Regulatory requirements related to the registration of generic orally inhaled drug products in the EU and US

–

A comparison of the European "stepwise approach" and US "weight of evidence approach"

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen

Fakultät der Rheinischen Friedrich-Wilhelms-

Universität Bonn

vorgelegt von

Carina Schunk

aus Mönchengladbach

Bonn 2019

Betreuer und 1. Referent: Dr. Birka Lehmann

Zweiter Referent: Dr. Ingrid Klingmann

Table of Content

List of Figures

List of Tables

General remarks

For ease of reading, the following simplifications have been made throughout the master thesis:

The "applicant" will be used interchangeably for the "sponsor" of a clinical study.

The terminology "bioequivalence" will be used interchangeably for the EU and US expressions, i.e. therapeutic equivalence and bioequivalence.

Both ICH regions share different positions whether an orally inhaled drug product can be considered generic or not, which will be discussed in detail in chapter "**3 Regulatory Pathways**." However, in order to facilitate reading it was decided to use the term "generic" consistently irrespective of the regulatory pathway.

List of Abbreviations

Abbreviation	Explanation
AMP	Adenosine monophosphate
ANDA	Abbreviated New Drug Application
APSD	Aerodynamic particle size distribution
AUC	Area under the plasma concentration curve
$AUEC_{0-t}$	Area under the effect curve calculated from zero time to the last measured activity
BE	Bioequivalence
Bio-IND	Investigational New Drug Application for Bioequivalence Studies
CE	Clinical endpoint
21 CFR	Code of Federal Regulations, Title 21 (US)
CHMP	Committee for Medicinal Products For Human Use
CI	Confidence interval
C_{max}	Maximum plasma concentration
COPD	Chronic obstructive pulmonary disease
CV	Coefficient of variation
DPI	Dry powder inhaler
DUSA	Dosage unit sampling apparatus
EC	European Commission
EEA	European Economic Area
e.g.	For example (exemplum gratum)
EMA	European Medicines Agency
eNO	Expired nitric oxide
EU	European Union
F	Relative bioavailability
FDA	Food And Drug Administration
FD & C Act	Federal Food, Drug, and Cosmetic Act
FPM	Fine particle mass
FEV_1	Forced expiratory volume in one second
FEV_{1max}	Maximum forced expiratory volume in one second
FEV_1AUC	Area under the FEV_1 curve
FPD	Fine particle dose
GDUFA	Generic Drug User Fee Amendments

Abbreviation	Explanation
GSD	Geometric standard deviation
HPA	Hypothalamic pituitary adrenocortical axis
ICH	International Conference On Harmonisation
ICS	Inhaled corticosteroids
ISM	Impactor-sized mass
IVIVC	In vivo/ *in vitro* correlation
LABA	Long-acting beta-2-agonist
LAMA	Long-acting muscarinic receptor antagonist
L/min	Liters per minute
mg	Milligrams
mcg	Micrograms
mL	Milliliters
(p)MDI	(Pressurised) metered dose inhaler
MMAD	Mass median aerodynamic diameter
MOC	Micro-orifice collector
NDA	New Drug Application
OIP	Orally inhaled product
Q1	Qualitatively the same composition (compared to reference product)
Q2	Quantitatively the same composition (compared to reference product)
QoL	Quality of life (questionnaire)
p	Probability value
PBE	Population bioequivalence
$PC_{20}FEV_1$	Concentration of provocation agent which produces a 20 % fall in FEV_1
$PD_{20}FEV_1$	Dose of provocation agent which produces a 20 % fall in FEV_1
PD	Pharmacodynamic
PEF	Peak expiratory flow
Ph. Eur.	European Pharmacopoeia
PIL	Patient information leaflet
PK	Pharmacokinetic
PKWP	Pharmacokinetic Working Party
PROMs	Patient reported outcome measures
PSD	Particle size distribution
RLD	Reference listed drug (US)

Abbreviation	Explanation
SABA	Short-acting beta-2-agonist
SAC	Single actuation content (US)
SmPC	Summary of product characteristics
t_{max}	Time to C_{max}
US	United States of America
USP	United States Pharmacopoeia

Acknowledgements

I would like to express my sincere thanks to Dr. Birka Lehmann and Dr. Ingrid Klingmann for the supervision, their useful remarks and highly appreciated feedback given during the preparation of my master thesis.

I would also like to thank Dr. Janet König for the constructive discussion and her thought-provoking impulses, which was very helpful for writing this work.

My special thanks go to my family and Fabian for their support and encouragement during the entire study period.

1 Introduction

The prevalence of respiratory diseases, such as asthma or chronic obstructive pulmonary disease (COPD), has increased worldwide in the past two decades [1–3]. This market has attracted interest for the pharmaceutical industry to develop new innovative drug products locally targeting the lungs. Under consideration of expiry of patents and data protection, the market for generic versions of these drug products experienced growth at the same time.

With focus on the European Union (EU) and United States of America (US) as the two biggest and highly regulated pharmaceutical markets [4] it becomes apparent that both regions have divergent views on recommendations and relevance of data required to grant approval for such rather complex generic drug products. Differences in regulatory approaches and regulatory frameworks between both regions pose therefore another burden for developers.

In general, orally inhaled products are categorized into three main delivery systems:

- device-metered (multi-dose) or pre-metered (unit-dose) dry powder inhalers,
- pressurised metered dose inhalers and
- drug products (solutions or suspensions) for nebulisation administered through a suitable nebuliser system.

The drug product performance does not solely rely on the drug product formulation itself. It is rather a function of the interaction between the device design, patient handling and formulation [5,6]. Due to this high complexity associated with these drug products, the development of generic orally inhaled drug products presents a rather unique challenge.

Therefore, the EU considers these drug products “non-standard” from a pharmaceutical perspective [7]. They are regulated as medicinal products according to Directive 2001/83/EC [8], where the inhaler is an integral part of the drug product. In contrast, a device-metered multi-dose inhaler, which can be reused by inserting a cartridge containing a powder reservoir, is subject to the medical device legislation [9]. Similarly, the US regards these drug products as critical products, which are treated as drug-device combination products consisting of a drug product and medical device constituent according to the definition laid down in 21 CFR 3.2(e) [10].

