

**Global Development Strategy for Generic Medicinal Products  
with Regard to Bioequivalence Studies – Special Focus on the  
Biowaiver Approach in Canada, Australia and Brazil**

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## LIST OF ABBREVIATIONS

ANDA	Abbreviated New Drug Application
ANVISA	Agência Nacional de Vigilância Sanitária
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
AUC	Area under the Plasma Concentration Curve
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
CFR	Code of Federal Regulations
$C_{\max}$	Maximum Plasma Concentration
$C_{\min}$	Minimum Plasma Concentration
CoPP	Certificate of Pharmaceutical Product
CRO	Contract Research Organisation
EMA	European Medicines Agency
EU	European Union
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IR	Immediate Release
MA	Marketing Authorisation
MR	Modified Release
MS	Member State(s)
NOC	Notice of Compliance
OIP	Orally Inhaled Products
OROS	Osmotic Release Oral System
PE	Paediatric Extension
RLD	Reference Listed Drug
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
SUPAC	Scale-Up and Post-Approval Changes
TDDS	Transdermal Drug Delivery System
TGA	Therapeutic Goods Administration
$t_{\max}$	Time until $C_{\max}$ is reached
TPD	Therapeutic Products Directorate
US	United States
USA	United States of America
USP	United States Pharmacopoeia
WHO	World Health Organisation

## 1. Introduction

For generic companies it is very important to develop generic medicinal products in high quality in a relative short timeframe and with limited expenses. Generally, development of medicinal products needs to satisfy the criteria of quality, time and costs. The most important criterion in pharmaceutical development is quality. With regard to the other criteria, time and costs, it could be a great advantage for an international company to perform one global development rather than to develop a product separately for each region in the world. The application dossier could then be presented worldwide with relatively minor regional-specific changes to certain sections of the documentation. This could result in one global generic medicinal product that has the same formulation and the same manufacturing process for all countries. Consequently, a reduced number or even only one bioequivalence study against the innovator product may be necessary for seeking marketing authorisations from regulatory agencies worldwide. But is this really possible?

In theory, this is an ideal strategy and could save enormous development time and costs. But in practice, generic companies face several challenges with such a global development approach. For instance, very often the innovator product is not identical in all regions of the world, for example, showing differences in excipient composition. This is a great challenge as one of the key factors for a generic marketing authorisation is the proof of bioequivalence of the generic product versus the innovator product. If the innovator product differs from country to country, it is very difficult, and sometimes not feasible, for a generic company to choose only one innovator product from one country as reference product for bioequivalence studies. In addition, many regulatory agencies insist on a bioequivalence study versus the innovator authorised in their own country, even if this is not always justified on the basis of scientific knowledge. But it is advantageous for reimbursement and substitution.

However, some regulatory agencies have accepted a more global view. For example, the Canadian Therapeutic Products Directorate (TPD) states that *“with the increasing globalization of the drug industry, many products are manufactured with the same formulations and under the same conditions to benefit from economies of scale and to facilitate registration with various regulatory agencies. On occasion, products are manufactured in only one location for worldwide distribution. In such instance, to reduce costs and to avoid unnecessary exposure of subjects to drugs, the Drugs Directorate will consider comparative bioavailability data which has been generated using a sample of the innovative product purchased outside Canada.”* <sup>[1]</sup> But of course, such comparative bioavailability data versus a foreign innovator product must comply with the general requirements for bioequivalence studies accepted by TPD.

Another very important factor is that drug metabolism can differ between ethnic populations as a result of both genetic and lifestyle differences. For example, variability in metabolism between certain Asian and Caucasian populations is common and well documented. As a consequence, it is questionable whether results of bioequivalence studies performed with Caucasian subjects are also valid for the Asian population. This uncertainty is usually

circumvented by performing separate bioequivalence studies with Caucasian and Asian populations. Nevertheless, in certain cases it is possible to argue for the transferability of clinical data from one ethnic population to another.

The general question is whether a global development strategy for generic medicinal products is really feasible. One of the major advantages of a global development for a generic company is that the number of bioequivalence studies could be reduced to a minimum level. By waiving bioequivalence studies which are not necessarily needed, generic companies can save a lot of time and costs in research and development and can consequently offer better prices for their products on the market. In light of price restrictions by governments and health insurance providers nowadays, a global development strategy offers an immensely competitive advantage. Last but not least, due to ethical reasons, no unnecessary human studies would need to be performed. <sup>[2, 21]</sup>

In this scientific thesis an overview of the options to reduce the number of bioequivalence studies is presented. The idea of a global development strategy for generic medicinal products is discussed. In this context, only conventional, chemical entities are considered (biosimilars or “follow-on biologics” are covered under a different regulatory framework and require more complex comparability studies as opposed to bioequivalence studies and are, therefore, not covered in the scope of this thesis). Special focus is laid on so-called biowaiver approaches in Canada, Australia and Brazil. Options will be considered on how bioequivalence studies can be waived and reduced to a minimum for generic submissions in these three important regions, for example, by seeking acceptance of “foreign” bioequivalence studies.

## **2. Current regulatory framework with regard to bioequivalence studies and biowaiver options for generic medicinal products**

### **2.1 General aspects**

As a basis for further discussion it is important to understand the principles of generic medicinal products and the basic requirements for bioequivalence studies. Generally, the requirements are identical for the members of the International Conference on Harmonisation (ICH) with some regional distinctions. The three regions of the ICH are the European Union (EU), the United States of America (USA) and Japan. Additionally, the World Health Organisation (WHO) and Canada act as observers. But will a certain study program, which is accepted by European regulatory authorities also be accepted by the US Food and Drug Administration (FDA)? What are the similarities and differences among the ICH regions with respect to bioequivalence requirements and what possibilities are there to waive in vivo bioequivalence studies? This information is essential for the discussion of a global generic development strategy. As already explained, there are specific ethnic topics to be considered with regard to bioequivalence studies for Asian, especially Japanese, populations. In the majority of cases, there will be a need for bioequivalence studies in Asian population, even if

the basic requirements are identical. Therefore, the ICH country Japan is usually regarded as a separate scope when thinking of a global generic development strategy and will not be further dealt with in detail in this master thesis.

In the following, an overview of the regulatory framework for the EU, USA and WHO is presented with regard to bioequivalence studies for generic medicinal products. Special focus is laid on the options to waive bioequivalence studies. In addition, some general aspects are described like ethical considerations, ethnic factors in the acceptability of foreign clinical data and the importance of several protection periods.

## 2.2 European Union

### 2.2.1 Directive 2001/83/EC, as amended <sup>[3]</sup>

The basis for generic applications in the EU is Article 10(1) of “*Directive 2001/83/EC, as amended*”. <sup>[3]</sup> The following is stated:

*“(…) the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a **reference medicinal product** which is or has been **authorised** under Article 6 for not less than eight years **in a Member State or in the Community**.*

*(…)*

*The first subparagraph shall **also apply if the reference medicinal product was not authorised in the Member State in which the application for the generic medicinal product is submitted**. In this case, the applicant shall indicate in the application form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference product and if necessary other relevant documentation.*” <sup>[3]</sup>

This article clearly defines that the reference product for a generic application must be or have been authorised in the EU, either in a Member State (MS) of the EU or, alternatively, in the Community which is equivalent to a centralised marketing authorisation (MA) issued by the European Commission. Thus, one of the basic principles of the so-called “**European reference medicinal product**” is that a generic application can also be submitted in a MS where the reference medicinal product has never been authorised. The corresponding MS will then exchange relevant information on the reference product. <sup>[4]</sup>

In Article 10(2) of “*Directive 2001/83/EC, as amended*” the terms reference product and generic product are defined:

*“(a) ‘reference medicinal product’ shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8;*



*(b) ‘generic medicinal product’ shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. (...) Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.”* <sup>[3]</sup>

Thus, the concept of bioequivalence is essential for a generic medicinal product. <sup>[5]</sup> Combining the information included in Articles 10(1) and 10(2) of “*Directive 2001/83/EC, as amended*”<sup>[3]</sup>, a generic medicinal product needs to demonstrate bioequivalence versus a reference product which is authorised in the EU. The reference product for bioequivalence studies must be part of the so-called global marketing authorisation (as defined in Article 6 of “*Directive 2001/83/EC, as amended*” <sup>[3]</sup>), that is, the initial marketing authorisation of the reference product - based on a full dossier according to Article 8 of “*Directive 2001/83/EC, as amended*” <sup>[3]</sup> - or any additional strength, pharmaceutical form or other extension. Bioequivalence studies versus a non-EU reference product are not foreseen.

Furthermore, Article 10(2) (b) of “*Directive 2001/83/EC, as amended*” <sup>[3]</sup> offers the opportunity to waive bioequivalence studies if relevant criteria are met. Exemptions from the need to demonstrate bioequivalence and the relevant criteria are defined in the “*Guideline on the investigation of bioequivalence*” <sup>[5]</sup> which is described in the following section 2.2.2 of this master thesis.

### 2.2.2 Guideline on the investigation of bioequivalence <sup>[5]</sup>

In the European Medicines Agency’s (EMA) “*Guideline on the investigation of bioequivalence*” (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) the basic requirements for the design, conduct and evaluation of bioequivalence studies for immediate release dosage forms with systemic action are specified. <sup>[5]</sup> It is the essential document for bioequivalence studies for regulatory purposes in the EU. The demonstration of bioequivalence versus the reference product is one of the key factors for generic medicinal products, but under certain circumstances bioequivalence can be presumed without further in vivo investigations. The relevant criteria under which bioequivalence studies are not necessarily required (so-called biowaivers) are also defined in this guideline. In the following, a brief overview of the basic requirements and waiver options for bioequivalence studies will be presented. It should be mentioned that only the most important issues are described which are necessary to understand and discuss the idea of a global generic development strategy later on.

### 2.2.2.1 *Relevant bioequivalence studies*

For registration purposes, all bioequivalence studies comparing the test product (that is the product applied for) and reference products marketed in the EU should be submitted – demonstrating either bioequivalence or non-bioequivalence of the two medicinal products. Bioequivalence studies versus non-EU reference products need not to be submitted.<sup>[5]</sup> This is a clear indicator for the importance of an EU reference product and for the fact that studies with non-EU reference products are not regarded as pivotal by European regulatory authorities.

### 2.2.2.2 *Study design*

A *randomised, two-period, two-sequence single dose crossover design* is recommended as standard; the treatment periods should be separated by a sufficient wash out period. Alternatively, the following study designs are described<sup>[5]</sup>:

- *Parallel design*, for substances with very long half-life
- *Replicate design*, for substances with highly variable pharmacokinetic characteristics
- *Multiple dose study in patients*, if a single dose study cannot be conducted in healthy volunteers due to tolerability reasons, and a single dose study is not feasible in patients
- *Multiple dose study in healthy volunteers*, as an absolute exception in case of limited sensitivity of the analytical method

### 2.2.2.3 *Reference and test product*

As a basic principle, the *reference product* for generic applications must be authorised (or must have been authorised) in a MS of the EU on the basis of a full dossier. The reference product for bioequivalence studies must be part of the so-called global marketing authorisation of this reference product for generic applications. It is either the initial marketing authorisation of the reference product itself - based on a full dossier - or any additional strength, pharmaceutical form or other extension.<sup>[3, 4, 5]</sup> Bioequivalence studies versus a non-EU reference product are not foreseen. Please refer to section 2.2.1 *Directive 2001/83/EC, as amended* of this master thesis for further details.

The *test product* used in bioequivalence studies should be representative of the generic product to be marketed. For instance, for oral solid forms for systemic action the batch size should be at least 1/10 of production scale or 100,000 units, whichever is greater. Alternatively, the batch size should be of full production scale.<sup>[5]</sup>

### 2.2.2.4 *Subjects*

At least 12 subjects should be enrolled in bioequivalence studies; the concrete number is defined by sample size calculation. Normally, healthy volunteers are included. For opioids or

oncological products, for example, it is unethical to involve healthy subjects; patients can be included under special precautions and supervision. The subjects should be 18 years or older and should have a body mass index between 18.5 and 30 kg/m<sup>2</sup>. They should be of both feminine and masculine sex, should be non-smokers and should have no history of alcohol or drug abuse. Prior study enrolment, clinical laboratory tests are performed, and the subjects are screened for their medical history.<sup>[5]</sup>

#### **2.2.2.5 Fasting or fed conditions**

As standard, bioequivalence studies should be performed under *fasting conditions*. For products where the Summary of Product Characteristics (SmPC) of the reference medicinal product recommends intake only in the fed state, the studies are usually performed under *fed conditions*.<sup>[5]</sup>

#### **2.2.2.6 Pharmacokinetic parameters and acceptance limits**

The *area under the plasma concentration curve (AUC)* and the *maximum plasma concentration (C<sub>max</sub>)* should be analysed. For both parameters the 90 % confidence interval for the ratio of test and reference products should lie within the acceptance range of 80.00 – 125.00 %. A statistical evaluation of the time until C<sub>max</sub> is reached (t<sub>max</sub>) is not required, but may be provided as supportive information.

For products with a so-called narrow therapeutic index, the acceptance range for AUC, and under certain conditions also for C<sub>max</sub>, should be tightened to 90.00 – 111.11 %.

For so-called highly variable drug products (for which the intra-subject variability for a certain parameter is larger than 30 %), the acceptance range for C<sub>max</sub> may be widened stepwise to a maximum of 69.84 – 143.19 % (so-called scaling) However, the acceptance range for AUC is still 80.00 – 125.00 %.<sup>[5]</sup>

#### **2.2.2.7 Parent compound or metabolites**

The *parent compound* should be analysed as a standard setup. If there are analytical difficulties in measuring the parent compound, the *metabolite* as a surrogate for the active parent compound can also be determined. However, a sound justification is necessary in the latter case. Even if the drug substance is an inactive pro-drug it is strongly recommended to measure the parent compound. Only if the pro-drug is metabolised very quickly and therefore not measurable it is acceptable to measure the metabolite.<sup>[5]</sup>

#### **2.2.2.8 Enantiomers**

Usually, it is acceptable to analyse the *racemate*. But if all the following conditions apply, the individual *enantiomers* should be determined<sup>[5]</sup>:

- The enantiomers show different pharmacokinetics
- The enantiomers show difference in pharmacodynamics
- The AUC ratio of enantiomers is modified by a difference in the rate of absorption

#### **2.2.2.9 Strength to be investigated ( → biowaiver for additional dose strengths)**

In section 4.1.6 of the “*Guideline on the investigation of bioequivalence*”<sup>[5]</sup>, the opportunity to waive bioequivalence studies for additional strengths is described. It is stated that “*if several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths and other product related issues described below. The strength(s) to evaluate depends on the linearity in pharmacokinetics of the active substance.*”<sup>[5]</sup>

In order to use this approach, at least the following general biowaiver criteria must be fulfilled for the strength(s) tested in the bioequivalence study and the strength(s) for which a waiver is considered:

- Same manufacturing process
- Same qualitative composition
- Proportional quantitative composition, that is, the ratio between the amount of each excipient to the amount of active substance is the same (coating components, capsule shell, colouring agents and flavours can differ slightly if not having a special functionality)
- Similarity of in vitro dissolution profiles should be demonstrated at different pH values (normally pH 1.2, 4.5 and 6.8)

Generally, the bioequivalence study should be performed with the strength(s) that are most sensitive to detect a potential difference between test and reference product. One of the key elements for deciding which strength should be tested in vivo is the linearity of pharmacokinetics of the active substance.

