, crossover in ≥12 healthy adults, analyzing parent in plasma, AUC_{0-t} and C_{max}	**IR formulations**: 2 studies: fasting plus fed-state, 2-way, single-dose, crossover in healthy subjects, analyzing parent (and metabolite, if applicable) in plasma
MR formulations: Delayed-release formulations: Similar to IR formulations Prolonged-release formulations: 3 studies: fasting single-dose plus fasting steady-state plus fed-state single-dose, waiver possible for additional strengths at steady-state, not for single-dose studies	**MR formulations**: 2 studies: fasting plus fed-state, similar to IR formulations, multiple-dose studies discouraged

EMA	US-FDA
LALAs: Clinical or PD studies	**LALAs:** Clinical studies with efficacy and safety endpoints and/or suitable in vitro studies plus additional fasting and fed-state studies investigating the degree of systemic exposure Sometimes PK endpoints feasible, possibly include PD endpoints
Waivers: BCS waiver BCS waiver for Class I and Class III APIs Waiver of strengths for lower doses Waiver e.g., for aqueous i.v. and oral solutions	**Waivers:** BCS waiver for Class I APIs Waiver of strengths Waiver e.g., for all i.v. solutions and qualitatively and quantitatively completely identical generics

4.1 Similarities in EMA and US-FDA requirements

Both the EMA and the US-FDA usually request BE studies against a reference product for generic applications and both have issued a number of guidelines in which they explain the requirements for the conduct and design of suitable BE studies for IR and MR formulations in detail. From the view of both agencies, fasting and/or fed-state single-dose 2-way crossover studies in at least 12 healthy volunteers and analysis of the parent drug in plasma are recommended for BE studies in general. Recommendations for food and water intake are identical apart from the recommendation for abstinence from alcohol that the US-FDA has added explicitly in general [7,10] and specifically in the Draft [11] with regard to the influence of alcohol on MR formulations.

Similar to the US-FDA, the EMA's latest approach is to provide product-specific guidance on the design of bioequivalence studies. As has been discussed in detail in **Section 3.3**, of the 16 product-specific guidances issued by the EMA so far which cover 20 IR formulations, for 11 formulations it would be possible to set up a

common BE study design in accordance with the product-specific guidances from the EMA and the US-FDA, in five cases supplemented by a second US-FDA-specific study. Furthermore, in two cases, further discussion with the EMA and the US-FDA could lead to a combined BE study for these drug products for both regions. Of course, the number of product-specific guidances issued by the EMA so far is too small compared to the vast amount of product-specific guidances available from the US-FDA to judge if the trend seen here is of significance for future product-specific guidances.

Another notable similarity is that both agencies request all BE studies conducted for one generic formulation to be submitted, not only the successful studies, as was common practice in the past. This is also in accordance with the current practice for all clinical trials.

4.2 Differences between EMA and US-FDA requirements

While on the first glance the recommendations from both the EMA and the US-FDA appear to be similar, the devil is in the details. Differences already arise in the number of studies requested by the EMA and the US-FDA in their general guidelines. While the EMA in general recommends one single fasting BE study, the US-FDA's view has obviously changed over time. In the currently approved guidelines one single-dose fasting study is considered to be sufficient for oral solid IR formulations of BCS Class I if the labeling does not highlight food effects, but in the latest Draft [11] the US-FDA recommends the conduct of two BE studies, one fasting- and one fed-state study for both IR and MR formulations in general. Apart from that, there is a difference between the EMA's and the US-FDA's requirements in the definition of "same" drug substance, as discussed in **Section 2.2**, giving a broad understanding of "same" in the EU *versus* a more confined definition in the USA. This is important for the selection of the reference product. So if the same reference product is approved both in the EU and in the USA and is listed as the RLD, one reference could be used for the BE studies, but still the EU reference needs to be purchased in the EU. If an RLD is listed in the USA and only a similar (not the same) product is approved in the EU, the bioequivalence needs to be confirmed against both the RLD and the EU reference product. Furthermore, while the EMA in general expects the highest dose to be tested for bioequivalence,

provided that the product shows linear (or more than proportional) pharmacokinetics [7], the US-FDA has also issued product-specific guidances where the second highest dose is recommended to be tested and a waiver is explicitly allowed for the highest dose (e.g. Alprazolam IR [52,53], see **Table 1 in Annex 1**). Also, the expected number of samples to be taken per subject and dose is explicitly given as 12-18 by the US-FDA, whereas the EMA only requests a suitable number of samples to be taken without mentioning any explicit numbers. [7,10]

When discussing the parallel design as an alternative for long half-life drugs, the US-FDA gives a clear definition of long half-life, i.e. more than 24 hours, in the draft Guidance for Industry "Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA" [11], whereas the EMA uses a similar term "very long half-life" in the "Guideline on the investigation of bioequivalence" [7] but without giving a measurable definition.