This master thesis elaborates on the regulatory approaches of the EU and US for the approval of generic orally inhaled products. Special focus hereby is on locally acting drug products for the treatment of asthma and COPD in adults. The comparison of the underlying requirements of both ICH regions aims to provide an overview of which considerations should be made throughout the pharmaceutical and clinical development to demonstrate bioequivalence. Ultimately, similarities and differences will be outlined in order to determine to what extent the development of these drug products can be harmonised.

General regulatory requirements concerning medical devices are out of scope of this master thesis and will therefore not be addressed.

2 Establishing Bioequivalence for Orally Inhaled Products

Unlike conventional orally administered dosage forms, such as film-coated tablets or capsules, orally inhaled products (hereafter 'OIPs') intended for the treatment of respiratory diseases are designed to act locally in the lungs. Consequently, the drug delivery is not necessarily directly linked to or rather dependent on the systemic circulation as illustrated in the subsequent figure.

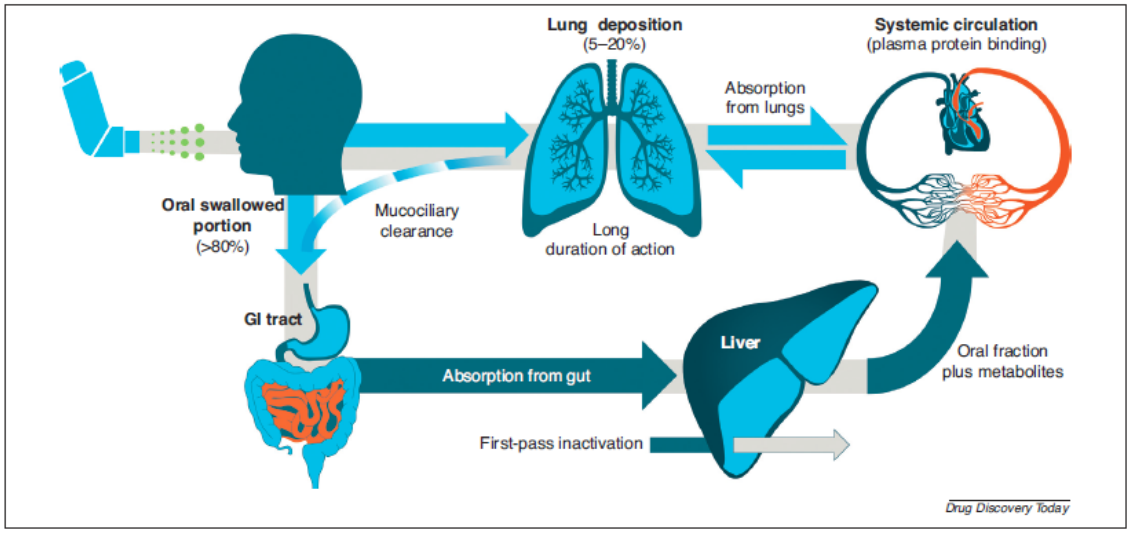

Figure 1 Metabolic pathway of locally acting orally inhaled products [11]

Rather, factors such as the drug product formulation but also the design and handling of the inhalation device play an important role with regard to the drug delivery and consequently the deposition pattern in the lungs [5,6].

Product dependent *in vitro* variables such as the delivered dose defined as the amount of drug substance released from the device (ex-actuator) or the aerodynamic particle size distribution (APSD) may also directly influence the airway deposition pattern. Additionally, drug delivery of dry powder inhalers can directly be influenced by the patient's inhalation manoeuvre [6], particularly where the generation of the aerosol is commonly driven by the patient's inspiratory flow.

Taking into account the aforementioned particularities, it becomes apparent that the traditional understanding of bioequivalence with regard to systemically acting drug products does not directly apply for OIPs. In addition, it should be noted that the general definition of bioequivalence differs among the regulatory regions EU and US.

The CHMP "Guideline on Investigation of Bioequivalence" (hereafter 'BE guideline') defines bioequivalence as follows:

> *"Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits* [12]*."*

According to this definition, it can be concluded that the term refers to the systemic exposure usually determined by pharmacokinetic (PK) studies [12]. Apparently, it is primarily reserved for drug products reaching their site of action through systemic circulation, whereas for locally acting OIPs the CHMP guideline uses the term "therapeutic equivalence" [13]. In contrast, according to 21 CFR 320.1 [14] FDA considers bioequivalence as

> *"the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study* [14]".

Hence, the US definition considers equivalence of the drug substance available at its site of action, which implies both systemically and locally acting drug products, i.e. including OIPs. This understanding is also substantiated by the following outtake of the Federal Food, Drug, and Cosmetic Act (FD & C Act) [15] where it states that

> "*For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect* [16]*."*

Consequently, following the aforementioned US definition, bioequivalence can also be demonstrated by using methods other than those used in pharmacokinetic studies (PK), for instance by pharmacodynamic (PD) studies provided they are sufficiently sensitive.

3 Regulatory Pathways

For a generic drug product to be authorised in the EU, the submission basis is defined by Article 10(1) and 10(2) of Directive 2001/83/EC [8]. Within this legal framework a generic drug product does not necessarily be equivalent to a reference medicinal product in every respect. In fact, demonstration of bioequivalence in terms of PK bioavailability is a prerequisite for a generic drug product being approved without performing new clinical trials and pre-clinical tests. Its marketing authorisation can be granted based on an abbreviated set of data encompassing *in vitro* data for evidence of consistent quality of the manufacturing process and in vivo bioequivalence studies [8].

However, due to the European definition of bioequivalence as specified in the preceding heading **"2 Establishing Bioequivalence for Orally Inhaled Products"** for which a generic is a product *"(...) whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies* [8]*"*, strictly speaking a generic OIP does not exist in the EU legislation. Instead, those drug products are required to be submitted pursuant to Article 10(3) of Directive 2001/83/EC as so-called "hybrid" or abridged applications as it states

> "*In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2 (b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-a`-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided"* [8].

Following this definition, bioequivalence of an OIP cannot be demonstrated through bioavailability studies. Neither can the term 'generic medicinal product' be applied as per definition pursuant to Article 10(1) of Directive 2001/83/EC [8].