If the active substance shows linear pharmacokinetics, a bioequivalence study with only one strength is sufficient, usually at the highest strength. Under certain circumstances, selection of a lower strength is also acceptable, for example, if the active substance is highly soluble (according to the definition of biopharmaceutics classification system [BCS]) or if the highest strength cannot be administered to healthy volunteers due to safety/tolerability reasons.

If the active substance shows non-linear pharmacokinetics, it is then distinguished between a “more than proportional” or “less than proportional” increase in AUC with increasing dose. In the case of a “more than proportional” increase, the highest strength should be tested in vivo. If

the active substance shows a “less than proportional” increase in AUC with increasing dose, bioequivalence should generally be demonstrated both at the highest and lowest strength.<sup>[5]</sup>

The above described cases represent more or less standard situations, but there are special cases that also need to be considered. For instance, problems regarding the sensitivity of the analytical method, non-linearity in pharmacokinetics because of saturation of uptake transporters, deviation from proportional composition. It is always a case-by-case decision which strength(s) should be tested in vivo and which strength(s) can be waived. For this decision it is essential to know the characteristics of the active substance and the pharmaceutical product as much as possible, based on either literature data or in-house development work. A sound and scientific justification of the choice of strength(s) for the bioequivalence study will always be needed.

#### **2.2.2.10 Variations applications (→ biowaiver for post approval changes)**

In section 4.4 of the “*Guideline on the investigation of bioequivalence*” it is stated that “*if a product has been reformulated from the formulation initially approved or the manufacturing method has been modified in ways that may impact on the bioavailability, an in vivo bioequivalence study is required, unless otherwise justified.*”<sup>[5]</sup>

This means that for post approval changes (such as changes in the composition or in the manufacturing process), it is generally required to demonstrate that such changes do not lead to changes in the bioavailability of the active substance. This should usually be demonstrated by performing a bioequivalence study, “*unless otherwise justified*”.<sup>[5]</sup> There is an opportunity to waive such bioequivalence studies for post approval changes provided that certain criteria are fulfilled. The justification for such a biowaiver can be based on general considerations of BCS in combination with in vitro dissolution profiles, or on investigations regarding in vitro/in vivo correlation. In any case, in vitro experiments need to be performed and the influence of excipients on the bioavailability needs to be discussed.

#### **2.2.2.11 Different dosage forms (→ biowaiver for specific dosage forms)**

In Appendix II of the “*Guideline on the investigation of bioequivalence*”<sup>[5]</sup>, the requirements of bioequivalence studies for different dosage forms are discussed. For some specific dosage forms, the opportunity to waive bioequivalence studies is described. The reason is that due to certain characteristics of some types of formulations, bioequivalence between the test and the reference product can be presumed without any further in vivo experiments.

For instance, biowaivers for the following dosage forms are possible<sup>[5]</sup>:

- Aqueous oral solution at time of administration (prerequisite: differences in excipients which may affect bioavailability of the active substance must be justified)

- Parenteral solutions (prerequisite: same type of solution and differences in excipients which may affect bioavailability of the active substance must be justified)
- Emulsions under certain preconditions
- Lipids for intravenous parenteral nutrition under certain preconditions
- Solutions which are locally applied and locally acting, for example eye drops, nasal sprays or cutaneous solutions (prerequisite: same type of solution, differences in excipients must be justified). Please compare with section 2.2.4.2 of this master thesis.

#### 2.2.2.12 BCS based biowaiver

With the latest revision of the “*Guideline on the investigation of bioequivalence*” <sup>[5]</sup> the BCS based biowaiver concept was introduced; it is described in detail in Annex III of the guideline. To make use of this approach the active substance must fulfill the following criteria <sup>[5]</sup>:

- Highly soluble (BCS class 1 or 3, see below)
- Known human absorption
- Not having a narrow therapeutic index

The BCS based biowaiver approach is applicable to immediate release, solid dosage forms for oral administration and systemic action. Other dosage forms like sublingual, buccal and modified release formulations are excluded from this concept. Orodispersible formulations might benefit from the BCS based biowaiver approach only if no absorption in the oral cavity takes place. <sup>[5]</sup>

But what does BCS based biowaiver mean?

For this biowaiver approach the BCS class of a drug substance, which is based upon aqueous solubility and intestinal permeability, is combined with the in vitro dissolution of the test and reference product. In addition, the excipients of the test and reference product need to be considered, especially with regard to a potential effect on the bioavailability of the active substance. Combining all these factors, one can presume in vivo equivalence and an in vivo bioequivalence study can, therefore, be waived. <sup>[5]</sup>

The principle behind is described in Appendix I of the “*Guideline on the investigation of bioequivalence*” <sup>[5]</sup>: “*If an active substance is considered highly soluble, it is reasonable to expect that it will not cause any bioavailability problems if, in addition, the dosage system is rapidly dissolved in the physiological pH-range and the excipients are known not to affect bioavailability.*”

The key factors for a BCS based biowaiver are:

- **BCS class of drug substance (→ solubility and intestinal permeability)**

- **In vitro dissolution similarity** of test and reference product
- **Excipients**
- **No narrow therapeutic index** of drug substance (risk of an incorrect biowaiver decision to be minimised)

These factors are explained in the following.

### BCS class

The BCS classifies a drug substance into one of four classes:

BCS class 1	→	High solubility, high permeability
BCS class 2	→	Low solubility, high permeability
BCS class 3	→	High solubility, low permeability
BCS class 4	→	Low solubility, low permeability

A drug substance is regarded as highly soluble “*if the highest single dose administered as immediate release formulations(s) is completely dissolved in 250 ml of buffers within the range of pH 1 – 6.8 at  $37 \pm 1$  °C.*”<sup>[5]</sup>

A drug substance is regarded as highly permeable when “*the extent of absorption is  $\geq 85$  %*”. From complete absorption it can generally be concluded to high permeability.<sup>[5]</sup>

For known drug substances it is usually accepted to assign the BCS class based on literature data.

Generally, a BCS based biowaiver is possible for drug substances belonging to either BCS class 1 or 3 (both highly soluble). But biowaiver approaches for BCS class 3 drug substances are more critically reviewed and the requirements with regard to in vitro dissolution similarity and excipient composition are stricter than for BCS class 1 drug substances.

### In vitro dissolution similarity

Due to the fact that the BCS based biowaiver approach is only applicable to drug substances with high solubility (BCS class 1 or 3) and to immediate release, solid dosage forms, the in vitro dissolution is expected to be either very rapid ( $> 85$  % within 15 min) or similarly rapid (85 % within 30 min). The test and reference product should show similar dissolution profiles across the physiological pH range of 1 - 6.8 (at least pH 1.2, 4.5, and 6.8). It is not allowed to use any surfactant for the in vitro dissolution testing. Generally, 12 units should be tested for each of the test and reference product for each experiment in order to allow a statistical evaluation and determination of the so-called similarity factor ( $f_2$  value). The  $f_2$  value should be between 50 and 100 in order to suggest similarity of the dissolution profiles of the tested products. In case of very rapid dissolving drug products ( $> 85$  % within 15 min), the  $f_2$  value

need not to be determined, and the dissolution profiles are considered to be similar without further mathematical evaluation. <sup>[5]</sup>

### Excipients

Excipients can generally influence the bioavailability of drug substances. So, it is very important to discuss their potential influence on the bioavailability and solubility of the drug substance. Basically, well known excipients in common amounts should be used to develop a generic medicinal product. The qualitative composition of the reference product is usually known, but the quantitative amounts of the excipients normally not. By performing deformulation experiments the quantitative amounts of excipients can be determined. Any differences in the composition of excipients should be critically discussed with regard to a potential influence on the bioavailability of the drug substance:

*“Excipients that might affect bioavailability, for example sorbitol, mannitol, sodium lauryl sulfate or other surfactants, should be identified as well as their possible impact on:*

- *Gastrointestinal motility*
- *Susceptibility of interactions with the drug substance (for example complexation)*
- *Drug permeability*
- *Interaction with membrane transporters*

*Excipients that might affect bioavailability should be qualitatively and quantitatively identical in the test and reference product.” <sup>[5]</sup>*

### No narrow therapeutic index

A BCS based biowaiver approach is only applicable for drug substances not having a narrow therapeutic index, that is, which have a relatively broad margin between minimum effective and minimum toxic plasma concentration and do not require careful dosage titration or patient monitoring. The risk of an incorrect biowaiver decision should thus be minimised.

### **2.2.3 Note for guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation) <sup>[6]</sup>**

The special aspects to be considered for the bioequivalence study program for modified release oral and transdermal dosage forms with systemic action are defined in EMA’s “*Note for guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation)*” (CPMP/EWP/280/96 Corr). <sup>[6]</sup> Modified release oral dosage forms can be either prolonged or delayed release forms. For both forms, special focus should be laid on a potential food interaction. It is important to investigate the influence of food on the bioavailability of the active substances in modified release oral dosage forms. In addition, it



must be ensured that for all these dosage forms no unexpected drug release (so-called dose dumping) occurs. <sup>[6]</sup>

#### Prolonged release oral dosage forms

To demonstrate bioequivalence between prolonged release test and reference products a *single dose* as well as a *multiple dose study under fasting conditions* are necessary. The latter is relevant to prove that the test and reference products show an equivalent behaviour even at steady state. Additionally, a *single dose study under fed conditions* is necessary in order to investigate if the effect of food on both formulations is comparable. For this purpose, a predefined high fat meal is given to the study subjects immediately before dosing.

The evaluation of bioequivalence is based on the pharmacokinetic parameters AUC,  $C_{\max}$  and  $C_{\min}$ . The corresponding acceptance limits comply with that of immediate release dosage forms as described in section 2.2.2.6 *Pharmacokinetic parameters and acceptance limits* of this master thesis.

If the prolonged release oral dosage form consists of a single unit formulation and is available in different strengths, a single dose study under fasting conditions is necessary for each strength. The multiple dose study may be conducted with only the highest strength provided that the criteria to waive the studies for the lower strengths are fulfilled. Reference is made to section 2.2.2.9 *Strength to be investigated* (→ *biowaiver for additional dose strengths*) of this master thesis.

If the prolonged release oral dosage form consists of a multiple unit formulation (for instance pellets filled in a hard gelatine capsule) and is available in different strengths with linear pharmacokinetics, a single dose study under fasting conditions only with the highest strength is acceptable under certain preconditions. <sup>[6]</sup>

#### Delayed release oral dosage forms

The assessment of bioequivalence between delayed release test and reference products follows the same principles as for immediate release dosage forms. In addition, a bioequivalence study under fed condition is required in order to investigate if the influence of food on the test and reference formulation is comparable. <sup>[6]</sup>

#### Transdermal drug delivery systems (TDDS)

To demonstrate bioequivalence between a test and reference TDDS the following study program should be considered <sup>[6]</sup>:

- Single dose study
- Multiple dose study

- Replicate design is recommended; required in case of different release mechanisms between test and reference TDDS (reservoir versus matrix)
- In case of multiple strengths: bioequivalence studies with the highest strength acceptable under certain preconditions (exact proportionality and in vitro release test)
- Application of the test and reference TDDS in the same body area
- Comparative investigation of local irritation, adhesiveness to the skin, phototoxic potential and sensitization

#### **2.2.4 Further guidelines**

Some further guidelines are relevant for bioequivalence studies for generic products others than immediate or modified release oral dosage forms or TDDS with systemic action. These guidelines are listed and shortly described in the following for completeness, but will not be further discussed with respect to the idea of a global development strategy.

##### ***2.2.4.1 Guideline on clinical development of fixed combination medicinal products*** <sup>[7]</sup>

A fixed combination medicinal product consists of at least two active substances combined in one single pharmaceutical form. It can show either an immediate or a modified release mechanism. For generic applications of a fixed combination, the required study program follows the same principles as for immediate release or modified release oral dosage forms or TDDS with systemic action containing only one active substance.

If the fixed combination is available in multiple strengths there is an option to demonstrate bioequivalence only with one strength and to waive the others <sup>[7]</sup>. As a prerequisite, the conditions described in section 2.2.2.9 *Strength to be investigated* (→ *biowaiver for additional dose strengths*) of this master thesis must be fulfilled for each active ingredient.

The BCS based biowaiver approach is also applicable for immediate release fixed combination medicinal products if all active substances belong to either BCS class 1 or 3 and the other conditions (similarity of in vitro dissolution profiles and excipients, no narrow therapeutic index) are fulfilled <sup>[5, 7]</sup> as described in section 2.2.2.12 *BCS based biowaiver* of this master thesis.

##### ***2.2.4.2 Clinical requirements for locally applied, locally acting products containing known constituents*** <sup>[8]</sup>

Locally applied, locally acting products – as obvious from the name – are locally applied and are intended to act purely locally (for example dermatological products). Any systemic action is

not desired. Therefore, it is not possible to measure plasma levels of the drug substances; if so, this might be relevant for safety reasons, but not for efficacy. As a consequence, a classical bioequivalence study comparing the plasma concentration levels of the drug substance of the test and reference product is not feasible. The generic applicant has to submit a so-called hybrid application according to Article 10(3) of “*Directive 2001/83/EC, as amended*”.<sup>[3]</sup> The therapeutic equivalence between the generic and the reference product must be demonstrated by performing human pharmacodynamics studies, local availability studies or even animal or in vitro studies. In addition, local tolerance and safety studies may be necessary.<sup>[8]</sup> There is no need for full toxicological and clinical data, but the study program is quite extensive and more complex than for systemically acting generic products.