Regarding narrow therapeutic index drugs (NTIs), the need for narrowing the AUC range is still under discussion at the US-FDA [44], while the EMA gives a limit of 90.00-111.11% [7]. So if a common study design should be set up for an NTI, the narrower limits of the EMA would need to be followed.

Regarding oral locally applied and locally acting drugs (LALAs) in the gastrointestinal tract, the US-FDA had already issued some guidance in the past [10,11], while more specific guidance from the EMA for this subgroup of LALAs is still awaited, as announced in the "Concept paper on the development of a guideline on the demonstration of therapeutic equivalence for locally applied and locally acting products in the gastrointestinal tract" [41].

While from the 20 formulations covered by the EMA product-specific guidances, for 11 formulations the recommendations between the EMA and the US-FDA are similar and for two more formulations a discussion with the EMA and/or the US-FDA might be helpful as described in **Section 3.3** above, there are also currently four cases where such a common approach is not possible. Here the product-specific recommendations vary too much between the EMA and the US-FDA, and

in three cases there is no comparable dosage form described in the US-FDA's product-specific guidances at all. This is due to the fact that the US-FDA issues separate guidance documents for different dosage forms, while the EMA so far issued combined guidance documents for different IR formulations of a drug substance, where applicable. Even for capsules and tablets, the US-FDA issues separate guidance documents, e.g., for Etodolac [102,103] (see **Table 1 in Annex 1**), while the EMA regards these dosage forms as similar. It remains to be seen if the EMA's guidance documents will later on also incorporate the guidance for MR formulations of the same drug substance or if these will be covered in separate guidance documents.

5 Conclusion and outlook

On the first glance, the obstacles for conducting a combined BE study suitable for both the EU and the USA seem to be conquerable with thorough planning, and differences between the general recommendations of the EMA and the US-FDA seem to be manageable, so that the overall design of the BE studies could be similar and the conduct of a study that could be submitted for regulatory purposes both in the EU and in the USA is mainly depending on the availability of the US Reference Listed Drug within the EU. Even if different reference drugs need to be used, it could still be feasible to conduct a 3-arm study including an EU reference and a US reference, as is the EMA's point of view as well [7]. That would mean that with one 3-arm single-dose fasting study in healthy volunteers and a second fed-state study against the RLD in line with the US-recommendations both the EU and the US requirements could be fulfilled for a generic application. Nevertheless, as the comparison of the product-specific guidances issued by the EMA and the US-FDA shows, it is very much dependent on the drug product if a combined approach can be realized or separate studies with sometimes completely differing designs need to be conducted, as detailed in **Section 3.3** above. In a more general view, a risk that arises from this product-specific approach of both the EMA and the US-FDA is that the wording may differ inadvertently between similar cases over time, especially for the US-FDA between different dosage forms of the same active ingredient, as described in **Section 3.2.4** above and highlighted in **Table 1 in Annex 1**. And it cannot be easily judged by the applicant, if these

differences occur on purpose or inadvertently. Therefore, prediction of the design accepted by the US-FDA and the EMA for a specific drug product for which no product-specific guidances are available from the agencies so far may still be difficult. Also, other than a public commenting phase for new recommendations, countermeasures to achieve harmonization are not disclosed by the agencies [36,46]. For drug products currently not covered by product-specific advice from both the EMA and the US-FDA, the latest approach of these agencies to offer a three-party scientific advice might be helpful in order to achieve product-specific agreements.

Once more experience is gained with three-party scientific advices, it might be worth evaluating the outcome of such processes in a separate master thesis. It might also be interesting to complete the comparison of more product-specific guidelines from the USA against each other, evaluating differences and similarities, as started in extracts in **Section 3.2** above.

While LALAs in the gastrointestinal tract are already covered in the general US-FDA guidances, the EMA still needs to find a way to deal with this special subject. So the realization of the EMA's "Concept paper on the development of a guideline on the demonstration of therapeutic equivalence for locally applied and locally acting products in the gastrointestinal tract" [41] is awaited with great anticipation.