In this respect, a drug product can be designated as a reference medicinal product, if it still is or has been authorised in the EU or rather European Economic Area (EEA) for at least ten years based on a full dossier [17]. This means approval has been granted based on a dossier covering data on quality, pre-clinical and clinical studies, pursuant to 8(3) ("full dossier") or 10b ("fixed dose combination") of Directive 2001/83/EC [8]. Finally, after expiry of data protection and under consideration of patents, the submission of generic applications pursuant to Article 10(1) of Direction 2001/83/EC [8]

or abridged applications pursuant to Article 10(3) of Directive 2001/83/EC [8] is generally accepted in the EU.

Considering the aforementioned differentiation between generic drug products and "hybrid" products, the dossier of an OIP "hybrid" product should include data relating to the drug product performance, i.e. quality, as well as pre-clinical and clinical equivalence studies. Consequently, an application pursuant to Article 10(3) of Directive 2001/83/EC [8] consists of both - in part of pre-clinical and clinical study results for a reference product and in part on new data [17]. In addition to the reference medicinal product for which reference has been made concerning its legal submission basis, the clinical equivalence studies have to be carried out with a reference product, which is part of the global marketing authorisation of the aforementioned reference medicinal product pursuant to Article 6(1) second subparagraph of Directive 2001/83/EC [8].

On the contrary, according to the US definition FDA allows filing of a generic application for OIPs. The legal submission basis is given under section 505(j) of the FD & C Act [15] through the Abbreviated New Drug Application (ANDA) process. This type of application is appropriate for drug products, which are identical, compared to an already approved listed drug in terms of the amounts of active ingredient(s), route of administration, dosage form, dose strength, labelling, quality, performance characteristics and intended use. It permits the approval "*on the basis of chemistry and bioequivalence data, without the need for evidence from literature of effectiveness and safety* [18]." These listed drugs can be found in the FDA's Orange Book [19], a database for drug products approved by FDA. A new dug product (listed drug) thereby can be designated as a reference listed drug (RLD) to which an application can refer to provided approval by FDA has been granted in accordance with section 505(c) of the FD & C Act [15]. Likewise to the EU requirements concerning the reference medicinal product, its application should be based on a complete dossier encompassing investigations of quality, safety and efficacy. The submission route pursuant to section 505(j) of the FD & C Act [15] is one of the abbreviated approval pathways for which the legal basis was amended through the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman Amendments").

Another pathway, similar to the European provision, is the submission of an "hybrid" application pursuant to section 505(b)(2) [15] as a new drug application (NDA). It is a partially abbreviated approval process for a drug product that has a significant difference, but is still similar compared to a RLD, which has been approved under 505(c) of the FD & C Act [15]. In turn, this implies that the proposed "hybrid" product

does not necessarily need to be bioequivalent to this previously approved product [16]. The provision of section 505(b)(2) [15] generally aimed to avoid unnecessary duplication of studies already carried out for a RLD in such a way that parts of the application dossier may rely on studies not conducted by the applicant himself, which is similar to the EU submission basis pursuant to Article 10(3) of Directive 2001/83/EC [8].

Once an RLD is identified by the FDA's Orange Book [19], this drug product must be referenced as legal submission basis. In view of the in vivo bioequivalence studies to be conducted FDA selects a reference standard, which can also be found in the FDA's Orange Book. Commonly, the RLD and the reference standard for the in vivo bioequivalence is the same drug as far as the RLD is available on the US market [20]. For this reason, reference is consistently made to the "RLD" in the following chapters.

4 EU Stepwise Approach

The European Union advocates a stepwise approach for the demonstration of bioequivalence of OIPs. Following this approach pursuant to the CHMP "Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) including the Requirements for Demonstration of Therapeutic Equivalence between two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and For Use in the Treatment of Asthma in Children and Adolescents" [13] (hereafter 'OIP guideline', currently under revision [21]), bioequivalence is established as soon as the requirements of one "step" are fully met. Approval can thus be granted in case of sufficient evidence.

These major steps include *in vitro* equivalence studies (step 1), pharmacokinetic studies (step 2) and pharmacodynamic studies/ clinical studies (step 3) as graphically illustrated in the subsequent figure.