#### **2.2.4.3 Guideline on the requirements for clinical documentation for orally inhaled products (OIP)<sup>[9]</sup>**

For orally inhaled products there exist very specific requirements to prove the therapeutic equivalence between test and reference products for the purpose of abridged applications. The details are explained in the “*Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products (...)*” (CPMP/EWP/4151/00 Rev. 1).<sup>[9]</sup> Due to the specific application pathway, special importance is attached to the inhalation device of the test and reference product (metered dose inhalers including spacers and holding chambers; solutions and suspensions for nebulisation; or dry powder inhalers) and the in vitro performance, especially the flow-dependent particle size distribution. There is a biowaiver option described for abridged applications if the test product fulfils all of the pre-defined prerequisites. The biowaiver is based on comparative in vitro data between the test and reference product. In addition, special focus is laid on pulmonary deposition studies (pharmacokinetic or imaging studies). Such studies can be sufficient to demonstrate therapeutic equivalence if combined with safety studies (especially in case of new propellants or excipients). It might be that pharmacodynamic or clinical studies are necessary to demonstrate therapeutic equivalence of a test and reference OIP. Thus, there is a stepwise approach explained in the guideline: 1) in vitro studies, 2) pharmacokinetic studies, 3) pharmacodynamic studies. Altogether, the study program (in vitro and in vivo) for abridged applications of OIPs is very complex.<sup>[9]</sup> However, in practice the guideline requirements are not confirmed, there are a lot of discussions with regulatory authorities on-going. In future, the focus will very likely be on pharmacokinetic studies.

### **2.3 United States in comparison to European Union**

The basic principles for generic applications in the US and the corresponding bioequivalence studies between test and reference products are comparable to those of the EU. In the following, focus is laid on differences between USA and EU. Only the most important

regulatory framework is presented. Guidance documents for specific dosage forms - other than orally applied - will not be explained due to the complexity and limited volume of this paper.

### 2.3.1 Federal Food, Drug, and Cosmetic Act <sup>[10]</sup> – section 505(j) abbreviated new drug applications

The basis for generic applications in the US is section 505(j) of the “*Federal Food, Drug, and Cosmetic Act (FD&C Act)*” <sup>[10]</sup>, which defines the requirements for so-called abbreviated new drug applications (ANDAs) – a synonym for generic applications. Section 505(j)(2)(A)(iv) requires ANDA applicants to demonstrate bioequivalence of the test product in comparison to the reference listed drug (RLD), that is a product that has previously been approved by FDA. <sup>[10]</sup>

The need to prove bioequivalence of the test product versus the RLD is also reflected in 21 Code of Federal Regulations (CFR) part 314, where the types of “*applications for FDA approval to market a new drug*” <sup>[11]</sup> are described. In subpart C, abbreviated applications are detailed. 21 CFR part 314.94 (a) (3) defines the basis for ANDAs: “*An ANDA must refer to a listed drug. Ordinarily, that listed drug will be the drug product selected by the agency as the reference standard for conducting bioequivalence testing.*” <sup>[11]</sup>

In other words, the reference product for a generic application in the US – also used in the corresponding bioequivalence studies - has to be a listed drug which has been selected by the FDA. It is usually the US innovator product. Bioequivalence studies versus a non-US reference product are not foreseen.

US ↔ EU: For ANDA submissions in US the reference listed drug (US innovator) should be used as reference product for bioequivalence studies. For generic applications in EU bioequivalence needs to be demonstrated versus a European reference product.

### 2.3.2 21 CFR part 320: Bioavailability and bioequivalence requirements <sup>[12]</sup>

The principles for bioequivalence studies are described in 21 CFR part 320 “*Bioavailability and bioequivalence requirements*”. <sup>[12]</sup>

In several subsections details are explained, for example the “*guidelines for the conduct of an in vivo bioavailability study*” (§ 320.25) <sup>[2]</sup> or the “*criteria for waiver of evidence of in vivo bioavailability or bioequivalence*” (§ 320.22). <sup>[13]</sup> In the latter subsection, the following **biowaiver options** are listed amongst others: Waiver for specific dosage forms, waiver for additional dose strengths, waiver based on proven in vitro in vivo correlation, waiver for post approval changes. For all these biowaivers certain preconditions must be fulfilled.

### 2.3.3 Guidance for industry: Bioavailability and bioequivalence studies for orally administered drug products – general considerations <sup>[14]</sup>

One of the key documents for bioequivalence studies for regulatory purposes in the US is FDA's "*Guidance for industry: Bioavailability and bioequivalence studies for orally administered drug products – general considerations*". <sup>[14]</sup> It is applicable not exclusively but also for ANDAs. Generally, it is relevant not only for orally administered drug products (immediate release as well as modified release) but also for TDDS or other dosage forms with systemic action.

In principle, the requirements are comparable to the EU with regard to the following characteristics: study design (crossover versus parallel design, replicate versus non-replicate design, single dose versus multiple dose design, fasten versus fed condition), study population, pharmacokinetic parameters and acceptance limits, parent compound versus metabolites and enantiomers versus racemates.

US ↔ EU: One difference is that for modified release products in the EU, generally, single dose and multiple dose studies under fasting conditions as well as a single dose study under fed conditions are required. In the US only single dose studies under fasting and fed conditions are required, and the multiple dose study can be omitted. Additionally, the single dose study under fasting conditions needs to be performed with each strength in EU (in case of single unit formulation), whereas in US it is sufficient to perform this study only with the highest strength under certain preconditions.

The following biowaiver options are described in the "*Guidance for industry: Bioavailability and bioequivalence studies for orally administered drug products – general considerations*" <sup>[14]</sup>.

- **Biowaiver for additional dose strengths:** The basic requirements are the same as for EU; reference is made to section 2.2.2.9 *Strength to be investigated* (→ *biowaiver for additional dose strengths*) of this master thesis.

US ↔ EU: In the EU the qualitative composition of the different strengths need to be identical and the quantitative composition proportional. In the US the different strengths need to be proportionally similar. The definitions of proportional and proportionally similar differ slightly between the US and EU. In the EU the manufacturing process for the different strengths must be the same; in the US they must be produced by the same manufacturer.

- **Biowaiver for specific dosage forms:** The general considerations are comparable to the EU; reference is made to section 2.2.2.11 *Different dosage forms* (→ *biowaiver for specific dosage forms*) of this master thesis. There are only slight modifications in the listed dosage forms which can be challenged.

- **BCS based biowaiver:** The opportunity to demonstrate bioequivalence using an in vitro approach based on BCS is described but only “*for highly soluble, highly permeable, rapidly dissolving, and orally administered drug products.*”<sup>[14]</sup> For further details please see section 2.3.5 *Guidance for industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a BCS* of this master thesis.

US ↔ EU: In the EU the BCS based biowaiver approach is applicable for drug substances belonging to either BCS class 1 or 3, whereas in the US it is restricted to BCS class 1 drug substances; reference is made to section 2.2.2.12 *BCS based biowaiver* of this master thesis.

- **Biowaiver for post approval changes:** The opportunity to waive bioequivalence studies for minor post approval changes, based on in vitro dissolution data and theoretical considerations is described. Generally, this approach is comparable to the EU, but in the US there is more detailed guidance available, please refer to section 2.3.6 *SUPAC-IR* of this master thesis.

#### 2.3.4 Guidance for industry: Bioequivalence recommendations for specific products<sup>[15]</sup>

For many products in the US there exists product specific guidance for bioequivalence studies, that is, specific advice how to design the bioequivalence studies for a certain generic test product. Some of these guidance documents are still in the draft status, but others have been finalised. Such product specific recommendations are publicly available in the internet on the FDA drugs guidance page. The background is explained in the “*Guidance for industry: Bioequivalence recommendations for specific products*”.<sup>[15]</sup>

US ↔ EU: In the EU product specific recommendations for bioequivalence studies do not exist. This allows more flexibility for the applicant, but on the other hand the applicant could benefit from concrete product specific guidance, if available. Of course, there is always an opportunity to ask for scientific advice from regulatory agencies regarding study design, but this usually costs time and money.

#### 2.3.5 Guidance for industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a BCS<sup>[16]</sup>

First of all, reference is made to section 2.2.2.12 *BCS based biowaiver* of this master thesis, where the concept of BCS is explained in detail. In this section, only the differences between USA and EU will be presented.

In the FDA's "Guidance for industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a BCS" <sup>[16]</sup>, the opportunity to waive bioequivalence studies for ANDAs and post approval changes based on BCS is described. The key factors of the BCS based biowaiver approach are comparable to those in the EU, with some exceptions. The relevant differences are highlighted in the following comparison table (table 1):

**Table 1: Key factors for BCS based biowaiver: USA – EU (differences highlighted in bold)**

Key factors for BCS based biowaiver	USA <sup>[16]</sup>	EU <sup>[5]</sup>
<b>Solubility</b> of drug substance	<u>Definition of highly soluble:</u> Highest single dose completely dissolved in 250 ml of buffers across <b>pH range 1 – 7.5</b>	<u>Definition of highly soluble:</u> Highest single dose completely dissolved in 250 ml of buffers across <b>pH range 1 – 6.8</b>
<b>Permeability</b> of drug substance	<u>Definition of highly permeable:</u> <b>Absorption is <math>\geq 90</math> %</b>  <u>Determination of permeability:</u> <ul style="list-style-type: none"> <li>• Absolute bioavailability studies in humans (<math>\rightarrow</math> absorption)</li> <li>• Mass balance studies in humans</li> <li>• In vivo intestinal perfusion studies in humans or animal models</li> <li>• In vitro permeation studies with excised human or animal intestinal tissues</li> <li>• In vitro permeation studies across cultured epithelial cells</li> </ul>	<u>Definition of highly permeable:</u> <b>Absorption is <math>\geq 85</math> %</b>  <u>Determination of permeability:</u> <ul style="list-style-type: none"> <li>• Absorption studies in human</li> <li>• Absolute bioavailability studies in humans (<math>\rightarrow</math> absorption)</li> <li>• Mass balance studies in humans</li> </ul>
<b>BCS class</b> of drug substance	<b>BCS class 1</b>	<b>BCS class 1 or 3</b>
<b>In vitro dissolution similarity</b> of test and reference product	Similar dissolution profile across pH range 1 – 6.8  At least N = 12  f <sub>2</sub> value: 50 – 100  Rapid dissolution (> 85 % after 30 minutes); in case of very rapid dissolution no f <sub>2</sub> calculation necessary	Similar dissolution profile across pH range 1 – 6.8  At least N = 12  f <sub>2</sub> value: 50 – 100  Rapid dissolution (> 85 % after 30 minutes) for BCS class 1; in case of very rapid dissolution no f <sub>2</sub> calculation necessary

		<b>Very rapid dissolution (&gt; 85 % after 15 minutes) for BCS class 3</b> [if so, no $f_2$ calculation necessary]
<b>Excipients'</b> influence on bioavailability of drug substance	Excipients must be critically discussed; any difference in composition must be justified	Excipients must be critically discussed; any difference in composition must be justified
<b>No narrow therapeutic index</b> of drug substance	Only for drug substances with no narrow therapeutic index	Only for drug substances with no narrow therapeutic index
<b>Dosage form</b>	Only for immediate release, solid dosage forms for oral administration with systemic action (without absorption in the oral cavity)	Only for immediate release, solid dosage forms for oral administration with systemic action (without absorption in the oral cavity)

US ↔ EU: In summary, the criteria for BCS based biowaivers are comparable in the USA and EU, but FDA's criteria are slightly stricter than EMA's criteria. For instance, in the US high solubility of the drug substance needs to be demonstrated across a pH range of 1 – 7.5, whereas in the EU only from pH 1 to 6.8. In the US, the BCS based biowaiver is only applicable for drug substances belonging to BCS class 1, whereas in EU for BCS classes 1 and 3. Also, the definition of high permeability differs slightly. In the US a drug substance must show absorption of  $\geq 90\%$  in order to be classified as highly permeable. In the EU the corresponding limit is  $\geq 85\%$  absorption. On the other hand, the FDA accepts in vitro data to determine the permeability of drug substances. In the EU such data are accepted only in support of human absorption data.

### 2.3.6 SUPAC-IR<sup>[17]</sup>

SUPAC-IR stands for “*Immediate release solid oral dosage forms: Scale-up and post-approval changes: chemistry, manufacturing, and controls, in vitro dissolution testing, and in vivo bioequivalence documentation*”. SUPAC-MR is the corresponding document for modified release solid oral dosage forms.

Both documents describe the required in vitro dissolution and in vivo bioequivalence studies for post approval changes. Possible changes are clustered in different sub-groups, for example changes in components and composition, site changes, changes in batch size and changes in the manufacturing method. Each sup-group is divided into several levels, and the complexity increases from levels 1 through 3. For each level the required data package to support a certain change is described, especially if there is an in vivo bioequivalence study necessary or if such a study can be waived. Both documents (SUPAC-IR and SUPAC-MR) give detailed guidance to applicants and are very helpful for deciding to perform or to waive a bioequivalence study for



post approval changes. Generally, this approach is comparable to the EU, but in the US there is simply more detailed guidance available.

## 2.4 World Health Organisation

One important paper for bioequivalence studies for generic products is WHO's guidance document "*Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*" <sup>[18]</sup> (in the following cited as "*WHO's guidance*"). It can be regarded as the basis guidance for bioequivalence studies for generic products worldwide, and national competent authorities implement the content of this WHO guidance in their national guidelines.

In principle, the described requirements for bioequivalence studies for generic products are comparable to the relevant EU and US guidelines with regard to the following characteristics: study design (crossover versus parallel design, replicate versus non-replicate design, single dose versus multiple dose design, fasten versus fed condition), study population, pharmacokinetic parameters and acceptance limits, parent compound versus metabolites and enantiomers versus racemates.