If the OrBiTo project [34] started in October 2012 is successful in developing a rational *in vitro*- / *in silico*-based PK model for prediction of bioequivalence of oral formulations, this could even bring a completely new impulse to the regulatory requirements. Such a model could at least partly replace the current *in vivo* BE studies and support waiver strategies. The discussion around the right reference product for *in vivo* BE studies might then become obsolete for a wide range of APIs, as performance in comparison with diverse reference products could then probably be simulated easily and cost-effectively on the computer, if the results would be accepted by the agencies without further *in vivo* studies.

6 Summary

This master thesis provides an introduction to the field of bioequivalence studies, focussing on generic oral immediate-release and modified-release formulations with one chemical drug substance. After a short overview of the scientific background of bioequivalence, it summarizes the relevant regulations and guidelines issued by the European Medicines Agency and the United States Food and Drug Administration, pointing out similarities and differences in the recommendations. Additional attention is given to recommendations regarding oral locally applied drugs acting locally in the gastrointestinal tract. An approach is made to evaluate in a general manner as well as for specific selected drug substances and formulations, if a common study design can be found that supports a generic application according to the Directive 2001/83/EC, Article 10.1 in the European Union as well as an Abbreviated New Drug Application according to the Code of Federal Regulations, Title 21, Section 314.94 in the United States of America. Furthermore, a short outlook is provided regarding currently ongoing scientific developments that might revolutionize the whole approach for establishing bioequivalence between two drug formulations.

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Annex 1

Annex 1

Table 1 - Exemplary product-specific US-FDA recommendations

Grey shading/no shading: alternating to distinguish between different products

Drug substance (Reference [Ref])	**Route of administration**	**Dosage form**	**Studies requested**	**Comments**
Acetazolamide [48]	Oral	Tablet	**1 study** (**fasting**): single-dose, 2-way, crossover, 250 mg, normal healthy m + f, general population **(f not pregnant or lactating, abstentious or using contraception)**; analyze parent in plasma	Draft Jul 2008 Waiver for lower strength[1] Dissolution: 12 dosage units each of all strengths of test and reference
Acetazolamide [51]	Oral	ER[2] capsule	**2 studies** (**1 fasting / 1 fed**): single-dose, 2-way, crossover, 500 mg, healthy m + **nonpregnant** f, general population; analyze parent in plasma	Draft Feb 2010 Waiver N/A Dissolution: 12 dosage units each of all strengths of test and reference products, **App I / II, pH 1.2, 4.5, 6.8, surfactant allowed**

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance [Ref]	**Route of administration**	**Dosage form**	**Studies requested**	**Comments**
Alprazolam [52]	Oral	Tablet	2 studies (1 fasting / 1 fed): single-dose, 2-treatment, 2-period crossover, 1 mg, normal healthy m + f, general population; analyze parent in plasma	Draft; revised May 2008, Sep 2008 Waiver for additional lower **and higher** strengths[1] Dissolution: 12 dosage units each of all strengths of test and reference
Alprazolam [53]	Oral	Orally disintegrating tablet	2 studies (1 fasting / 1 fed): single-dose, 2-treatment, 2-period crossover, 1 mg, normal healthy m + f, general population; analyze parent in plasma	Draft Sep 2008 Detailed description of administration, waiver for additional lower **and higher** strengths[1] Dissolution: 12 dosage units each of all strengths of test and reference
Alprazolam [54]	Oral	ER[2] tablet	2 studies (1 fasting / 1 fed): single-dose, 2-treatment, 2-period crossover, 3 mg, normal healthy m + f, general population; analyze parent in plasma	Draft May 2004, Nov 2007 Waiver for additional **lower** strengths[1] Dissolution: 12 dosage units each of all strengths of test and reference, **App I / II, pH 1.2, 4.5, 6.8, surfactant allowed**