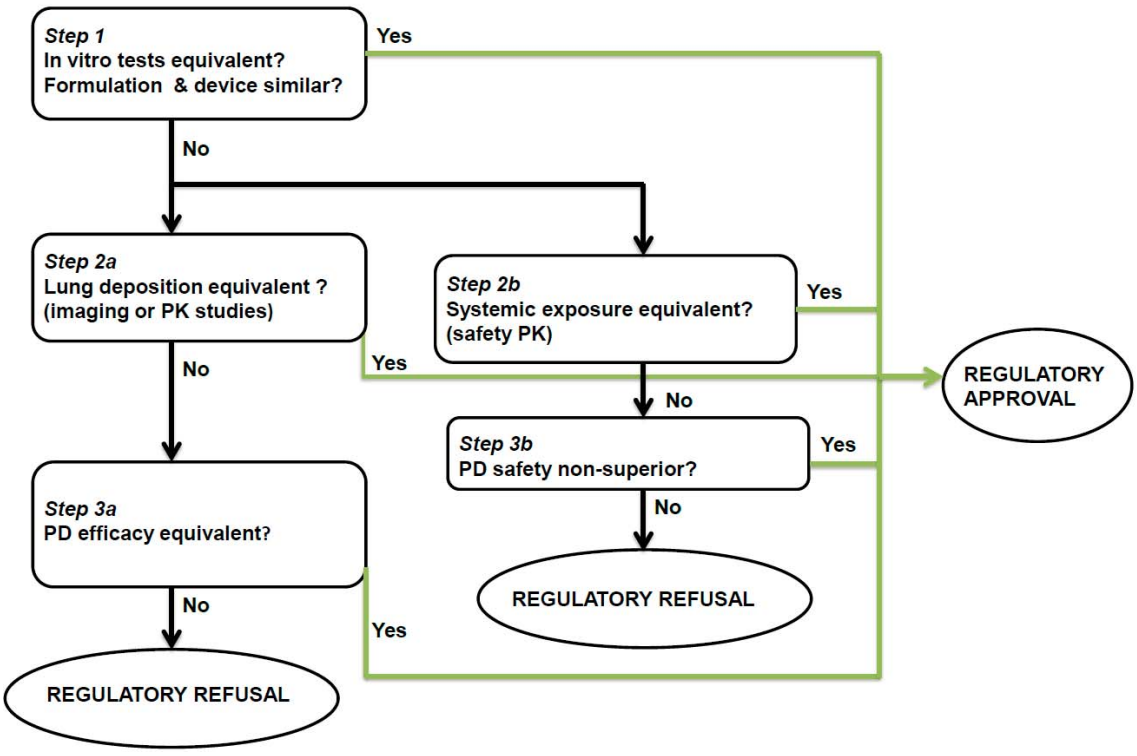

Figure 2 Schematic illustration of the stepwise approach advocated by CHMP

4.1 Step 1: *In vitro* studies

Generic products, i.e. oral dosage forms, can be approved based on *in vitro* data provided the acceptance criteria pursuant to the BE guideline are fulfilled [12]. With respect to locally acting orally inhaled products the use of *in vitro* data as surrogate for in vivo studies is also feasible as per EU jurisdiction, though no proper models for an in vivo/ *in vitro* correlation (IVIVC) has been established so far for specific products. According to the European perspective, this is not essential. The more important is the discriminatory power of *in vitro* methods assuming to be sensitive relating to the detection of drug product performance differences [22,23].

Equivalence criteria

In vitro studies might be sufficient for granting approval of OIPs containing known drug substances in cases unexceptionally all listed criteria prescribed as per OIP guideline [13] are satisfied:

- ✓ The drug product contains the same drug substance as the reference product in terms of the salt, ester, hydrate, solvate etc.
- ✓ The pharmaceutical dosage form is identical.
- ✓ In case where the drug substance is in the solid state, i.e. as a powder or suspension, different crystalline structures and/ or different polymorphic forms should do not affect the product performance.
- ✓ Qualitative and/ or quantitative differences in composition have no impact on the drug product performance or inhalation behaviour of the patient.
- ✓ Qualitative and/ or quantitative differences in composition do not affect the drug safety.
- ✓ The inhaled volume through the device is similar, i.e. 15 % deviation is allowed.
- ✓ The handling of the device is similar compared to the reference drug product.
- ✓ The device resistance is similar, i.e. 15 % deviation is allowed.
- ✓ The target delivered dose (ex-actuator) is similar, i.e. 15 % deviation is allowed.

Aerodynamic particle size distribution (APSD)

In addition to the above listed criteria, the complete APSD profiles determined by using validated multistage impactor or impinger methods should be similar.

Statistical assessment of differences should be based on the 90 % confidence interval (CI) preferably at each individual impactor stage or at grouped stages covering not less than four relevant groups. In this regard, the OIP guideline [13] suggests the 90 % CI

for the ratio of log transformed means of test product (this refers to the generic OIP) and the reference product (T/R), should not deviate more than 15 % (85.00 – 117.65 %). The choice of stages in case of grouping is in the responsibility of the applicant and needs to be justified based on the expected physiological lung deposition. In order to reflect the amount of drug substance reaching the lungs *in vitro* data encompassing the lower impactor stages representing the fine particle mass[1] should be submitted. In addition, information on the fraction potentially being swallowed is required, which is reflected by the upper stages of the impactor [13].

Furthermore, the mass median aerodynamic diameter (MMAD) should be calculated, defined as the diameter around which the mass aerodynamic diameters of delivered drug substance particles are equally distributed. The variability of the aerodynamic particle diameters can be measured by their geometric standard deviation (GSD), which is also an important statistical parameter required in the assessment of comparable APSD [24].

Concerning the extent of batches to be tested for the *in vitro* comparison, the guideline specifies a minimal number of three batches of the test product consecutively manufactured and three batches of the reference product. Due to the possibility of high variability between batches, (at least) three batches are required to compensate this variability and to provide *in vitro* results that are representative for the commercial product [13,22].

4.1.1 Analytical procedures

As the OIP guideline [13] only indicates, which equivalence criteria in terms of *in vitro* characteristics must be fulfilled, further guidance is needed concerning the required analytical procedures.

Analytical procedure for the determination of APSD or droplet size distribution

Generally, all generic OIPs need to be investigated for comparative APSD by a validated impactor method as previously specified in the beginning of paragraph "**4.1 Step 1: *In vitro* Studies**". Referring to this, the European Pharmacopoeia (Ph. Eur.)

[1] The fine particle mass represents the mass of particles, which are widely recognized as 5 micrometers or smaller, capable of reaching the lungs during inhalation of one actuation or dose of an OIP [24, 25]. Thus this fraction of the delivered drug substance is directly associated with the efficacy and safety of the drug product [13].

stipulates in the monograph 2.9.18 “Preparations for inhalation: aerodynamic assessment of fine particles” [25] the type of particle collecting apparatus, from which one should be chosen [apparatus A – glass impinger, apparatus C – multistage liquid impinger, apparatus D – Andersen cascade impactor, apparatus E – cascade impactor with seven stages and a micro-orifice collector (MOC)]. The corresponding test procedure and operating conditions depend on the pharmaceutical dosage form (**pMDIs** and **DPIs**).

For the investigation of the complete droplet size distribution of **solutions for nebulisation** the use of a laser diffraction method is acceptable according to the CHMP quality guideline on inhalation and nasal products [24] provided appropriately validated.

In vivo studies might be waived unexceptionally for this kind of OIPs, where the drug substance is completely solved in the formulation. Prerequisite is that the formulation is qualitatively and quantitatively the same compared to the reference product. However, similarity in terms of physicochemical characteristics, such as the viscosity or the pH, is also required [13,24].

Likewise as prescribed for pMDI or DPIs, the entire APSD over the individual cascade impactor stages should be compared for **suspensions for nebulisation** [13]. Ph. Eur. monograph 2.9.44 “Preparations for nebulisation: characterisation” [26] provides further details on the choice of apparatus and operating conditions. However, it is stressed in the OIP guideline [13] that generally in vivo studies should be carried out for this kind of OIP.

Analytical procedure for the determination of delivered dose

Furthermore, except of products for nebulisation, the target delivered dose needs to be determined for all OIPs, specified as the dose, which is delivered to the patient coming out of the actuator of the device (ex-actuator) [24].

The mean delivered dose as well as its uniformity should be analysed using the dosage unit sampling apparatus (DUSA) and the corresponding test procedure specified in the general Ph. Eur. monograph “Preparations for inhalation (0671)” [27]. For pressurised and non-pressurised metered dose inhalers a fixed flow rate of 28.3 L/min should be applied.