One interesting aspect is that the **choice of reference product** to be used in bioequivalence studies is described in detail in the WHO's guidance document. Several options are mentioned for the choice of the so-called comparator product, but the final decision is made by the relevant national competent authority of the country for which a MA is intended. The following alternatives for reference products are described in order of preference <sup>[18]</sup>:

- **National innovator:** Innovator product granted a national MA. This approach is utilised in the US and EU (in the EU the principle of the so-called European reference medicinal product is also applicable, see section 2.2.1 *Directive 2001/83/EC, as amended* of this master thesis). Also, for other important scopes such as Canada, Australia, Brazil, China, et cetera bioequivalence should in principle be demonstrated versus the corresponding national innovator. However, exemptions are becoming more feasible as will be further discussed (reference is made to sections 3.7 "*Bridging*" – *biowaiver for national bioequivalence study based on bioequivalence study versus foreign reference product* and 4. *Biowaiver approach in Canada, Australia and Brazil* of this master thesis).
- **WHO comparator product:** Product granted a MA with reference to a manufacturing site (a list of WHO comparator products exists)
- **ICH et al innovator:** Innovator product granted a MA in an ICH or associated country

- **Well selected comparator:** Only if no innovator product can be identified or is available and if no WHO comparator product is listed. Sound scientific justification is necessary.

In addition, the following **biowaiver options** are described in “*WHO’s guidance*”<sup>[18]</sup> (for comparison reference is made to sections 2.2.2 *Guideline on the investigation of bioequivalence* and 2.3.3 *Guidance for industry: Bioavailability and bioequivalence studies for orally administered drug products – general considerations* of this master thesis):

- **Biowaiver for specific dosage forms:** The general considerations are comparable with the EU and US. There are only slight modifications in the listed dosage forms which could be challenged.
- **Biowaiver for additional dose strengths:** The basic requirements are the same as for the EU and US.
- **BCS-based biowaiver:** The basic principles are comparable with the EU and US, but there is some differentiation (reference is made to section 3.4 *Biowaiver based on BCS* of this master thesis). The definition of high solubility and high permeability in the WHO’s guidance is in accordance with EU requirements, but differ slightly from the US requirements. In the US, BCS based biowaivers are generally only possible for BCS class 1 drug substances, and in EU for BCS class 1 and 3. WHO opens an additional option for BCS class 2 weak acids under certain preconditions.
- **Biowaiver for post approval changes:** The idea of waiving bioequivalence studies for minor post approval changes based on in vitro dissolution and BCS classification is comparable with the EU and US.

## 2.5 Ethical aspects and Good Clinical Practice

There are ethical objections to perform unnecessary bioequivalence studies, for instance using identical reference products from different markets. According to the WHO “*Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products*”<sup>[19]</sup>, “*it is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks or benefits of a particular clinical trial be thoroughly considered and that the chosen options be scientifically sound and ethically justified*”. The ICH “*Guideline for Good Clinical Practice*” (CPMP/ICH/135/95)<sup>[20]</sup>, also known as ICH topic E6 (R1), defines GCP as an “*international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.*” In addition, the US 21 CFR part 320.25 “*Guidelines for the conduct of an in vivo bioavailability study*”<sup>[2]</sup> states under “(a) *Guiding principles: (1) The basic principle in an in vivo bioavailability study is that no unnecessary human research should be done.*” The principles of GCP as well as ethical

principles - based on the Declaration of Helsinki <sup>[21]</sup> - must be followed when performing clinical studies for regulatory purposes. <sup>[20]</sup> Therefore, it is essential to justify each clinical trial with regard to ethical considerations. And each clinical trial must fulfil GCP requirements.

## **2.6 Note for guidance on ethnic factors in the acceptability of foreign clinical data <sup>[22]</sup>**

The “*Note for guidance on ethnic factors in the acceptability of foreign clinical data*” (CPMP/ICH/289/95) <sup>[22]</sup> is also known as ICH topic E5 (R1). It describes the possible impact of ethnic factors upon the efficacy and safety of a drug product and the consequences for regulatory and development strategies. It is mainly relevant for the development of innovative medicinal products, but the basic thoughts are also relevant for generics.

In terms of bioequivalence studies for generic products, if the pharmacokinetic behaviour of a drug product is comparable between ethnic groups, the study results are generally considered to be transferable between the three major ethnic groups of the ICH regions (namely Asian, Black and Caucasian). Ethnic differences might influence the pharmacokinetics of a drug substance. There are intrinsic ethnic factors related to genetics and physiology (for example genetic polymorphism, gender, weight, organ dysfunction) as well as extrinsic ethnic factors like environment and culture (for example medical practice, diet, use of tobacco, use of alcohol, and exposure to pollution). <sup>[22]</sup>

Not all drug substances are sensitive to ethnic factors. This depends for instance on the metabolism of a drug substance by enzymes which show genetic polymorphism. Normally, generic applicants can find useful information in the scientific literature to determine if a drug substance will be sensitive to ethnic factors. This is important information in order to discuss the acceptance of foreign clinical data in a certain region or to decide to perform an additional bioequivalence study with the ethnic population of that region.

Innovator companies usually perform so-called bridging studies in order to evaluate if the efficacy and safety of a drug product is comparable between different ethnic populations. If so, the clinical data package determined in a certain patient population can be transferred to another patient population. But for generic companies, such bridging studies are not reasonable due to the fact that the total number of subjects involved in a standard bioequivalence study is relatively low. Therefore, generic companies generally perform separate bioequivalence studies for certain ethnic populations. In addition, many countries principally require local bioequivalence studies independent of a potential ethnic influence. Nevertheless, depending on the amount and quality of literature data, generic applicants can argue that bioequivalence results of a certain study population (for instance Caucasian) should seek acceptance in another population (for instance Asian). Of course, one prerequisite is that the regulatory requirements regarding bioequivalence studies are fulfilled in the region where the MA is applied for, for

example the acceptance limits of the pharmacokinetic parameters, the GCP status or the level of detail of the presented data.

## 2.7 Protection periods and CoPP

When planning a global development strategy for generic medicinal products some protection periods should be kept in mind, namely the data/market exclusivity and the patent protection. They are in fact relevant for the regulatory strategy, but not necessarily for the development strategy. Nevertheless, development and regulatory strategy cannot be regarded independently. For instance, protection periods are important when deciding for which regional scope the first bioequivalence studies should be planned and which scopes should follow. It only makes sense to perform a bioequivalence study when there is a realistic chance to use the study results for receiving a MA and consequently marketing a product within a clear timeframe. All these periods of market protection – the data exclusivity, the market exclusivity and the patent protection – have a strong impact on registration strategies for generic applications and consequently also on generic development strategies. In addition, global generic strategies are influenced by the fact that in certain countries a so-called Certificate of Pharmaceutical Product (CoPP) is necessary for MA applications. The different protection periods as well as CoPPs are explained in short in the following.

### 2.7.1 Data and market exclusivity

The pre-clinical and clinical data of an innovator product are protected for a certain period of time, during which a generic application with reference to these data is not allowed. This protection is called *data exclusivity*; it must be expired at the time of a generic application in the concerned country.<sup>[3, 4]</sup> The data exclusivity is important for originator companies in order to amortise the costs for the development of innovative products. The data exclusivity varies from country to country. For instance, in the EU it is eight years starting from the first MA as part of the global MA of the innovator product within the EU. But other countries have different data exclusivity periods. It is very important for generic companies to know in which countries the data exclusivity expires first, because these are the first countries where a generic application is possible. As a logical consequence, the development strategy including the bioequivalence study program will focus on those countries in a first step, followed by countries where the data exclusivity will expire next. Some countries have no data exclusivity at all, but these are usually economically insignificant countries.

In a few countries, for instance in the EU, there is an additional *market exclusivity* period, during which the innovator product is exclusively on the market, that is, no generic competition is allowed. Even if a generic MA is granted, the corresponding generic product must not be placed on the market until the market exclusivity is expired.<sup>[3, 4]</sup> In the EU, the market exclusivity is in total ten years starting from the first MA as part of the global MA of the innovator product within the EU. During the two years between the end of the data exclusivity

and the end of the market exclusivity, generic applications are possible and the corresponding generic MA can be granted, but the generic MA holder is not allowed to place the product on the market. The market exclusivity in the EU can be extended to eleven years if a new therapeutic indication is authorised for the reference medicinal product. This new indication must have a significant clinical benefit in comparison with existing therapies, and it must be approved during the first eight years since the initial MA.<sup>[3, 4]</sup> However, most countries do not have separate market exclusivity in addition to the data exclusivity.

An overview of the data/market exclusivity in different important countries is presented in *Annex 1* of this master thesis.

### **2.7.2 Patent protection**

In order to understand how generic companies decide on their registration and development strategies, the patent protection has to be taken into account as well. Patents hinder competitors from bringing products onto the market which infringe upon those patents. They are essential for innovator companies to ensure their exclusive rights to a medicinal product, at least for a limited period of time. The duration of patents vary from country to country. In the EU the patent protection of a drug substance consists of the basis patent with duration of 20 years and the so-called supplementary protection certificate (SPC) with an additional protection of a maximum of five years.<sup>[23]</sup> The combined duration of patent protection (basis patent plus SPC) after the first MA of a medicinal product in a MS is however limited to 15 years in total. As an exception to this rule, the SPC can be extended by six months if paediatric studies are performed<sup>[23, 24]</sup>, that is the so-called paediatric extension (PE). In addition to the drug substance patent, companies usually also apply for further patents in order to protect drug substance syntheses, drug product formulations, special manufacturing technologies or certain indications. However, those patents can more easily be circumvented by competitors than the drug substance patent itself.

In the EU the patent protection is not part of the regulatory assessment process; the regulatory authorities do not check the patent situation of medicinal products. In contrast, the FDA reviews the patent protection of the reference product during the generic application procedure.

In most countries of the world it is allowed to perform research and development work with a drug substance during patent protection of that substance. It is just not allowed to produce the corresponding medicinal product for launch purposes and of course the launch itself is forbidden as long as patent protection exists. Consequently, the patent expiry dates of a reference medicinal product around the world (also called patent landscape) are very important to know for generic companies, and they must be considered when preparing strategies for the development, regulatory and launch phases.

### 2.7.3 Certificate of pharmaceutical product (CoPP)

A CoPP is a product specific certificate establishing the status of a pharmaceutical product in the exporting country. It is used by regulatory authorities of importing countries from low regulated markets to assess the quality of a medicinal product as well as the Good Manufacturing Practice (GMP) status of its manufacturing site. The CoPP is a prerequisite for the submission and/or approval in many countries. The CoPP can pertain to different phases of the registration process in the exporting country; consequently, it can have different statuses, such as “submitted/under consideration”, “approved”, and “marketed”. The requirements vary from country to country. In some countries, it is sufficient for the initial submission to have a CoPP referring to a medicinal product which is approved in the country of the manufacturing site. But for final approval, it is necessary that the product that the CoPP is referring to is placed on the market. Some countries even require legalization of the CoPP by a notary or embassy. The format of the CoPP was introduced by WHO.

The need for a CoPP in certain countries is important for generic strategies. For instance, for an approval in Brazil it is required to submit a CoPP with status “marketed in any country” or “registered in the country of origin” (synonymous to country of the manufacturing site). On the other hand, regulatory data exclusivity is not specified in Brazil and patents are very often not existent or expire much earlier than in the EU or US. But even without data and patent protection, it is not allowed to submit without a CoPP in Brazil. First, a submission in a highly regulated market is necessary, and the corresponding CoPP needs to be issued. So, the timing of submissions in Brazil depends on the submission/approval status in other countries, preferably in the country of origin.

For an overview of the necessity of a CoPP for submission/approval in certain important countries please refer to *Annex 2* of this master thesis.

## 3. Biowaiver – different options and impact on global development strategy

For details regarding different biowaiver approaches, reference is made to the relevant information in sections 2.2 *European Union*, 2.3 *United States in comparison to European Union* and 2.4 *World Health Organisation* of this master thesis. For a global development strategy the biowaiver opportunities of different regional scopes should be consistent. Otherwise, it is necessary to perform a bioequivalence study for a certain scope, even if it is not necessary for another scope. As a consequence, no real uniform global development strategy with regard to bioequivalence studies would be feasible. In the following, a brief summary of the different biowaiver options is presented.

### 3.1 Biowaiver definition

“WHO’s guidance”<sup>[18]</sup> gives the following definition for biowaiver: „*The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than in vivo bioequivalence test.*“

In other words, biowaiver means an exemption for in vivo bioequivalence studies. By applying biowaiver approaches whenever possible generic companies can save a lot of resources. With regard to global development strategy it is important to know the criteria for the applicability of biowaivers in the different geographic scopes.

### 3.2 Biowaiver for specific dosage forms

Due to certain characteristics of some types of formulations bioequivalence between the test and the reference product can be presumed without any further in vivo experiments.<sup>[5, 14, 18]</sup> For instance, such a biowaiver is theoretically possible for aqueous oral solutions, parenteral solutions or solutions which are locally applied and locally acting, for example eye drops. One of the major prerequisites is that the excipients are not known to influence the bioavailability of the active substance. The conditions for this biowaiver are identical in most countries.

### 3.3 Biowaiver for additional dose strengths

If several strengths of a generic drug product are developed it can be sufficient to demonstrate bioequivalence versus the reference product only with one or two strengths depending on certain product characteristics.<sup>[5, 14, 18]</sup> In vivo bioequivalence studies for additional strengths can thus be waived. Also for this biowaiver the basic requirements are identical in most countries.

### 3.4 Biowaiver based on BCS

For drug substances belonging to a certain BCS class a complete biowaiver for bioequivalence studies might be possible if certain criteria are met. The eligibility for BCS based biowaivers differs between USA, EU and WHO. Therefore, BCS biowaivers are not very common for global generic development strategies. In the following table (table 2), the main differences between USA, EU and WHO with regard to BCS based biowaivers are summarized.