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Reference [Ref])	**Route of administration**	**Dosage form**	**Studies requested**	**Comments**
Amoxicillin [59]	Oral	Capsule	2 studies (1 fasting / 1 fed): single-dose, 2-treatment, 2-period, crossover, 500 mg, healthy m + nonpregnant f, general population; analyze parent in plasma	Draft Apr 2013 Waiver for additional lower strength[1] Dissolution: 12 dosage units each of all strengths of test and reference
Amoxicillin [60]	Oral	ER[2] tablet	2 studies (1 fasting / 1 fed): single-dose, 2-way, crossover, 775 mg, normal healthy m + f, general population (**f not pregnant or lactating, abstentious or using contraception**); analyze parent in plasma	Draft Sep 2012 Waiver N/A Dissolution: 12 dosage units each of all strengths of test and reference products, **App I / II, pH 1.2, 4.5, 6.8, surfactant allowed**
Atovaquone [55]	Oral	Tablet	2 studies (1 fasting / 1 fed): single-dose, 2-treatment, 2-period crossover **or parallel, truncated AUC_{0-72h} (long half-life)**, normal healthy m + f, general population; analyze parent in plasma	Draft May 2005, Nov 2007 Waiver: N/A Dissolution: 12 dosage units each of all strengths of test and reference, **if necessary in high alcoholic medium (practically insoluble in both water and 0.1M HCl)**

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Reference [Ref])	**Route of administration**	**Dosage form**	**Studies requested**	**Comments**
Atovaquone [56]	Oral	Suspension	2 studies (1 fasting / 1 fed): single-dose, 2-way crossover, 750 mg/5 mL, healthy m + **nonpregnant** f, general population; analyze parent in plasma	Draft Dec 2009 Waiver: N/A Dissolution: 12 dosage units each (labeled strength in mL) of all strengths of test and reference from 12 different bottles
Azithromycin [57]	Oral	Tablet	2 studies (1 fasting / 1 fed): single-dose, 2-way, crossover, 600 mg, normal healthy m + f, general population; analyze parent in plasma	Draft Jan 2008 Waiver for additional lower strengths[1] Dissolution: 12 dosage units each of all strengths of test and reference
Azithromycin [58]	Oral	Suspension	2 studies (1 fasting / 1 fed): single-dose, 2-way, crossover, 200 mg/5 mL, normal healthy m + f, general population; analyze parent in plasma	Draft Dec 2008 Waiver for additional lower strength[1] Dissolution: 12 dosage units each of all strengths of test and reference from 12 different bottles
Azithromycin [49]	Oral	ER[2] suspension	**1 study: fasting**, single-dose, 2-way, crossover **or parallel, truncated $AUC_{0\text{-}72h}$ (long half-life)**, 2 mg, normal healthy m + f, general population, analyze parent in plasma	Draft Jul 2008 Waiver N/A Dissolution: 12 dosage units each of all strengths of test and reference

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Reference [Ref])	**Route of administration**	**Dosage form**	**Studies requested**	**Comments**
Etodolac [102]	Oral	Tablet	2 studies (1 fasting / 1 fed): single-dose, 2-way, crossover, 500 mg, healthy m + **nonpregnant** f, general population; analyze parent in plasma	Draft Nov 2013 Waiver for additional lower strength[1] Dissolution: 12 dosage units each of all strengths of test and reference
Etodolac [103]	Oral	Capsule	2 studies (1 fasting / 1 fed): single-dose, 2-way, crossover, 300 mg, healthy m + **nonpregnant** f, general population; analyze parent in plasma	Draft Nov 2013 Waiver for additional lower strength[1] Dissolution: 12 dosage units each of all strengths of test and reference

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Table 2 - Comparison of product-specific recommendations of EMA and US-FDA

Shaded grey: EMA guidances, no shading: US-FDA guidances, broad line: separates the different drug substances from each other

Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Capecitabine (EU) [73]	Oral	Tablet [104]	IR	1 study: **fed**, single-dose, crossover, 500 mg, **patients**, analyze AUC_{0-t}, C_{max} of parent in plasma	Anti-cancer drug, **unstable in acidic medium, thus no BCS classification possible**, fed-state to reduce vomiting, linear PK
Capecitabine (USA) [32]	Oral	Tablet	IR	**BCS waiver or** *in vivo* study **1 study: fed**, single-dose, 2-way crossover, 500 mg, **patients stable on bid dosing**, analyze parent in plasma	Waiver for additional strength[1] Dissolution: 12 dosage units each of all strengths of test and reference products Detailed dosing regimen and explanations
Carglumic acid (EU) [67]	Oral	Dispersible tablet [105]	IR	1 study: fasting, single-dose, crossover, 200 mg, healthy volunteers, **analyze AUC_{0-72h}**, C_{max} of parent **in plasma**	Low solubility compound