4.1.2 Particularities depending on the pharmaceutical dosage form

Investigation of flow rate dependency of DPIs

Comparative *in vitro* data for DPIs should also encompass investigations of flow rate dependency obtained with clinically relevant flow limits, i.e. a justified range of flow rates representative for the concerned patient population the reference product has been approved for. These tests aim to determine any deviations in drug product performance in terms of delivered dose uniformity and fine particle mass [24], which is in particular relevant for breath-operated DPIs [13]. In this respect, OIP guideline [13] recommends the investigation of the minimum, median and maximum flow rate as a surrogate for the peak inspiratory flow the intended patient population is capable of.

Specific analytical methods required for nebulisation products

With respect to nebulisation products, in principle all *in vitro* investigations need to be generated with the same nebuliser and respective settings as used in the clinical studies. Information on the certain nebuliser system used in the development of the drug product should be indicated in the summary of product characteristics (SmPC) and patient information leaflet (PIL) [13]. Specific *in vitro* parameters for this kind of products are the output rate and total drug output, which also need to be compared with those of the reference product [24].

Use of spacers/ valve holding chambers for pMDIs

Furthermore, regarding pMDIs the APSD behaviour of the test product should also be compared with the reference product using a spacer or a valved holding chamber as these devices increase the amount of fine particles reaching the lungs while reducing the oropharyngeal drug deposition during the administration of the drug product [13,24]. This is of special interest e.g. for orally inhaled corticosteroids when the orally inhaled product is intended to be applied in paediatrics (or elderly) as spacers aim to enhance the drug therapy by simplifying the coordination of device actuation and simultaneous inhalation and by reducing the amount of swallowed fractions.

As this master thesis primarily addresses generic OIPs in the adult patient population, this issue is solely mentioned for the sake of completeness of European requirements.

4.1.3 Investigation of multiple strengths products

With respect to multiple strengths products, the OIP guideline [13] stipulates the investigation of dose linearity *in vitro* both for the test product and for the reference product across all strengths. Further details on *in vitro* parameters to be tested are given thereof in the "Quality question & answers" by the EMA [28]. These recommendations specify that the entire APSD, preferably in single impactor stages with a maximum allowable deviation of 15 %, should be investigated at clinically relevant flow ranges. If the investigations are not successful for either product, they are not deemed equivalent [13].

If dose linearity has been confirmed at *in vitro* level, bioequivalence might be established in vivo via PK studies with only one of the dose strengths proposed [26]. On the other hand, in case of non-linearity across the range of relevant flow rates, CHMP recommends equivalence should be established by PK studies with a so called bracketing approach. These studies should explore the extremes of strengths, i.e. those, which were the most similar and the most different during *in vitro* comparison studies [28]. Further details on the choice of dose strength to be tested in the PK studies, if required, will be presented in the following paragraph of this master thesis.

4.2 Step 2: Pulmonary deposition studies

If the claim of therapeutic equivalence cannot be supported at *in vitro* level, it may be established by demonstration of equivalent pulmonary deposition along with data that support adequate safety of the test product versus the reference product. This approach applies for single entity drug products as well as for fixed dose combination products, which contain more than one drug substance [13,29]. Concerning equivalent pulmonary deposition two study types are generally accepted by CHMP, i.e. pharmacokinetic studies and imaging studies.

4.2.1 Pharmacokinetic studies

Purpose of PK studies

Within the European jurisdiction PK studies are utilized to measure the pulmonary absorption of the inhaled drug substance in the lungs for the assessment of equivalent efficacy of two drug products. Furthermore, PK studies aim to demonstrate that the test product provides a comparable systemic exposure and is consequently comparably

safe with regard to the reference product [13].

Study design

The European jurisdiction envisages double blind, crossover PK studies using doses and dose strengths clinically relevant [13]. With respect to the doses to be tested recommendations of the BE guideline [12] should be considered in conjunction to the specific recommendations for OIPs [13]. According this guideline it is generally acceptable to perform the study at several dose levels including doses exceeding the highest therapeutic dose (supra-therapeutic dose) [12]. This will increase the sensitivity of the PK study, which is known to be required in some cases due to insufficient measurable plasma concentrations [13].

Unlike the recommendations for PK studies specified for orally applied dosage forms, the OIP guideline advocates that these studies should be carried out in the target population [13]. However, it is acknowledged by now that the recruitment of healthy subjects reduces the variability in lung deposition or systemic exposure [30]. Provided both products do not show any or at least a similar *in vitro* flow rate dependency with regard to the fine particle dose (the amount of fine particles per dose, FPD) and APSD with a justified range of flow rates (commonly 30 – 90 L/min), CHMP accepts the enrolment of healthy subjects [28]. Only under these conditions, it might be possible to extrapolate the outcome of PK studies from healthy volunteers to the intended patient population.

Bioequivalence parameters and criteria

The evaluation of equivalence should be based on conventional bioequivalence criteria, which are the maximum or peak plasma concentration (C_{max}), the area under the plasma concentration curve (AUC) and time to C_{max} (t_{max}). For the primary variables, AUC and $C_{max,}$ the two-sided 90 % confidence interval (CI) of the test product (T) and the reference product (R) ratio T/R should be within the range of 80.00 % - 125.00 % [13].

In view of the assessment of pulmonary deposition, the extent of deposition is reflected by AUC representing the amount of drug substance, which has reached the lungs. Its pattern on the other hand is mirrored by the shape of the AUC during the phase of drug absorption and is characterized by C_{max} and t_{max} [31].

Variation of these equivalence criteria is only accepted and might be necessary under the subsequent conditions: The OIP guideline [13] prescribes tighter limits for drug

substances with a narrow therapeutic index, which however are not further specified in this guidance. Therefore, it might be reasonable to apply the limits proposed in the BE guideline [12], where a range of 90.00 - 111.11 % is envisaged for AUC_{0-t} and C_{max}. Since there is no exhaustive list of criteria that defines "*narrow therapeutic index drugs"* [12] in the EU, it is always a case by case decision that should be made on clinically and scientifically sound reasons.

Choice of suitable matrix

According to OIP guideline [13] either plasma or urinary PK studies are acceptable options to evaluate the lung absorption, but without an explicit recommendation on the sampling schedule. However, since the OIP guideline specifies bioequivalence criteria relevant for the assessment of blood samples (C_{max}, t_{max}, AUC) as evidence for the drug exposure, it is assumed that plasma PK studies should be preferred. Even for orally applied drug products the BE guideline [12] explicitly restricts the use of urinary data for determination of systemic exposure to cases when AUC cannot reliably be measured for the parent drug.