**Table 2: Key factors for BCS based biowaiver: USA – EU – WHO (differences highlighted in bold)**

Key factors for BCS based biowaiver	USA <sup>[16]</sup>	EU <sup>[5]</sup>	WHO <sup>[18]</sup>
<b>Solubility</b> of drug substance - definition of highly soluble	Highest single dose completely dissolved in 250 ml of buffers across <b>pH 1 – 7.5</b>	Highest single dose completely dissolved in 250 ml of buffers across <b>pH 1 – 6.8</b>	Highest single dose completely dissolved in 250 ml of buffers across <b>pH 1.2 – 6.8</b>
<b>Permeability</b> of drug substance - definition of highly permeable	<b>Absorption ≥ 90 %</b>	<b>Absorption ≥ 85 %</b>	<b>Absorption ≥ 85 %</b>
<b>BCS class</b> of drug substance	<b>BCS class 1</b>	<b>BCS class 1 or 3</b>	<b>BCS class 1 or 3</b>  <b>BCS class 2 weak acids</b>
<b>In vitro dissolution similarity at pH 1.2, 4.5 and 6.8</b> of test and reference product	<u>BCS class 1:</u> rapid dissolution (> 85 % after 30 minutes)	<u>BCS class 1:</u> rapid dissolution (> 85 % after 30 minutes)  <u>BCS class 3:</u> very rapid dissolution (> 85 % after 15 minutes)	<u>BCS class 1:</u> rapid dissolution (> 85 % after 30 minutes)  <u>BCS class 3:</u> very rapid dissolution (> 85 % after 15 minutes)  <u>BCS class 2 weak acids:</u> rapid dissolution (> 85 % after 30 minutes) at pH 6.8 and similar dissolution at pH 1.2, 4.5 and 6.8

The other criteria for BCS based biowaivers, like influence of excipients on the bioavailability of the drug substance or the therapeutic index of the drug substance, are identical in the US, EU and WHO guidance documents. <sup>[16, 5, 18]</sup> In the US, a BCS based biowaiver is only applicable for drug substances belonging to BCS class 1 <sup>[14, 16]</sup>, whereas in the EU it is applicable for BCS class 1 and 3 drug substances. <sup>[5]</sup> “WHO’s guidance” <sup>[18]</sup> describes an additional biowaiver approach for BCS class 2 drug substances, which are highly soluble at pH 6.8, but not at pH 1.2 and 4.5. For such weak acids of BCS class 2, it will not be possible to establish a global BCS based biowaiver strategy, because the FDA as well as the EU regulatory authorities will very



likely not accept this approach. In this context, the existence of individual biowaiver monographs should be mentioned, that is, a classification of a number of drug substances from the WHO Model List of Essential Medicines <sup>[25]</sup> for their solubility and permeability based on available literature data. These monographs are very useful to convince regulatory authorities of a BCS based biowaiver.

### 3.5 Biowaiver for scale up and post approval changes

During the life cycle of a medicinal product, there are usually several post approval changes. Some of these changes require a new bioequivalence study in order to prove the equivalence of the changed generic medicinal product to the reference product. However, the applicant can justify that there is no need for an additional bioequivalence study provided that certain preconditions are fulfilled. Such a justification is the so-called *biowaiver for scale up and post approval changes*. These preconditions are comparable in different geographical scopes. <sup>[5, 14, 17, 18]</sup>

### 3.6 Biowaiver for “same product”

If the generic medicinal product is a 1:1 copy of the reference product, bioequivalence between the test and reference product can be presumed based on demonstration of identity and comparative in vitro data. The basis for this biowaiver approach is the sameness of the test and reference product. It is not officially described in regulatory guidance documents, but in theory it is possible if the generic applicant knows exactly the qualitative and quantitative composition (with regard to active substance(s) and excipients) as well as the galenical characteristics and manufacturing process of the reference product. In practice however, it is often not feasible due to patent issues to develop qualitatively and quantitatively the same product like the innovator. Altogether, this approach is not very common but sometimes possible, for instance in the case of simple gelatine capsules filled only with the active ingredient without any excipients. Regulatory authorities worldwide must be convinced of this biowaiver approach on a case-by-case basis.

### 3.7 “Bridging” - biowaiver for national bioequivalence study based on bioequivalence study versus foreign reference product

Last but not least, there is the so-called “bridging” approach in order to waive unnecessary national bioequivalence studies. Many countries require so-called local bioequivalence studies, that is, bioequivalence studies versus the local reference product and very often with subjects from the local population. Especially Asian countries (for instance China, South Korea, Thailand, and Japan) usually insist on such local bioequivalence studies. But also Russia, Canada, Australia, Brazil, Mexico and other countries require bioequivalence studies versus the

corresponding local reference product. In the case of ethnic sensitivity relating to the metabolism of the drug substance, it makes sense to demonstrate bioequivalence in different ethnic populations (please refer to section 2.6 *Note for guidance on ethnic factors in the acceptability of foreign clinical data* of this master thesis). However, the need to use the local reference product is not always justified, because innovator products are very often identical in different countries around the world.

The “bridging” biowaiver concept convinces regulatory authorities to accept the results of bioequivalence studies which have been performed versus a foreign reference product and not versus the national reference product approved in the country where the application is made. The study results versus the foreign reference product are “bridged” via product likeness to the locally/nationally approved reference product. If the foreign and local/national reference products are considered to be essentially the same, an additional bioequivalence study may not be necessary. Of course, one prerequisite is that general study requirements like GCP are fulfilled and that potential ethnic differences in pharmacokinetics can be excluded. In the following section 4. *Biowaiver approach in Canada, Australia and Brazil* of this master thesis the details of the bridging approach are explained for these countries.

## 4. Biowaiver approach in Canada, Australia and Brazil

### 4.1 Biowaiver approach in Canada

#### 4.1.1 Regulatory framework

Part C of the Canadian “*Food and Drug Regulations*”<sup>[26]</sup> includes guidance regarding drugs. In division 8 of part C, the requirements for new drugs are explained<sup>[26]</sup>. As a basic requirement in Canada, generic applicants need to demonstrate bioequivalence of the generic medicinal product versus the Canadian reference product, that is, the innovator product registered and marketed in Canada. However, the Canadian regulatory authority, the Canadian Therapeutic Products Directorate (TPD), provides in section C.08.002.1 of the “*Food and Drug Regulations*”<sup>[26]</sup> the following alternatives for the so-called Canadian reference product:

- Reference product approved and marketed in Canada by the innovator company
- Reference product for bioequivalence study in case the innovator product is no longer marketed in Canada
- Reference product for bioequivalence study other than the Canadian innovator product

The latter opens the opportunity to use a non-Canadian reference product for demonstrating bioequivalence of a generic medicinal product. The relevant criteria are outlined in the “*Drugs Directorate Policy regarding the use of a non-Canadian Reference Product*”<sup>[1]</sup> and are

explained in detail in section *4.1.2.2 Biowaiver based on bridging approach* of this master thesis.

## 4.1.2 Biowaiver options

### 4.1.2.1 Overview about biowaiver options

The Canadian “*Food and Drug Regulations*” <sup>[26]</sup> do not explicitly mention biowaiver options, except for the bridging approach. But in principle there is an opportunity to waive unnecessary bioequivalence studies, for example for specific dosage forms like oral solutions, for additional dose strengths and for scale up and post approval changes if certain preconditions are fulfilled (detailed in guidance “*post-notice of compliance (NOC) changes*” <sup>[27]</sup>). The prerequisites are comparable to those in the EU or USA. The BCS concept is still not applied in Canada. However, the basic BCS considerations, for example the solubility and permeability of the drug substance, the in vitro dissolution behaviour of the drug product and some other product specific characteristics play an important role for the bridging approach (details are explained in the following section *4.1.2.2 Biowaiver based on bridging approach* of this master thesis).

### 4.1.2.2 Biowaiver based on bridging approach

A generic application in Canada should generally include at least one bioequivalence study of the generic medicinal product versus the innovator product marketed in Canada. In order to use study results versus a non-Canadian reference product and to extrapolate this data to be relevant for the Canadian reference product, the generic applicant must demonstrate identity of the reference product used in the bioequivalence study to the Canadian innovator product. Even if there are slight differences between the reference products, the TPD might accept the bridging approach if the following general criteria are met.

Criteria for bridging according to “*Drugs Directorate Policy regarding the use of a non-Canadian Reference Product*” <sup>[1]</sup> issued 1995:

- **Dosage form**
  - Conventional, immediate-release solid oral dosage form
- **Drug substance**
  - Aqueous solubility of more than 1 %
  - “Uncomplicated”, for example
    - No narrow therapeutic index
    - No steep dose/response relationship

- No risk of serious undesired effects
  - No complicated or variable pharmacokinetics (for instance, non-linear pharmacokinetics, variable or incomplete absorption, an absorption window, more than 40 % first-pass metabolism, an effective half-life of more than 24 hours)
- No documented evidence of bioavailability problems
- **Reference products** (reference product used in the bioequivalence study and Canadian innovator product)
  - No documented evidence of bioavailability problems
  - Reference product used in the study must be authorised in a country with a regulatory system comparable to Canada
  - Marketed by the same innovator company (licensing arrangement are acceptable)
  - Contain only a single drug substance
  - Contain the same quantity of drug substance
  - Have the same colour, shape, size, weight, type of coating
  - Exhibit comparable dissolution profiles (in at least three media across pH range 1 - 7.5, for example water, 0.1 N HCl, and buffers at pH 4.5, 6.5 and 7.5. If a BP or USP monograph exists the corresponding dissolution medium should be applied)
  - Certificates of Analysis (according to the proposed specifications of the generic product) of both reference products must be provided
  - Copies of the labelling of both reference products must be provided

The generic applicant must submit a justification for not performing a bioequivalence study versus the Canadian reference product, but instead versus another reference product from a highly regulated market. Such a justification should address all of the above mentioned criteria.

Although the TPD document states *“If any of the above conditions are not met, the manufacturer must demonstrate the equivalence of the second-entry product to the innovator’s product marketed in Canada by the appropriate comparative in-vivo study or studies”*<sup>[1]</sup>, if any of the criteria are not met, the applicant may choose to present sound and scientific justification demonstrating that such criteria are not relevant for that particular drug product. The TPD may accept this argumentation on a case-by-case basis. In any event, it is recommended to consult the TPD for scientific advice in advance to the submission.

## 4.2 Biowaiver approach in Australia

### 4.2.1 Regulatory framework

The Therapeutic Goods Administration (TGA), the regulatory authority for medicinal products in Australia, issued the “*Australian regulatory guidelines for prescription medicines (ARGPM)*”<sup>[28]</sup> in 2004. These guidelines describe the following different categories of applications:

Category 1 applications: Applications for new medicinal products or changes to medicinal products not belonging to other categories, for example new strengths, new dosage form or new indications. Generic applications are generally category 1 applications.

Category 2 applications: Applications for medicinal products which have already been approved in two acceptable countries, for instance “*in Canada, Sweden, the Netherlands, the United Kingdom and the United States of America*”.<sup>[28]</sup>

Category 3 applications: Applications for changes to medicinal products without the necessity of supporting bioequivalence studies.

With regard to bioequivalence studies the TGA has in principle adopted the European guidelines with some additional TGA specific amendments. It is a requirement for generic applications in Australia that bioequivalence of the generic medicinal product should generally be demonstrated versus the Australian reference product. The specific aspects of biopharmaceutic studies and biowaiver approaches for applications in Australia are outlined in Appendix 15 of the “*ARGPM*”<sup>[28]</sup> (in the following cited as “*Appendix 15*”<sup>[29]</sup>).

### 4.2.2 Biowaiver options

#### 4.2.2.1 General aspects for biowaivers in Australia

“*Appendix 15*”<sup>[29]</sup> includes in chapter 2 “*Products for which biopharmaceutic data are not normally required*” a number of applications for which bioequivalence studies can usually be waived. In addition, the applicant has the opportunity to justify on a case-by-case basis why no bioequivalence studies have been performed. Such a justification for biowaivers should discuss at least the following criteria mentioned in chapter 4 “*Justification for not submitting biopharmaceutic data*” of “*Appendix 15*”<sup>[29]</sup>:

- Specific characteristics of the dosage form
- Solubility of the active substance(s)
- Pharmacokinetics of the active substance(s) like permeability, linearity, first pass effect

- Similarity of in vitro dissolution profiles across pH range 1 - 7.5 between the products being considered (for example between test and reference product or between different strengths of the test product)
- Therapeutic index of the drug substance
- Comparative data between the formulations being considered (for example excipient composition)

#### **4.2.2.2 Biowaiver for specific dosage forms**

Some dosage forms are applicable for a biowaiver without further justification. These are listed in chapter 2 “*Products for which biopharmaceutic data are not normally required*” of “*Appendix 15*”<sup>[29]</sup>, for instance oral solutions, solutions for injection, simple aqueous solutions for infusion – provided that the same active substance in the same amount is included as in a currently registered product and that no excipients are included which might influence the bioavailability of the active substance.

#### **4.2.2.3 Biowaiver for additional dose strengths**

Bioequivalence studies for additional strengths can be waived under the following preconditions:

- The formulations of the different strengths are qualitatively identical and quantitatively proportional
- The different strengths are manufactured at the same site
- The drug substance shows linear pharmacokinetics
- Comparative in vitro dissolution profiles demonstrate similarity between the different strengths

The general biowaiver aspects as described in chapter 4 “*Justification for not submitting biopharmaceutic data*” of “*Appendix 15*”<sup>[29]</sup> need to be addressed.

#### **4.2.2.4 Biowaiver based on BCS**

A biowaiver based on BCS is not explicitly mentioned in Australian regulatory guidance. Nevertheless, applying the general principles of chapter 4 “*Justification for not submitting biopharmaceutic data*” of “*Appendix 15*”<sup>[29]</sup>, it could theoretically be possible to use the BCS based biowaiver approach. This chapter covers the general criteria for the BCS biowaiver, namely the solubility and permeability of the drug substance, the in vitro dissolution similarity between test and reference products, the influence of excipients on the bioavailability of the drug substance, the therapeutic index and the dosage form itself. Applicants can justify the lack of bioequivalence studies based on these arguments, but it will be difficult to convince the

TGA. The BCS concept is still not officially applied in Australia, even if the TGA has in principle adopted the EU "*Guideline on the investigation of bioequivalence*" <sup>[5]</sup> in which biowaivers for drug substances of BCS class 1 and 3 are mentioned.

#### **4.2.2.5 Biowaiver for scale-up and post approval changes**

Certain changes of an already approved medicinal product do not need to be supported by bioequivalence studies <sup>[28]</sup>. Such changes can be submitted as category 3 applications (see section 4.2.1 *Regulatory framework* of this master thesis). In chapter 2 of "*Appendix 15*" <sup>[29]</sup> exemplary changes are listed, such as minor changes in excipient composition or changes to the manufacturing method provided that some preconditions are fulfilled.

#### **4.2.2.6 Biowaiver based on bridging approach**

A generic application in Australia should generally include a bioequivalence study of the generic medicinal product versus the reference product marketed in Australia. <sup>[28, 29]</sup> However, in chapter 7 "*Choice of the reference product for bioequivalence of generic medicines*" of "*Appendix 15*" <sup>[29]</sup>, it is stated that "...TGA may accept bioequivalence studies carried out using a batch of reference product obtained from outside Australia, provided the sponsor can support this with compelling evidence that the formulation of the product used is the same as the formulation marketed in Australia."