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Carglumic acid (USA) [81]	Oral	Tablet for dispersion	IR	**1 study: fasting**, single-dose, 2-way crossover, 200 mg (100 mg/kg), normal healthy m + nonpregnant, not lactating f abstentious or using contraception, general population, analyze parent **"in appropriate biological fluid"** [81]	Waiver N/A Dissolution: 12 dosage units each of all strengths of test and reference products
Dasatinib (EU) [62]	Oral	Tablet [106]	IR	1 study: fasting, single-dose, crossover, **140 mg**, healthy volunteers, analyze AUC_{0-t}, C_{max} of parent in plasma	Low solubility compound, linear PK
Dasatinib (USA) [75]	Oral	Tablet	IR	2 studies (1 fasting, 1 fed): single-dose, 2-way crossover, **100 mg**, healthy m + nonpregnant f, excluding women of child-bearing potential and nursing mothers, analyze parent in plasma	Embryo-fetal toxicity, secretion into breast milk Waiver for additional strengths[1] Dissolution: 12 dosage units each of all strengths of test and reference products

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Erlotinib (EU) [68]	Oral	Tablet [107]	IR	1 study: fasting, single-dose, crossover, 150mg, healthy volunteers, analyze **$AUC_{0\text{-}72h}$**, C_{max} of parent in plasma	Low solubility compound, linear PK
Erlotinib HCl (USA) [82]	Oral	Tablet	IR	**1 study: fasting**, single-dose, 2-way crossover, 150 mg, normal healthy m+ nonpregnant, not lactating f abstentious or using contraception, general population, analyze parent in plasma	Waiver for 2 additional[1] Dissolution: 12 dosage units each of all strengths of test and reference products
Imatinib (EU) [39]	Oral	Capsule [108]	IR	1 study: **fasting (preferred) or fed**, single-dose, crossover, 400 mg, healthy volunteers, analyze **$AUC_{0\text{-}72h}$**, C_{max} of parent in plasma	High permeability, unknown solubility, linear PK at 25-1000 mg, in guidance [39] no distinction between capsule and tablet

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Imatinib (EU) [39]	Oral	Tablet [109]	IR	1 study: **fasting (preferred) or fed**, single-dose, crossover, 400 mg, **healthy volunteers**, analyze **$AUC_{0\text{-}72h}$**, C_{max} of parent in plasma	High permeability, unknown solubility, linear PK at 25-1000 mg, in guidance [39] no distinction between capsule and tablet
Imatinib **mesylate** (USA) [86]	Oral	Tablet	IR	1 study: **fed (light breakfast)**, single-dose, 2-way crossover, 400 mg, **patients stable on 400 mg**, analyze parent in plasma	Waiver for additional strength[1] Dissolution: 12 dosage units each of all strengths of test and reference products
Memantine (EU) [69]	Oral	Tablet	IR	1 study: fasting, single-dose, crossover, any strength for the tablets, healthy volunteers, analyze **$AUC_{0\text{-}72h}$**, C_{max} of parent in plasma, BCS waiver possible	BCS class I, linear PK at 10-40 mg

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Memantine **HCl** (USA) [89]	Oral	Tablet	IR	**BCS waiver or** *in vivo* studies **1 study: fasting or fed**, single-dose, 2-way crossover, **10 mg**, healthy m + nonpregnant f, general population, analyze parent in plasma	Waiver for additional strength[1] Dissolution: 12 dosage units each of all strengths of test and reference products
Memantine HCl (USA)	Oral	Solution [97]	IR	**No product-specific guidance available**	

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Memantine **HCl** (USA) [96]	Oral	Capsule	**ER**	**3 studies (1 fasting, 1 fed, 1 fasting sprinkle)**: single-dose, 2-way crossover, **28 mg**, healthy m + nonpregnant f, general population, analyze parent in plasma	"Fasting sprinkle" [96]: prior to administration sprinkle entire content of capsule on spoonful of applesauce Long half-life: alternative use of truncated AUC Detailed description of test meal Waiver for additional strength[1] Dissolution: 12 dosage units each of all strengths of test and reference products, additional requirements for MR formulations to be fulfilled
Miglustat (EU) [63]	Oral	Capsule [110]	IR	**1 study: fasting**, single-dose, crossover, 100 mg, healthy volunteers, analyze AUC_{0-t}, C_{max} of parent in plasma	No data for BCS classification available, waiver could be applicable, linear PK at 50-100 mg