Choice of analyte

With reference to the BE guideline [12] plasma concentrations of the active metabolite should only be chosen for the evaluation of bioequivalence in certain justified circumstances. Thus, PK data of the parent drug should be the first choice as its C_{max} is considered to be more sensitive in detecting differences in drug formulation.

However, in certain circumstances, such as

- the plasma concentration of the parent drug is too low to be reliably measured with the applied bioanalytical method,
- the parent drug exhibits a rapid metabolism or elimination,
- the bioanalytical method provides a low sensitivity for the parent drug or
- the formation of the metabolite is not saturated at clinical standard doses,

the measurement of the metabolite could be accepted in the bioequivalence-decision making [12].

Expected extent of PK studies

Pulmonary deposition as surrogate for efficacy

Demonstration of equivalent pulmonary deposition as surrogate for efficacy may be investigated by PK studies or by lung imaging scintigraphy of radiolabelled OIPs, which is further described under the heading "**4.2.2 Imaging studies**" [13]. In order to capture solely the amount of drug substance absorbed from the lungs, exclusion of gastrointestinal absorption due to potentially swallowed fractions must be guaranteed. EU legislation recommends the use of a validated charcoal block thereof. This might be in particular of high importance with regard to drug substances with high bioavailability where the potential unknown contribution to the systemic circulation should be avoided [13,22].

Total exposure as surrogate for safety

Generally, a second PK study without the use of charcoal block is required for the establishment of bioequivalence of OIPs in the EU. This type of PK study is accepted as surrogate in the assessment of systemic safety effects since the absorption in the lungs as well as in the gastrointestinal tract can be measured [13]. Consequently, equivalent systemic safety can be concluded in case of equivalent systemic exposure measured by AUC and C_{max} [31].

Generally, PK studies on systemic exposure (without charcoal block, surrogate for safety) are required by CHMP. However, in certain circumstances, PK studies on the pulmonary deposition (with charcoal block, surrogate for efficacy) can be omitted:

Only one PK study without charcoal can be accepted for both the assessment of safety and efficacy when the drug substance is poorly absorbed in the intestine or is subject to a pronounced first-pass effect (e.g. known for the inhaled corticosteroid fluticasone) [31].

By contrast, in the event of significant intestinal absorption of the drug substance, two PK studies are required – one study for the assessment of safety without charcoal block and another study for the assessment of efficacy in the presence of charcoal. This is particularly necessary when the oral and pulmonary absorption of drug substance cannot be separated from another [32].

Multiple dose strengths products

As already described in subparagraph "**4.1.3 Investigation of multiple strengths products**" it is sufficient for a multiple dose strengths product to assess PK criteria of only one dose strength. However, the so called biowaiver claim for the remaining dose strengths is only acceptable in case of *in vitro* dose linearity.

According to the BE guideline [12] it is generally accepted by CHMP to conduct the PK study with the highest dose strength provided the drug product exhibits a linear pharmacokinetic. Furthermore, there should be no safety or tolerability reasons. In this respect, a linear pharmacokinetic between is confirmed if the "*difference in dose-adjusted mean AUCs is no more than 25 %"* [12].

In order to overcome detection limits of the PK and thus to enhance assay sensitivity a commonly acceptable method is to perform the investigations at several dose levels [33]. This is also in line with the recommendations of the current version of the OIP guideline [13] though it suggests the investigation of the lowest strength instead of the highest dose strength. These discrepancies will hopefully be considered in the guideline revision [21].

Taking into account the complexity of those drug products and the ordinarily low amount of drug substance concentration to be measured in plasma relating thereto, the investigation of the highest strength seems to be reasonable. That is why it is often the most sensitive strength towards the detection of differences in product formulations, which is the prerequisite to waive in vivo bioequivalence studies for the other strengths [12].

A bracketing approach, as specified in the aforementioned subparagraph of this master thesis, might be acceptable in case demonstration of *in vitro* dose linearity failed [31].

High inter-/ intra-batch variability of the reference product

It is known that the drug product performance of OIPs can significantly be affected due to storage or rather aging effects in terms of the APSD or the amount of fine particle dose [32]. This is most importantly challenging when the reference product is concerned. Variability within one batch (intra-variability) as well as between batches (inter-variability) might aggravate the *in vitro* comparison of a generic product. Therefore, CHMP recommends the analysis of several batches of both products in regard of differences in APSD or FPD to identify representative batches that can be used to establish bioequivalence. These investigations should be carried out prior to in

vivo PK and PD studies and should cover a minimum of five or six batches from the reference product from different EU markets. Variation of maximum 15 % in terms of the APSD or FPD is acceptable [28,31].

Highly variable drugs/ high intra-subject variability

Furthermore, the question arises whether widening of bioequivalence acceptance limits would be an option to overcome a potential high intra-subject variability associated with the reference product. In this regard, a high variability is defined by the coefficient of variation (% CV), which is larger than 30 % [12].

CHMP clearly discourages scaling of acceptance limits in case of variable amounts of FPD of different reference product batches. In contrast, C_{max} might be expanded to a maximum range of 69.84 – 143.19 % provided *in vitro* properties were shown to be equivalent [12,29]. The extent of widening of the acceptance range for C_{max} depends on the extent of the "within subject CV" and should be specified in the study protocol prior to conduct of the PK study [12]. It should be stressed that especially for OIP the extension of the acceptance limit for C_{max} may be acceptable up to a maximum of 75 – 133 % [13]. However, with any extension of acceptance limits, which need to be clinically justified, CHMP stipulates a replicate study design [12,31].

4.2.2 Imaging studies

Lung imaging through gamma scintigraphy of a radiolabelled drug substance is one further way to demonstrate equivalent lung deposition between test product and reference product. These studies aim to quantify the regional lung deposition within the different zones of the lungs [13].

However, due to limitations of the imaging studies associated with the bioequivalence decision making the current OIP guideline [13] clearly states that these studies cannot replace PK efficacy studies. These data should rather serve as being supportive for the evaluation of therapeutic efficacy and should be substantiated with PK studies or clinical studies [13]. In the course of the revision of the OIP guideline [13], this subchapter will probably be revised as suggested in the "Concept paper on revision of the guideline on the requirements for clinical documentation for orally inhaled products (OIP) (...)" [21]. For this reason, these studies are solely listed for completeness.