The generic applicant must demonstrate the identity of the reference product used in the bioequivalence study and the Australian brand product. For this purpose, he can submit a declaration from the innovator company confirming the identity of the overseas and Australian innovator products with respect to all product characteristics like composition and manufacturing method. But usually, such a declaration cannot be provided by generic applicants.

As an alternative, the following criteria must be met in order to use study results versus a non-Australian reference product and to bridge this data as being relevant to the Australian reference product. In exceptional cases the generic applicant can justify why a certain criterion is not relevant for a specific application.

Criteria for bridging according to chapter 7 "*Choice of the reference product for bioequivalence of generic medicines*" of "*Appendix 15*" <sup>[29]</sup> issued 2004:

- **Dosage form**
  - Conventional, immediate-release, oral dosage form or
  - Enteric coated oral dosage form which releases the active substance immediately after disintegration of the enteric coating

- Sustained release tablets/capsules case-by-case
- **Drug substance**
  - Well described dose response curve
  - No narrow therapeutic index
  - No steep dose/response relationship
  - No risk of serious undesired effects
  - No complicated or variable pharmacokinetics (for instance, non-linear pharmacokinetics, variable or incomplete absorption, an absorption window, more than 40 % first-pass metabolism)
- **Reference products** (reference product used in the bioequivalence study and Australian innovator product):
  - Reference product used in the study must be from a country with a regulatory system comparable to Australia
  - Marketed by the same innovator company (licensing arrangement are acceptable)
  - Contain the same quantity of drug substance
  - The excipients must be qualitatively identical (exception: colourants and inks)
  - Have the same size, weight and type of coating
  - Exhibit comparable dissolution profiles (in at least three media across pH range 1 - 7.5, including 0.1 N HCl, a pH 4.5 and a pH 6.8 buffer. If a BP or USP monograph exists the corresponding dissolution medium should be applied)
  - Certificates of Analysis (according to the proposed specifications of the generic product) of both reference products must be provided
  - Product Information of both reference products must be provided
  - Physicochemical and chemical evidence of identity, so-called deformulation study, of at least two (preferably three) batches of both reference products must be provided (for instance FTIR spectra, X-ray diffraction spectra, quantitative chemical analyses of the excipients)

Generally, a scientific advice with the TGA is strongly recommended in order to discuss such a bridging approach in advance to the submission. If the drug substance shows low solubility and low permeability the requirements will be interpreted in a stricter way. But for drug substances with high solubility and high permeability (that is, BCS class 1), it is possible to argue that



some of the requirements need not to be followed. This is an indicator that TGA is likely willing to discuss BCS based approaches in the future. It will always be a case-by-case decision, and applicants need to provide a sound justification why certain criteria are not relevant for the bridging approach.

### **4.3 Biowaiver approach in Brazil**

#### **4.3.1 Regulatory framework**

The regulatory authority for medicinal products in Brazil, namely Agência Nacional de Vigilância Sanitária (ANVISA), requests generic applicants to demonstrate bioequivalence of the generic medicinal product versus the innovator product registered and marketed in Brazil. Specific aspects of bioequivalence studies and biowaiver approaches are outlined in the following two guidelines published beginning of August 2011:

- “*Resolution – RDC N° 37, 3 August 2011*”<sup>[30]</sup> (guidance for bioequivalence exception/biowaiver)
- “*Normative instruction – N° 4, 3 August 2011*”<sup>[31]</sup> (list of drugs applicable for biowaiver based on BCS)

Both guidelines are applicable to innovator as well as to generic medicinal products. In the following, the relevant issues for generic applications and the corresponding biowaiver options are presented.

#### **4.3.2 Biowaiver options**

##### ***4.3.2.1 Biowaiver for specific dosage forms***

In chapter II, section I, Article 4 of “*Resolution – RDC N° 37, 3 August 2011*”<sup>[30]</sup>, the option to waive bioequivalence studies for certain dosage forms is described, for example for aqueous oral solutions, aqueous parenteral solutions or oily parenteral solutions. As a prerequisite, the same drug substance in the same amount and excipients of the same function must be included as is in the reference product. Any differences in excipient composition must be justified, especially for excipients which might influence the bioavailability of the drug substance.

##### ***4.3.2.2 Biowaiver for additional dose strengths***

In chapter II, section II, Article 5 of “*Resolution – RDC N° 37, 3 August 2011*”<sup>[30]</sup>, the possibility to waive bioequivalence studies for additional strengths is presented. The following criteria must be met:

Immediate release dosage forms: The different strengths must have the same pharmaceutical form, proportional formulations and must be produced by the same manufacturer.

Modified release dosage forms: The different strengths must have the same pharmaceutical form, the same release mechanism, proportional formulations and must be produced by the same manufacturer at the same manufacturing site.

Independent of the dosage form, the in vitro dissolution profiles between the different strengths must be similar. The bioequivalence study should be performed with highest and/or lowest dose strength, depending on the linearity of pharmacokinetics or any safety concerns.

#### **4.3.2.3 Biowaiver based on BCS**

A biowaiver approach based on BCS is described in chapter II, section III of “*Resolution – RDC N° 37, 3 August 2011*”.<sup>[30]</sup> Only drug substances of BCS class 1 are acceptable for this biowaiver in Brazil. A list of drugs eligible as candidates for a BCS based biowaiver is published in “*Normative instruction – N° 4, 3 August 2011*”.<sup>[31]</sup> As usual, for BCS based approaches the following data need to be provided:

- Data to prove the high solubility and permeability of the drug substance
- Data to demonstrate rapid and similar dissolution across pH 1.2 – 6.8 between test and reference products (preferably according to the monograph of the Brazilian Pharmacopoeia)
- Data to prove that the excipients do not affect bioavailability (preferably the same excipients should be included in the test and reference product)

Fixed combinations are explicitly mentioned as having access to a BCS based biowaiver if the criteria are met for all drug substances included in such a fixed combination. The BCS based biowaiver is not applicable for substances of low therapeutic index, for certain product categories (contraceptives, vitamins) and for modified release dosage forms.

#### **4.3.2.4 Biowaiver for scale up and post approval changes**

According to chapter I, section I, Article 3 of “*Resolution – RDC N° 37, 3 August 2011*”<sup>[30]</sup> it is possible to waive unnecessary bioequivalence studies based on BCS argumentation in case of changes in composition or manufacturing process. In addition, there exists the “*Resolution - RDC N° 48, 6 October 2009*”<sup>[32]</sup>, which describes SUPAC and the corresponding waiver options in more detail; SUPAC can be waived if certain preconditions are fulfilled.

#### 4.3.2.5 Biowaiver based on bridging approach

The bridging approach is not foreseen by ANVISA. It is still required for generic applications in Brazil to demonstrate bioequivalence of the generic medicinal product versus the innovator product from the Brazilian market. Even if the identity of the reference product used in the bioequivalence study and the Brazilian innovator product can be proven, it will be very difficult to convince ANVISA to accept the study results versus the non-Brazilian reference product. From a scientific point of view it may not be necessary to perform additional bioequivalence studies versus the Brazilian innovator product. Nevertheless, ANVISA is still not willing to accept study results versus foreign reference products.

### 4.4 Comparison of biowaiver approaches in Canada, Australia and Brazil

#### 4.4.1 Biowaiver options in Canada, Australia and Brazil in comparison to EU, USA and WHO

In the table below (table 3) the different options to waive bioequivalence studies for generic medicinal products are summarized for the countries/regions considered.

**Table 3: Biowaiver options: Canada – Australia – Brazil – EU – USA - WHO**

Biowaiver option	Canada [1, 26, 27]	Australia [28, 29]	Brazil [30, 31, 32]	EU [5]	USA [13, 14, 16, 17]	WHO [18]
Specific dosage form	+	+	+	+	+	+
Additional strengths	+	+	+	+	+	+
BCS based	-	-	+	+	+	+
			BCS 1	BCS 1 BCS 3	BCS 1	BCS 1 BCS 3 BCS 2 weak acids
SUPAC	+	+	+	+	+	+
Bridging	+	+	-	-	-	+

+ biowaiver accepted (provided that certain preconditions are fulfilled)

- biowaiver not accepted

All these countries/regions accept in principle biowaivers for specific dosage forms, additional dose strengths and scale up and post approval changes. But there are differences with regard to the acceptance of BCS based biowaivers and the bridging approach.

BCS based biowaivers are still not accepted in Canada and Australia, whereas in Brazil this is possible for BCS class 1 drug substances. Also, in EU, USA and the WHO region

bioequivalence studies for BCS class 1 drug substances can be waived provided that certain preconditions are fulfilled. In addition, the EU and the WHO regions allow for a BCS based biowaiver for BCS class 3 drug substances. The WHO gives the farthest interpretation of BCS based biowaivers by also including weak acids of BCS class 2.

Regarding the bridging approach, the EU and USA insist on a bioequivalence study program versus the EU and US innovator product, respectively. They do not accept study results versus foreign reference products. Also, Brazil is still not open to accept the bridging approach; bioequivalence of a generic medicinal product must be demonstrated versus the local Brazilian innovator product. The WHO defines several alternatives for the reference product of generic bioequivalence studies. In principle, the bridging approach is covered by the WHO. In Canada and Australia, generic applicants have good chances to convince the local health authorities to accept bioequivalence studies performed versus a foreign reference product of a highly regulated market, for example the EU or USA. The criteria for such a bridging approach differ slightly between Canada and Australia. The details are explained in the following section 4.4.2 *Comparison of bridging approach in Canada and Australia* of this master thesis.

#### **4.4.2 Comparison of bridging approach in Canada and Australia**

The criteria for bridging of bioequivalence studies for generic applications in Canada and Australia are compared in the table below (table 4); differences are highlighted in bold.

Generally, one can conclude that the Canadian requirements are a bit more restrictive than the Australian. For example, in Canada bridging is only allowed for conventional, immediate-release solid oral dosage forms, whereas in Australia the solid state is not preconditioned, that is, bridging is theoretically also possible for suspensions. Additionally, enteric coated tablets and sustained release dosage forms (on a case-by-case basis) can be bridged in Australia. Canada requires some additional characteristics of the drug substance, for instance aqueous solubility must be more than 1 % and the half-life less than 24 hours. These requirements are not mentioned in the Australian guidance. Furthermore, Canada attaches great importance to the same colour and shape of the reference product used in the bioequivalence study and the Canadian innovator product. In Australia, the colour is not such important. Last but not least, Canada restricts the bridging approach only to drug products including one active substance; in Australia combination products are not explicitly excluded from bridging.

On the other hand, Australia requires a so-called deformulation study, that is, a physicochemical and chemical evidence of the identity of the reference product used in the bioequivalence study and the Australian innovator product (except for some slight variations for example the colour). Such a deformulation study is usually quite complex and expensive and not each company has the necessary analytical equipment in-house to perform a complete deformulation of the reference products.

**Table 4: Criteria for bridging: Canada – Australia (differences highlighted in bold)**

Criteria for bridging in CANADA <sup>[1]</sup>	Criteria for bridging in AUSTRALIA <sup>[29]</sup>
<b>Dosage form</b>	
<ul style="list-style-type: none"> <li>Conventional, immediate-release <b>solid</b> oral dosage form</li> </ul>	<ul style="list-style-type: none"> <li>Conventional, immediate-release, oral dosage form</li> </ul>
	<ul style="list-style-type: none"> <li><b>Enteric coated oral dosage form</b></li> </ul>
	<ul style="list-style-type: none"> <li><b>Sustained release tablets/capsules case-by-case</b></li> </ul>
<b>Drug substance</b>	
<ul style="list-style-type: none"> <li><b>Aqueous solubility of more than 1 %</b></li> </ul>	
<ul style="list-style-type: none"> <li>No steep dose/response relationship</li> </ul>	<ul style="list-style-type: none"> <li><b>Well described dose/response curve</b></li> <li>No steep dose/response relationship</li> </ul>
<ul style="list-style-type: none"> <li>No narrow therapeutic index</li> </ul>	<ul style="list-style-type: none"> <li>No narrow therapeutic index</li> </ul>
<ul style="list-style-type: none"> <li>No risk of serious undesired effects</li> </ul>	<ul style="list-style-type: none"> <li>No risk of serious undesired effects</li> </ul>
<ul style="list-style-type: none"> <li>“Uncomplicated”/No complicated or variable pharmacokinetics, for instance: <ul style="list-style-type: none"> <li>- Non-linear pharmacokinetics</li> <li>- Variable or incomplete absorption</li> <li>- Absorption window</li> <li>- More than 40 % first-pass metabolism</li> <li>- <b>Half-life of more than 24 hours</b></li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>No complicated or variable pharmacokinetics, for instance: <ul style="list-style-type: none"> <li>- Non-linear pharmacokinetics</li> <li>- Variable or incomplete absorption</li> <li>- Absorption window</li> <li>- More than 40 % first-pass metabolism</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li><b>No documented evidence of bioavailability problems</b></li> </ul>	
<b>Reference products (used in study and local innovator)</b>	
<ul style="list-style-type: none"> <li>Reference used in study from a country with comparable regulatory system</li> </ul>	<ul style="list-style-type: none"> <li>Reference used in study from a country with comparable regulatory system</li> </ul>
<ul style="list-style-type: none"> <li>Same innovator company</li> </ul>	<ul style="list-style-type: none"> <li>Same innovator company</li> </ul>
<ul style="list-style-type: none"> <li>Same quantity of drug substance</li> </ul>	<ul style="list-style-type: none"> <li>Same quantity of drug substance</li> </ul>
<ul style="list-style-type: none"> <li><b>Only a single drug substance</b></li> </ul>	
	<ul style="list-style-type: none"> <li><b>Excipients qualitatively identical (exception: colourants and inks)</b></li> </ul>
<ul style="list-style-type: none"> <li><b>Same colour, shape, size, weight, type of coating</b></li> </ul>	<ul style="list-style-type: none"> <li>Same size, weight and type of coating</li> </ul>
<ul style="list-style-type: none"> <li>Comparable dissolution profiles</li> </ul>	<ul style="list-style-type: none"> <li>Comparable dissolution profiles</li> </ul>
<ul style="list-style-type: none"> <li>Certificates of Analysis</li> </ul>	<ul style="list-style-type: none"> <li>Certificates of Analysis</li> </ul>
<ul style="list-style-type: none"> <li>Labelling</li> </ul>	<ul style="list-style-type: none"> <li>Labelling <b>and Product Information</b></li> </ul>
	<ul style="list-style-type: none"> <li><b>Deformulation: Physicochemical and chemical evidence of identity</b></li> </ul>
<ul style="list-style-type: none"> <li><b>No documented evidence of bioavailability problems</b></li> </ul>	

Summarizing, the Canadian requirements for bridging are more extensive than the Australian. However, Australia sets more value on the identity of the reference product used in the bioequivalence study relative to the Australian innovator and requires a complete

deformulation. In practice, however, voluntary deformulations are often performed also for Canadian biowaiver petitions.