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Miglustat (USA) [76]	Oral	Capsule	IR	**2 studies (1 fasting, 1 fed)**: single-dose, 2-way crossover, 100 mg, normal healthy m + nonpregnant f abstentious or using contraception, general population, analyze parent in plasma	Dissolution: 12 dosage units each of all strengths of test and reference products
Oseltamivir (EU) [38]	Oral	Capsule	IR	**1 study: fasting**, single-dose, crossover, 75 mg, healthy volunteers, analyze AUC_{0-t}, C_{max} of parent in plasma	No data for BCS classification available, waiver could be applicable
Oseltamivir **phosphate** (USA) [91]	Oral	Capsule	IR	**2 studies (1 fasting, 1 fed)**: single-dose, 2-way crossover, 75 mg, healthy m + nonpregnant f, general population, analyze parent **and metabolite (C_t, C_{mean}, PK parameters, geometric means and ratios of means for AUC and C_{max})** in plasma	Waiver for additional strengths[1] Dissolution: 12 dosage units each of all strengths of test and reference products

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Oseltamivir (EU) [38]	Oral	**Solution**	IR	**Waiver for solution, if same amount of sorbitol as in the reference product**	No data for BCS classification available
Oseltamivir phosphate (USA) [92]	Oral	Powder for suspension [111]	IR	2 studies (1 fasting, 1 fed): single-dose, 2-way crossover, 12 mg/mL, healthy m + nonpregnant f, general population, analyze parent and metabolite (C_t, C_{mean}, PK parameters, geometric means and ratios of means for AUC and C_{max}) in plasma	Waiver N/A Dissolution: 12 dosage units each of all strengths of test and reference products
Posaconazole (EU) [70]	Oral	Suspension [94]	IR	**1 study: fed**, single-dose, (alternative: replicate) crossover, 400 mg, healthy volunteers, analyze **$AUC_{0\text{-}72h}$**, C_{max} of parent in plasma	Low solubility, high permeability

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Posaconazole (USA) [77]	Oral	Suspension	IR	**2 studies (1 fasting, 1 fed)**: single-dose, 2-treatment, 2-period crossover, 40 mg/mL (400 mg), normal healthy m + nonpregnant, not lactating f abstentious or using contraception, analyze parent in plasma	Waiver N/A Dissolution: 12 dosage units each of all strengths of test and reference products
Posaconazole (USA)	Oral	Delayed-release tablet [98]	**DR**	**No product-specific guidance available**	
Repaglinide (EU) [64]	Oral	Tablet [112]	IR	**1 study: fasting**, single-dose, crossover, 2 mg **and glucose solution**, healthy volunteers, analyze AUC_{0-t}, C_{max} of parent in plasma	Low solubility

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Repaglinide (USA) [78]	Oral	Tablet	IR	**2 studies (1 fasting, 1 fed)**: single-dose, 2-way crossover, 2 mg **and glucose solution**, normal healthy m + f, analyze parent in plasma	Detailed description of glucose administration Waiver for additional strengths[1] Dissolution: 12 dosage units each of all strengths of test and reference products
Sirolimus (EU) [74]	Oral	Tablet	IR	**4 2-way or 2 4-way studies: fasting and fed**, single-dose, crossover, **5 mg and 0.5 mg**, healthy volunteers, analyze **AUC_{0-t}**, C_{max} of parent **in blood**	Low solubility, dose proportionality only between 2-5 mg, **narrow therapeutic index drug (NTI): CI(90%) = 80.00-125.00 for C_{max} and 90.00-111.00 for AUC_{0-t}**
Sirolimus (USA) [93]	Oral	Tablet	IR	2 studies (1 fasting, 1 fed): single-dose, 2-treatment, 2-period crossover, **2 mg**, healthy m + nonpregnant f, general population, analyze **AUC_{0-72h}**, C_{max} of parent in **whole blood**	Long half-life Waiver for additional lower strengths[1] Dissolution: 12 dosage units each of all strengths of test and reference products

[1] for proportionally similar formulations with acceptable *in vitro* dissolution profile