4.3 Step 3: Pharmacodynamic studies

At the last step of the European stepwise approach, PD studies (or clinical studies) are required in cases where *in vitro* studies and PK data were insufficient or failed to demonstrate therapeutic equivalence. In that sense these studies aim to provide evidence that differences in PK do not alter the safety or efficacy level of the test product compared to the reference product [13].

In case the approved indication of the reference product covers both asthma and COPD, therapeutic equivalence studies are required only in one population. Preferably these studies should be performed in asthma patients since easier to carry out. Moreover, it seems evident to enrol asthma patients as the recommendations concerning the study program given in the OIP guideline [13] specifically focus on this kind of patient population. However, key prerequisite to receive a marketing authorisation in both indications is the successful *in vitro* performance concerning APSD across the flow rates and pressure drop ranges clinically relevant for all intended patient populations [13].

Key prerequisite of PD efficacy and safety studies is the assay sensitivity, which enables the differentiation of efficacy and safety of treatments or rather formulations [13,34]. Sensitivity is confirmed when one of two studied "*non-zero"* dose levels shows superiority [13]. Consequently, a minimum of two dose levels should generally be investigated for both products. It is in particular important that investigations of these dose levels occur at the steep part of the dose-response curve in order to draw a reliable and valid conclusion on therapeutic equivalence of both products [13].

General considerations concerning demonstration of equivalent efficacy

Statistical approaches

General suggestions are made regarding the approach on how the dose-response relationship may be analysed as a crucial factor of the evaluation of PD efficacy study outcomes. The EU jurisdiction requires the calculation of relative potency or rather dose-scale, which expresses the ratio of biological activity of the test product and reference product or in other words, it represents the dose of the test product which creates the same biological effect as "*one unit of the dose of the reference product*" [13]. Additionally, the response-scale analysis should be used to analyse the equivalence of both products by comparing PD endpoint results for both products at a minimum of two dose levels [13].

Equivalence criteria

Concerning equivalence criteria CHMP does not give any detailed recommendations. Suggestions are solely made for acceptance criteria regarding the relative potency analysis, i.e. a range of 67 – 150 % is stipulated. [13].

General considerations concerning demonstration of equivalent safety

Following the general suggestions for demonstration of equivalent systemic exposure and consequently equivalent safety, evaluation should be "*based on pharmacokinetic data, relevant cardiovascular, biochemical and physiological parameters, and monitoring of adverse effects*" [13]. Regardless of the therapeutic class of drug substance, the safety profile should be always be analysed in PD studies focusing on safety at the highest recommended dose level. In addition to purely safety PD studies, CHMP stipulates that safety should also be monitored in efficacy studies irrespective of the studied dose level [13]. Study models and corresponding PD endpoints or biomarkers generally differ depending on the characteristics of each therapeutic class of drug substance, i.e. bronchodilators and inhaled corticosteroids [13].

Equivalence criteria or non-inferiority margin

With regard to acceptance criteria OIP guideline [13] leaves a margin for the applicant as no limits are specified. There should be solely no evidence that the test product is worse compared to the reference product in terms of safety variables tested and adverse effects [13]. Thus, it can be concluded that it is sufficient to demonstrate that the generic product is non-superior. In this context, PKWP also states that the total exposure of the test product should be lower compared to the one of its reference product (i.e. 90 % CI should be below 125.00 %) [31]. Taking into account that clinical studies are also acceptable to demonstrate equivalence at "step 3" of the stepwise approach, it seems to be more appropriate in line with the CHMP "Guideline on the choice of the non-inferiority margin" [35] to define a "non-inferiority margin" rather than "equivalence criteria."

4.3.1 Bronchodilators

Inhaled bronchodilating agents can generally be categorised into three classes, namely short-acting beta-2-agonists (SABA), long-acting beta-2-agonists (LABA) and inhaled anticholinergics or long-acting muscarinic receptor antagonists (LAMA). According to the OIP guideline [13] recommendations for study designs both for demonstration of

PD efficacy and safety of these drug substance classes resemble each other. Nevertheless, they need to be modified depending on their respective PD properties.

Efficacy

Study design

The measurement of the bronchodilation effect can directly provide evidence of equivalent efficacy of two compared inhaled bronchodilators. Thus, the conduct of bronchodilatation studies is one acceptable study design. Another option is the investigation of the test product's ability to protect the lungs against bronchoprovocative agents, so-called bronchoprotection studies [13].

In this respect, there are two ways of investigations: On the one hand, directly provoking agents such as methacholine, acetylcholine or histamine can be used. On the other hand, studies can be performed with indirect provoking agents such as adenosine monophosphate (AMP) or mannitol. According to the OIP guideline [13] the applicant may decide whether to conduct one or both study types.

For both types of efficacy studies the OIP guideline [13] favours a single-dose, double blind, double dummy cross-over design using two dose levels for each product (i.e. a four armed study). This implies both a suitable washout phase between treatments and the measurement of a baseline prior to each treatment [13].

Primary endpoint of bronchodilatation studies

For SABA, LABA and (short- and long-acting) anticholinergics CHMP recommends the same endpoints or rather biomarkers, but notes that different PD characteristics, especially the onset of action, duration of effects and the maximum response need to be considered in the design of the study, respectively. As primary efficacy variable serves the change in forced expiratory volume in one second (FEV_1) measured at appropriate time points. Furthermore, the area under the FEV_1 curve (FEV_1AUC) should be measured over at least 80 % of duration of action after one single inhalation [13].

Primary endpoint of bronchoprotection studies

For both types of investigations OIP guideline [13] recommends to monitor the concentration or dose of the provocating agent resulting in a 20 % reduction of FEV_1 ($PC_{20}FEV_1$ or $PD_{20}FEV_1$) as primary variable. The primary endpoints are the same for

SABA, LABA and anticholinergics, though the provocation agent should be a cholinergic agonist when studying anticholinergics.

Study population

Both PD models should enrol *"patients with asthma who demonstrate reversibility of airway function"* [13]. Reversibility of airway function implies in this regard the improvement in FEV_1 of ≥ 12 % and ≥ 200 mL 15 minutes after the administration of a SABA (such as salbutamol sulfate) [13].