#### **4.4.3 Experience and practical aspects regarding bridging approach in Canada, Australia and Brazil**

In the following, some practical experiences regarding bridging approaches in Canada, Australia and Brazil are described. The examples reflect real cases but are made anonymous due to confidentiality concerns.

**Canada – experience 1:** Drug substance A, 10 mg and 20 mg, immediate release tablet/bioequivalence study with 20 mg strength versus the EU innovator/all criteria for waiver of study with 10 mg strength met/all bridging criteria met, except for elimination half-life (drug substance A shows a half-life of 50 hours) → TPD accepted bridging to the study versus the EU innovator and stated that a long elimination half-life as the only critical pharmacokinetic parameter is not sufficient to reject the use of a foreign-sourced reference product.

**Canada – experience 2:** Drug substance B (opioid), 10/20/30/40 mg, osmotic release oral system (OROS)/study program versus EU innovator according to relevant EU guideline<sup>[6]</sup> and scientific advice with EU regulatory authority (single dose fasten with each strength, single dose fed and multiple dose fasten with 40 mg)/criteria for strengths waiving met/bridging criteria not met, because OROS is not an immediate release oral dosage form and drug substance B shows extensive first pass metabolism of around 70 % → TPD accepted bridging to the study program versus the EU innovator. *Justification:* Both the EU and the Canadian reference product provide the identical mechanism of drug release based on the OROS technology which is a highly predictable and reliable technology for controlled drug release on the market for more than 20 years. Further studies versus the Canadian reference product would be clinically redundant and provide no additional information with respect to the risk/benefit ratio of drug substance B. The extensive first pass metabolism was justified to be clinically irrelevant because it is stereo selective and concerns primarily the inactive L-enantiomer.

**Australia - experience 1:** Drug substance C, 20 mg, gastro resistant tablet/study program versus Canadian innovator (fasten and fed)/all bridging criteria met → TGA accepted bridging to the study program versus Canadian innovator.

**Australia – experience 2:** Drug substance D (opioid), 5/10/20/30/40 mg, TDDS/study program versus EU innovator according to relevant EU guideline<sup>[6]</sup> and scientific advice with EU regulatory authority (study program only with 10 mg strength due to safety concerns)/criteria for strengths waiving not met (TDDS in Australia: study with lowest and highest strength needed)/bridging criteria not met (TDDS not foreseen) → TGA accepted bridging to the study program versus EU innovator. *Justification:* Different strengths are punched from identical

laminates/dissolution profiles across pH range 1 – 6.8 are comparable between all strengths/drug substance D is dissolved in the patch/TDDS regarded as simple sustained release forms/all other bridging criteria met including complete deformation study to prove identity of EU and Australian reference products.

**Brazil – experience 1:** Drug substance E, 200 and 400 mg, immediate release tablet/bioequivalence study with 400 mg strength versus US innovator according to product specific US guideline/general bridging criteria as in Canada and Australia all met/deformation of US and Brazilian innovator products demonstrates identity/scientific advice with ANVISA → ANVISA refused bridging to the study versus the US innovator.

Summarizing, it is always worth trying to extrapolate study results obtained versus a foreign reference product to be relevant for the innovator product in Canada and Australia, even if not all of the bridging criteria are met. The basic principle behind the bridging approach is that the local reference product and the reference product used in the bioequivalence study are identical. Brazil is still not open to accept the bridging approach. Nevertheless, it is recommendable to challenge ANVISA's position case-by-case with a sound scientific justification. Bridging can save costs for additional bioequivalence studies and can shorten the timeline for development. For example, a situation could arise where there is a later patent expiration in Canada, Australia or Brazil but already finished development for the US or EU. In this situation, generic applicants should always ask the TPD, TGA and ANVISA, respectively, for scientific advice and discuss the potential of study bridging. If the bridging approach is not accepted in such a case, there is still enough time to perform additional studies versus the innovator product in Canada, Australia or Brazil.

## **5. Global generic development strategy – a fictive case study**

In the following, a potential global development strategy for a generic medicinal product is presented with regard to bioequivalence study programs; it reflects a fictive case study.

### **Innovator product:**

Drug substance F, 100/150/200 mg, immediate release hard gelatine capsule filled with pellets, worldwide registration and marketing

### **Target regions for generic company:**

EU, USA, Canada, Brazil, Mexico, Japan, China, Australia, South Korea, Russia, Ukraine, Turkey

**Analysis/deformulation of innovator product sourced from different countries:**

- Quantitative composition known from innovator's patents, confirmed by deformulation
- Proportional formulation over dose range 100/150/200 mg (different amount of same pellets filled in hard gelatine capsules)
- Comparative dissolution profiles between different strengths demonstrate similarity
- Deformulation studies with innovator product from several countries establishes identity of the reference product within target regions
- Solubility of drug substance F is low and pH-dependent (increasing solubility at acidic pH → use of a certain buffering excipient is patented by innovator; circumvention of patent very difficult because of instability of the formulation with alternative buffering excipients)

**Pharmacokinetics of drug substance F (literature based information):**

- BCS 2 (low solubility, high permeability)
- Linear pharmacokinetics over dose range 20 – 400 mg
- No food effect (bioavailability not significantly influenced by food)
- Ethnic differences in pharmacokinetics between Caucasian and Asian/Japanese subjects  
→ exposure in Japanese subjects results in about 25 % higher AUC than in Caucasian subjects

**On-going clinical studies by innovator:**

- Safety and tolerability studies in paediatric population → six months extension of SPC, so-called paediatric extension (PE), to be considered

**Protection periods and need for CoPP:**

The **data exclusivity** expires inconsistently, as usual due to the fact that the innovator was approved at different time points in the individual countries and the duration of data exclusivity varies from country to country. There is no unique “global” expiration date for data exclusivity. Some countries have no regulatory data protection at all, so a submission would be possible; but these are mostly low regulated countries which require a **CoPP** for submission, or at least for approval. The **patent situation** is quite complex, there are several patents and patent applications, respectively. The patent applications as well as some weak patents need to be closely monitored and eventually challenged by the patent department of the generic company. However, the basis patent (drug substance) and the formulation patent protecting the buffering excipient are strong and need to be followed closely. For details, please refer to the following table (table 5).



**Table 5: Expiry of data exclusivity/patent protection and need for COPP (fictive case study)**

Scope/ country	Data exclusivity expiry	Basis patent expiry (drug substance molecule)	Formulation patent expiry (buffering excipient)	CoPP necessary?
<b>EU</b>	18.03.2017	03/2018 (inclusive SPC & PE)	10/2017	-
<b>USA</b>	18.11.2015	03/2017 (inclusive SPC & PE)	10/2017	-
<b>Canada</b>	26.08.2015	02/2013	10/2017	-
<b>Brazil</b>	n/a	01/2015	12/2018	+
<b>Mexico</b>	18.03.2016	02/2015	12/2018	+
<b>Japan</b>	20.01.2020	02/2015 (extension possible)	09/2021	-
<b>China</b>	15.02.2017	02/2013	09/2019	+
<b>Australia</b>	24.11.2016	09/2017	05/2019	-
<b>South Korea</b>	20.05.2016	02/2013	02/2018	+
<b>Russia</b>	n/a	09/2017	09/2019	+
<b>Ukraine</b>	15.01.2017	09/2017	12/2018	+
<b>Turkey</b>	15.05.2017	03/2018	12/2018	+

[Source: Own table, fictive case study]

**Clinical strategy:****Decision for study design**

- Dosage form is an immediate release hard gelatine capsule filled with pellets (no biowaiver due to dosage form possible)
  - Drug substance F belongs to BCS class 2 (no BCS based biowaiver possible)
  - Ethnic differences in pharmacokinetics between Caucasian and Asian/Japanese subjects
  - Inconsistent expiry of data exclusivity and patent protection in target regions
- Single dose fasten bioequivalence study for each regional scope (special aspects for certain countries and considerations to reduce costs, see below)

**Strength to be investigated**

- Drug substance F shows linear pharmacokinetics across intended dose range

- Innovator strengths 100, 150 and 200 mg are qualitatively identical and quantitatively proportional; the different strengths of the generic medicinal product will be developed with dose proportional composition as well
- Comparative dissolution profiles demonstrate similarity between the strengths 100, 150 and 200 mg of the innovator product
- No safety concerns with highest strength in healthy volunteers
- Bioequivalence study only with the highest strength of 200 mg (biowaiver for lower strengths of 100 and 150 mg)

### Special aspects for certain countries

- USA: US individual guideline for drug substance F → fasten and fed study is required
- Ukraine and Turkey: No separate bioequivalence studies required as it is generally sufficient to submit the EU bioequivalence study

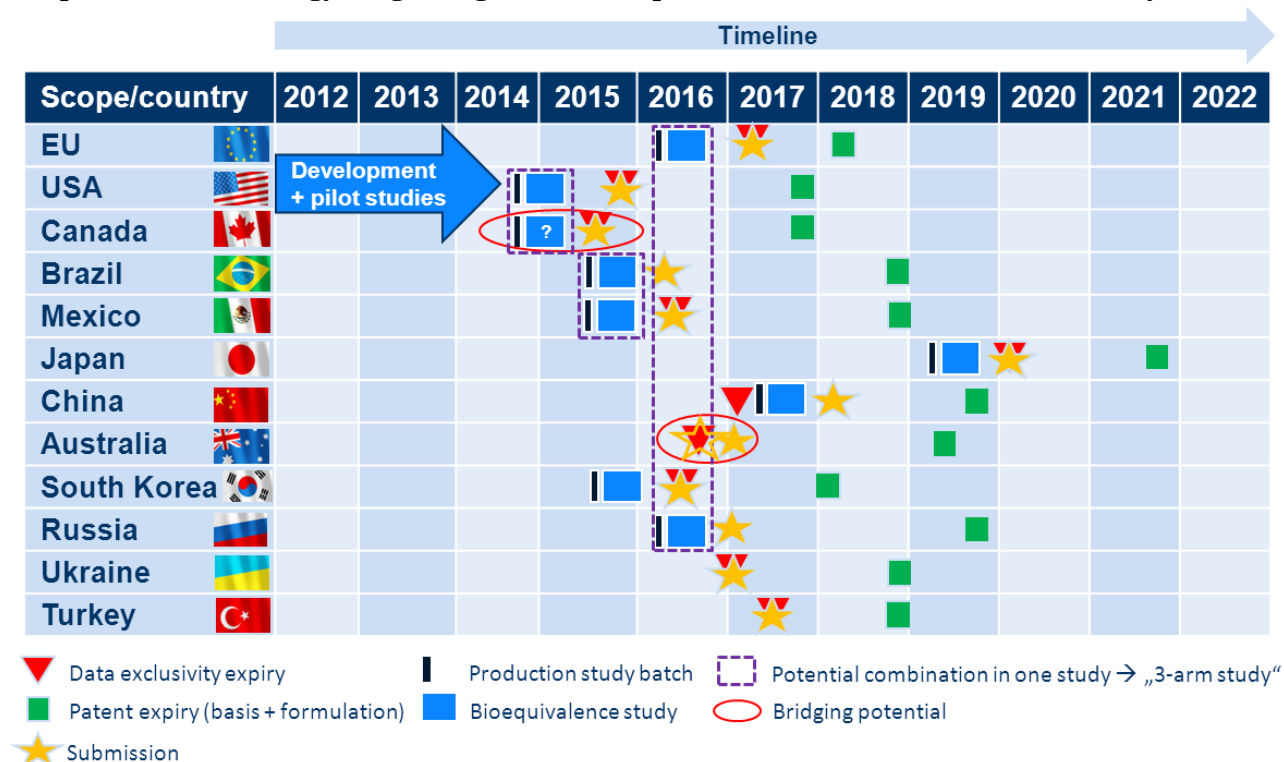
### Considerations to reduce costs

- Bridging approach in Canada: Questionable due to low solubility (BCS 2) of drug substance F (important bridging criterion not met). Scientific advice with TPD is recommended.
- Bridging approach in Australia: Seems realistic (in principle, all bridging criteria met; deformulation study confirms identity of Australian and EU as well as US innovator product). Scientific advice with TGA is recommended.
- Combination of multiple scopes/countries in one study: Might be feasible, depending on the time schedule of bioequivalence studies for the different scopes/countries.
- Sample size (number of subjects) reduction to be considered for certain scopes due to varying acceptance limits for bioequivalence, for example:
  - *Canada*: only ratio for  $C_{\max}$ , not the 90 % confidence interval, should be in range 80.0 - 125.0 %; 90 % confidence interval for AUC should be in range 80.0 - 125.0 % (both only one decimal place in contrast to other scopes) <sup>[33]</sup>
  - *China, Russia*: 90 % confidence interval for  $C_{\max}$  should be in range 75 - 133 % (AUC 80 - 125 %) <sup>[34, 35]</sup>

**Decision for contract research organization (CRO):** CRO for bioequivalence studies should have a valid GCP certificate and recent inspections by at least EU, FDA and ANVISA authorities with positive outcomes.

### Time schedule for bioequivalence studies:

At least two pilot bioequivalence studies are planned with the highest strength of 200 mg within the next two years, one under fasten and one under fed conditions. Two to three test formulations will be compared with the reference product. Depending on the results of these pilot studies, the decision for the final global test formulation (generic medicinal product) will be made. This will be tested in the pivotal bioequivalence studies according to the time schedule presented in the following graph (graph 1).

**Graph 1: Clinical strategy for global generic development – time schedule (fictive case study)**

[Source: Own diagram, fictive case study]

The **USA and Canada** are the first countries where submission is possible since their data exclusivity ends first. There are countries without data exclusivity, for example Russia. However, the patent protection will expire late in Russia (September 2019) and Russia needs a CoPP for submission. For the US scope, two pivotal bioequivalence studies are planned, one under fasten and one under fed conditions according to the US individual guideline for drug substance F.