[2] IR: immediate-release, ER: extended-release, DR: delayed-release

Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Sirolimus (EU) [74]	Oral	Solution	IR	**2 2-way or 1 4-way study: fasting and fed**, single-dose, crossover, 1 mg/mL, healthy volunteers, analyze AUC_{0-t}, C_{max} of parent **in blood**	Low solubility, **narrow therapeutic index drug (NTI): CI(90%) = 80.00-125.00 for C_{max} and 90.00-111.00 for AUC_{0-t}**
Sirolimus (USA)	Oral	Solution [99]	IR	**No product-specific guidance available**	
Sorafenib (EU) [71]	Oral	Tablet [113]	IR	1 study: fasting, single-dose, crossover, 200 mg, healthy volunteers, analyze **AUC_{0-72h}**, C_{max} of parent in plasma	Low solubility Non-linear PK at 400-800 mg (200 mg only available strength)

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Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Sorafenib **tosylate** (USA) [83]	Oral	Tablet	IR	**1 study: fasting**, single-dose, 2-way crossover **(alternative: parallel)**, 200 mg, healthy m + nonpregnant f both using contraception, analyze parent in plasma	Long half-life: alternative use of truncated AUC, Teratogenic, clastogenic, Waiver N/A Dissolution: 12 dosage units each of all strengths of test and reference products
Sunitinib (EU) [95]	Oral	Capsule [114]	IR	1 study: fasting, **single-dose**, cross-over, 50 mg, **healthy volunteers**, analyze **$AUC_{0\text{-}72h}$**, C_{max} of parent in plasma	BCS class III, linear PK
Sunitinib malate (USA) [90]	Oral	Capsule	IR	1 study: **steady-state**, 2-period, 2-treatment **crossover or parallel**, 50 mg, **patients stable on Sunitinib malate capsules**, analyze Sunitinib in plasma	Waiver for lower strengths[1] Dissolution: 12 dosage units each of all strengths of test and reference products

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Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Tadalafil (EU) [72]	Oral	Tablet [115]	IR	**2 studies (1 fasting, 1 fed)**: single-dose, crossover, 20 mg, healthy volunteers, analyze **$AUC_{0\text{-}72h}$**, C_{max} of parent in plasma	Low solubility, linear PK at 2.5-20 mg
Tadalafil (USA) [79]	Oral	Tablet	IR	2 studies (1 fasting, 1 fed): single-dose, 2-way crossover, 20 mg, healthy m, general population, analyze parent in plasma	Detailed description of test meal Waiver for additional strengths[1] Dissolution: 12 dosage units each of all strengths of test and reference products
Telithromycin (EU) [65]	Oral	Tablet [116]	IR	**1 study: fasting**, single-dose, crossover, 400 mg, healthy volunteers, analyze $AUC_{0\text{-}t}$, C_{max} of parent in plasma	Maybe high solubility, not BCS class I or III, non-linear PK at 400-1600 mg

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Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Telithromycin (USA) [80]	Oral	Tablet	IR	**2 studies (1 fasting, 1 fed)**: single-dose, 2-way (alternative: replicate) crossover, 400 mg, normal abstinent healthy m + nonpregnant f abstentious or using contraception, analyze parent in plasma	Suspected hepatotoxicity Waiver for additional strength[1] Dissolution: 12 dosage units each of all strengths of test and reference products
Telithromycin (USA)	Oral	Capsule [100]	IR	**No product-specific guidance available**	
Voriconazole (EU) [66]	Oral	Tablet	IR	1 study: fasting, single-dose, crossover, 200 mg, healthy volunteers, analyze AUC_{0-t}, C_{max} of parent in plasma	Low solubility
Voriconazole (USA) [84]	Oral	Tablet	IR	**1 study: fasting**, single-dose, 2-way crossover, 200 mg, healthy m + nonpregnant f, general population, analyze parent in plasma	Waiver for additional strength[1] Dissolution: 12 dosage units each of all strengths of test and reference products

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Drug substance (Region) [Ref]	**Route of administration**	**Dosage form [Ref] if different**	**IR/ER/ DR[2]**	**Type of studies requested**	**Comments**
Voriconazole (EU) [66]	Oral	Powder for suspension	IR	1 study: fasting, single-dose, crossover, 200 mg, healthy volunteers, analyze AUC_{0-t}, C_{max} of parent in plasma	Low solubility
Voriconazole (USA) [85]	Oral	Powder for suspension [117]	IR	**1 study: fasting**, single-dose, 2-way crossover, 200 mg/5 mL, healthy m + nonpregnant f abstentious or using contraception, analyze parent in plasma	Dissolution: 12 dosage units each of all strengths of test and reference products

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