The need for a separate study versus the Canadian reference product should be challenged during a scientific advice procedure with TPD, but the chance to succeed with a bridging approach using the US study is relatively low. If bridging is accepted by the TPD, then only the US study program will be performed. If bridging is not accepted, the Canadian and US fasten study can be combined in a 3-arm study in order to reduce the study costs. The latter scenario is more realistic. Therefore, the Canadian study is incorporated in the clinical strategy.

The next country with data exclusivity expiry is Mexico, followed by South Korea. Due to known ethnic differences in the pharmacokinetics of drug substance F, it is not possible to include the same population in the studies for Mexico and South Korea. Therefore, a combination in a 3-arm study is not feasible.

For **South Korea** a separate local bioequivalence study with Asian population versus the innovator product in South Korea will be performed; it is scheduled for end 2015. Submission is possible at time of data exclusivity expiry. For approval a CoPP with status marketed is

needed, so the MA will not be granted until such a CoPP is available (around beginning of 2018 referring to the launch in USA or Canada at patent expiry in October 2017).

The bioequivalence study for **Mexico** can be combined with the one for **Brazil** in a 3-arm study. The CoPPs for the submission in Brazil and Mexico can refer to the submission in Canada or USA.

The data exclusivity for scope **EU** expires in March 2017. Therefore, the study versus the EU innovator is scheduled in the second half of 2016.

For the submission in **Australia**, the bridging approach is more realistic than in Canada. A scientific advice with the TGA is planned in order to clarify the details. For the clinical strategy, no study is currently scheduled. The preferred scenario is a bridging to the EU study. Using this strategy, submission at data exclusivity expiry for AU is not possible. However, due to the late patent expiry in Australia, this is acceptable. Alternatively, bridging to the US and/or CA bioequivalence study can be considered. In this case, submission at data exclusivity expiry is feasible.

The study for **Russia** can be combined in a 3-arm study with the study for the EU scope (generic test product compared with the EU and Russian reference product). Russia does not have data exclusivity, but the patent protection expires quite late. The study start could be synchronized with EU.

The submission in **Ukraine and Turkey** are planned at expiry of data exclusivity; the EU study will be submitted, no separate studies are planned.

**China** needs a CoPP with status “marketed” for submission. The data exclusivity expires in February 2017, which is still during patent protection in all countries; therefore, no CoPP with status “marketed” will be available at that point of time. The first countries expected to launch the product are USA and Canada because they have the earliest patent expiry date (October 2017) and a MA is very likely by that time. The CoPP for submission in China can refer to Canada or USA. The availability of the CoPP is realistic beginning 2018. Therefore, the study for China is scheduled in the second half of 2017 and submission is planned for the beginning of 2018.

The last country in this fictive case study is **Japan**. It has a long patent protection until 2021 and also the data exclusivity does not expire until 2020. A local bioequivalence study in the Japanese population versus the innovator product from Japan is scheduled for 2019.

Summarizing, there will be more “waves” of bioequivalence studies depending on the timing of submission in certain countries. Most countries require studies versus their national reference product. Only the Ukraine and Turkey generally accept the EU study. Whenever it is possible, a

bridging approach – relevant for Canada and Australia - or at least a combination of different scopes in a more-arm study should be considered.

This fictive case study reflects a quite simple situation: immediate release dosage form, linear pharmacokinetics, identical innovator product worldwide. Nevertheless, an intensive bioequivalence study program is necessary for a global generic development strategy. In the case of modified release dosage forms, complicated or variable pharmacokinetics, or deviating innovator products in different countries, the generic development strategy and the bioequivalence study program will be much more complex.

## 6. Discussion

When considering a global generic development strategy, various regulatory guidance documents have to be considered, and the regulatory framework is quite complex. In principle, EU, US and WHO guidance describes the same requirements for generic medicinal products and the corresponding bioequivalence studies except for some slight regional distinctions. Basically, these requirements are also applicable in Asia, but it is very important to consider the possible ethnic influence on the pharmacokinetics of a drug substance. In the majority of cases, separate bioequivalence studies are necessary for the Asian region.

Regarding the choice of reference product, most countries insist on a bioequivalence study versus their national reference product even if this is not always justified based on scientific reasons. European regulatory authorities generally accept bioequivalence studies versus a reference product authorised in any EU country. In order to save both time and money, it may be advantageous to include additional reference products (for instance EU and US innovator) along with the test product in one study program, for example in a 3-arm study.

Not only due to resource issues in the pharmaceutical industry, but also due to ethical reasons no unnecessary human research should be performed. This could be achieved by waiving studies whenever it is accepted by regulatory authorities. Biowaivers can save time and costs in drug development and also in the reviewing process by authorities. Again, for a global development strategy it is important to compare the different biowaiver opportunities in different regional scopes. In theory, most of the prerequisites for biowaivers are comparable in the EU, US and WHO guidance, but not all. For example, in the EU there is a chance to obtain a biowaiver for a BCS class 3 substance, whereas in USA there is definitely a need for a bioequivalence study for such drug substances. However, practical experience shows that even within EU there is still no common view between regulatory authorities concerning biowaivers. Those regional differences make it very complex to plan a global development strategy.

Another fact that makes a global strategy difficult is that the data/market exclusivity and patent protection periods in varying countries end at different time points. Only after expiry of data exclusivity a generic application is possible, and the launch of a generic product is not allowed until expiry of market exclusivity and patent protection. In addition, in most countries outside

ICH the registration process is dependent on the submission/approval status in the country of origin or at least in a highly regulated market like EU or USA. Submissions in lower regulated countries require a CoPP and will, therefore, follow behind submissions in highly regulated countries. Consequently, bioequivalence studies for such low regulated scopes will start at a later time point.

Last but not least, a global development strategy does not end with approval of the medicinal product but is also relevant throughout the entire lifecycle of the product. Thus, it is also important to plan the post approval changes and try to harmonise the maintenance strategy on a global level as much as possible.

The expanding globalisation of the drug industry has resulted in increasingly more innovator products being manufactured with the same formulations at the same manufacturing sites for worldwide registration and marketing. In order to reduce costs and to avoid unnecessary exposure of subjects to drugs, regulatory authorities should become more willing to embrace the bridging approach, that is, bioequivalence studies performed versus innovator products from foreign countries. In a first step, they could accept the bioequivalence study data package, in a second step they could even rely on the evaluation performed by another regulatory body. The latter aspect is not realistic in the near future. Authorities should agree to exchange more information regarding reference products, especially regarding their identity; but even if there are slight differences between products, these might have no therapeutic consequence. Applicants should have access to such information as well. A kind of “global information sharing point” could be established to enable regulatory authorities as well as pharmaceutical companies to have the same information available. In addition, the acceptance of bridging by authorities should be extended to further dosage forms and also to combination products. The principle behind is the identity or at least essential similarity of innovator products in different countries. There is no scientific reason why only simple products should have access to the bridging approach.

In some countries it is advantageous not only for regulatory approval but also for reimbursement by governments and health insurance providers to perform local bioequivalence studies. This fact should be challenged based on pure scientific knowledge. Only in case of ethnic sensitive drug substances bioequivalence studies with the local population are justified. In this context, it is worth to mention that some countries, for example the USA, consist of a multi ethnic population, a mixture of Caucasian, Asian and Black ethnics. So on the other hand, the validity of a bioequivalence study versus only Caucasian subjects for regulatory purpose in the US can be questioned anyhow. One of the consequences of the expanding globalisation could be that in case of ethnic sensitive drug substances all ethnic populations must be included in generic bioequivalence study programs in the future.

Besides the bioequivalence study program, it is essential for a global generic development strategy to develop one global generic medicinal product. The drug substance and drug product specifications must be in accordance with different Pharmacopoeias, such as the European/United States/Japanese/British Pharmacopoeia. Furthermore, a global stability

program covering all relevant climatic zones is necessary. Last but not least, routine inspections of manufacturing sites and CROs by at least the EU, FDA and ANVISA authorities with positive outcomes are important. Based on such a global generic medicinal product the bioequivalence study program can be planned. For this purpose, generic companies need to specify any biowaiver options for the intended scopes. Then, the study design, the reference product(s) and CRO need to be decided. There is still no unique way of planning a global generic development strategy with regard to bioequivalence studies. It would be very important that regulatory authorities agree on a common view with regard to biowaiver opportunities, acceptance limits of pharmacokinetic parameters, harmonised statistical analysis of the raw data and an identical level of detail of the presented data. In addition, GCP inspections of CROs performed by one authority should seek acceptance by another authority. All these necessary steps could be achieved, for instance, under the supervision of ICH by starting a program to harmonise the requirements for bioequivalence studies and biowaivers.

## **7. Conclusion and outlook**

A complete uniform global development strategy for generic medicinal products with regard to bioequivalence studies is still currently not feasible, but by investing resources in strategic planning generic companies can optimize development strategies and maximize time and savings. The most important markets for generic companies are the EU, USA and the Asian region. For most of the Asian countries usually separate bioequivalence studies are necessary due to both possible ethnic differences in metabolism and specific national requirements. Also for the EU and USA separate bioequivalence studies are required, each versus the respective innovator product. But whenever possible, one uniform global generic medicinal product will be developed for worldwide registration. This is generally feasible when the innovator product is identical in many different countries. With regard to the bioequivalence study program and biowaiver opportunities there is still no consensus between different regulatory authorities. Especially the BCS based biowaiver approach is controversially discussed.

At present, Canada and Australia generally accept bioequivalence studies performed versus the EU or US innovator product under certain preconditions. This so-called bridging approach is almost always worth attempting, even if not all official criteria are fulfilled. In Brazil the bridging approach is still not accepted, but should be challenged whenever possible. In future, it might even be acceptable to submit a bioequivalence study versus the EU innovator to the FDA or vice versa if the identity of the US and EU innovator product is proven. Some Asian countries, for instance Thailand and South Korea, are more and more open-minded about biowaivers like the BCS based or bridging approach. The latter only, if ethnic differences in metabolism can be excluded. Thus, the international requirements with regard to bioequivalence studies, also in other important markets like Russia or China, need to be closely monitored by generic companies and integrated in their global generic development strategy.

## 8. Summary

With the increasing globalisation of the drug industry many medicinal products are manufactured with the same formulation at the same manufacturing site for worldwide registration and distribution. If so for an innovator product, generic companies have one global reference product available and can consequently develop one global generic medicinal product. With regard to the necessary bioequivalence studies, harmonised requirements in different countries would be a great advantage. Ideally, only one global study program may be necessary for seeking marketing authorisations from regulatory authorities worldwide. But at present, there is still no uniform way of planning such a global bioequivalence study program for generic medicinal products. Most countries still insist on a bioequivalence study versus their national reference product. This is not always justified on the basis of scientific knowledge, but very often required for reimbursement and substitution purposes. In order to reduce costs and to avoid unnecessary exposure of subjects to drugs, regulatory authorities should become more willing to embrace the bridging approach, that is, bioequivalence studies performed versus innovator products from foreign countries. European regulatory authorities generally accept bioequivalence studies versus a reference product authorised in any EU country; FDA requires studies versus the US innovator product. Canada and Australia accept bridging to relevant bioequivalence studies versus EU or US innovator products provided that certain criteria are fulfilled, whereas in Brazil the bridging approach is still not accepted.

Whenever it is possible, unnecessary bioequivalence studies should be waived. So-called biowaivers are usually accepted for specific dosage forms, for additional dose strengths, for scale-up and post-approval changes, or can be based on the BCS or the bridging approach. For a global development strategy it is important to know the different biowaiver opportunities in different countries. There is still no consensus between regulatory authorities concerning biowaivers and bioequivalence study programs. Those regional differences make it very complex to plan a global development strategy for generic medicinal products with regard to bioequivalence studies; but by investing resources in strategic planning generic companies can optimize development strategies and maximize time and savings.



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## Annexes

### Annex 1: Data/market exclusivity – exemplary overview in important countries

Table 6

Scope/country	Data/market exclusivity in years <sup>[36]</sup>
European Union	8 + 2 (+ 1)
Switzerland	10
Turkey	6
United States of America	4 + 1
Canada	6 + 2
Australia	5
Brazil	Not specified
Mexico	5
Russia	Not specified
Ukraine	5
China	6
Japan	8
South Korea	6 (new drugs; line extensions, e.g. new strengths, new route of administration)  4 (new indications, other drugs deemed necessary by South Korean authority)

**Annex 2: CoPP – necessity for submission/approval in important countries****Table 7**

<b>Scope/country</b>	<b>CoPP necessary (+) not necessary (-)</b>	<b>“Status” of CoPP for submission/approval (no, under consideration, registered, marketed; in any country, in country of origin*)</b>
<b>European Union</b>	-	➤ no CoPP (submission/approval)
<b>Switzerland</b>	-	➤ no CoPP (submission/approval)
<b>Turkey</b>	+	➤ no CoPP (submission) ➤ CoPP / registered / any country (approval)
<b>United States of America</b>	-	➤ no CoPP (submission/approval)
<b>Canada</b>	-	➤ no CoPP (submission/approval)
<b>Australia</b>	-	➤ no CoPP (submission/approval)
<b>Brazil</b>	+	➤ CoPP / under consideration or US application letter (submission) ➤ CoPP / marketed / any country (approval) <u>or</u> ➤ CoPP / registered / country of origin* (approval)
<b>Mexico</b>	+	➤ CoPP / under consideration (submission) ➤ CoPP / registered in EU, Australia, Switzerland, Brazil, Norway, New Zealand, USA, Iceland, Israel, Japan, Canada, preferable country of origin* (approval)
<b>Russia</b>	+	➤ CoPP / registered / country of origin* <u>or</u> any country + clarification why not registered in country of origin* (submission/approval)
<b>Ukraine</b>	+	➤ CoPP / under consideration (submission) ➤ CoPP / registered / country of origin* (approval)
<b>China</b>	+	➤ CoPP / marketed / any country (submission/approval)
<b>Japan</b>	-	➤ no CoPP (submission/approval)
<b>South Korea</b>	+	➤ no CoPP (submission) ➤ CoPP / marketed / any country (approval)

\* country of origin = country of manufacturing site

[source: company internal data base, status: September 2011]

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen  
als die angegebenen Hilfsmittel verwendet zu haben.

München, den 01. Mai 2012

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Carolin Wedel