Safety

Investigation of safety in terms of total exposure should primarily be carried out through PK studies, if feasible, following one single dose. However, if PK studies fail or the concentration is too low to be reliable measured by PK, PD studies should be performed to demonstrate equivalent safety.

The same study design as favoured for PD efficacy studies should be used.

Vital signs, biochemical parameters and frequency of adverse effects should be recorded and evaluated for all types of bronchodilators at the maximum recommended dose [13]. Since it is known that safety effects are often not observed at clinical (approved) doses [22,36]. It is, however, accepted to carry out the safety PD study at supra-therapeutic doses. Commonly, healthy volunteers are recruited as they are not confounded by conditions of their disease [22].

4.3.2 Inhaled corticosteroids

In contrast to bronchodilating agents, the demonstration of bioequivalence through PD or clinical studies seems to be notably challenging for inhaled corticosteroid (ICS) due to a flat dose-response curve [13,23]. This is particularly highly significant for the demonstration of systemic efficacy through PD studies, which impedes the evidence of assay sensitivity [13].

Efficacy

Study design

Two PD models (bronchodilatation studies and bronchoprovocation studies after chronic dosing) are applicable for demonstration of comparative efficacy of ICS in the EU [13].

It should be noted that the focus of bronchodilatation studies in this context is on the measurement of improved airway function due to the anti-inflammatoric properties of ICS rather than on the direct assessment of bronchodilatation. A double-blind, randomized parallel group study design should be adopted for both PD models. Alternatively a double-blind, randomized crossover study design with suitable washout periods and baseline measurements at the beginning of each treatment might be accepted by EU jurisdiction, but should be justified along by literature [13].

The favoured study design should cover at least two doses of the test product and reference product (i.e. four treatment arms) at the steep part of the dose response curve. It is emphasised on the potentially need of multiple actuations to obtain the required dose. As this might pose a higher safety risk for the patient, the use of an OIP with a higher strength product might be acceptable in this case. Justification for the choice of strength should cover *in vitro* data supporting dose proportionality. Each dose level should be administered for at least four weeks [13].

Study population

Patients recruited for bronchodilatation studies with ICS *"should have demonstrable room for improvement in pulmonary function to respond differently to the two doses/strengths of the inhaled corticosteroid and should be symptomatic"* [13]. In addition, patients should be responsive to ICS and as homogenous as possible to enhance the sensitivity to detect formulation differences [13]. For bronchoprotection studies CHMP only states that subjects should be "*representative of the target population but with recruitment of patients with mild asthma and known bronchial hyperresponsiveness* [13]."

Primary endpoints for bronchodilatation studies

FEV_1 measured on a regular basis daily at home should serve as primary efficacy variable, if feasible. Alternatively the peak expiratory flow (PEF) measured in the morning and recorded daily at home might be accepted. This biomarker is also

accepted as secondary efficacy variable or alternatively, the FEV_1 measured in the clinic at a minimum interval of two weeks [13].

Primary endpoints for bronchoprotection studies

The envisaged primary efficacy variable is the observed change in provocative concentration or dose of a provoking agent such as AMP that produces a 20 % reduction of FEV_1 ($PC_{20}FEV_1AMP$ or $PD_{20}FEV_1AMP$). As secondary variable "*symptom scores, percentage of symptom-free days frequency of use of reliever/rescue medication and exacerbation"* [13] should be gathered. Since there is to date less experience with this PD model in demonstration of equivalent efficacy, the biomarker is required to be justified based on its assay sensitivity and has consequently to be validated.

Further efficacy endpoints are solely briefly listed, which are the expired nitric oxide (eNO), sputum eosinophils, validated quality of life (QoL) questionnaire and validated patient reported outcome measures (PROMs) [13].

Safety

In case PD safety studies are required, i.e. when PK failed to demonstrate equivalent safety, they aim to assess the effect on the hypothalamic pituitary adrenocortical axis (HPA axis). AUC and C_{max} should be calculated during 24 hours measurement of plasma cortisol and the change from the recorded baseline of both parameters should be repeatedly assessed. No specific study duration is pre-defined, but the OIP guideline [13] underlines that steady-state must be reached.

There are also no specific restrictions made with respect to the study population or study design. It is simply stated that PD safety studies should involve patients with asthma, but it is highlighted that measurements are to be "*carried out in a controlled, fully tested environment* [13]*."*

4.3.3 Fixed dose combination products

For fixed dose combination products containing more than one drug substance bioequivalence needs to be demonstrated for each component. In general, the study design is dependent on the specific drug substance as specified in subsections of "**4.3 Step 3: Pharmacodynamic studies.**"

For a commonly used fixed dose combination of ICS and LABA one study might be accepted by CHMP for demonstration of equivalent efficacy and safety. However,

regarding the demonstration of efficacy co-primary variables should be defined for each component, respectively. For a statistically meaningful dose-relationship two doses of test product and reference product need to be investigated [13].

The other option is the investigation of therapeutic equivalence by means of two single studies, one for each drug substance. With respect to efficacy for the LABA component, one single dose should be studied for using the bronchodilation study or bronchoprotection study design. On the contrary for demonstration of equivalent efficacy of the ICS component multiple applications over time are recommended [13].

4.3.4 Multiple strengths products

In case of multiple strengths products it is required to test only one dose strength. As already discussed in previous sections, the major prerequisite is the successful demonstration of *in vitro* dose linearity. Due to safety reasons it is commonly accepted to test solely the lowest dose strength [13]. However, in practice, the choice of dose strength to be tested mainly depends on the outcome of PK studies. This implies that the strength, which failed in the PK studies to demonstrate equivalent efficacy or non-superiority with respect to safety, needs to be chosen for PD studies.

5 US Weight of Evidence Approach

The FDA endorses an integrated approach concerning the approval of generic OIPs, which stems from the authorisation of the Generic Drug User Fee Amendments (GDUFA) in 2012 and pre-GDUFA research activities [37]. In this way FDA aimed to enhance the understanding of various characteristics of bioequivalence of OIPs, which were still found being a challenge.

Pursuant to the schematic overview of the weight of evidence approach presented in figure 3, comparative *in vitro* tests, PK studies, PD or clinical studies in humans, formulation and device similarities (and the patient compliance in terms of the exchangeability relating thereto) are closely linked from the FDA's point of view and should therefore be considered in a holistic way.

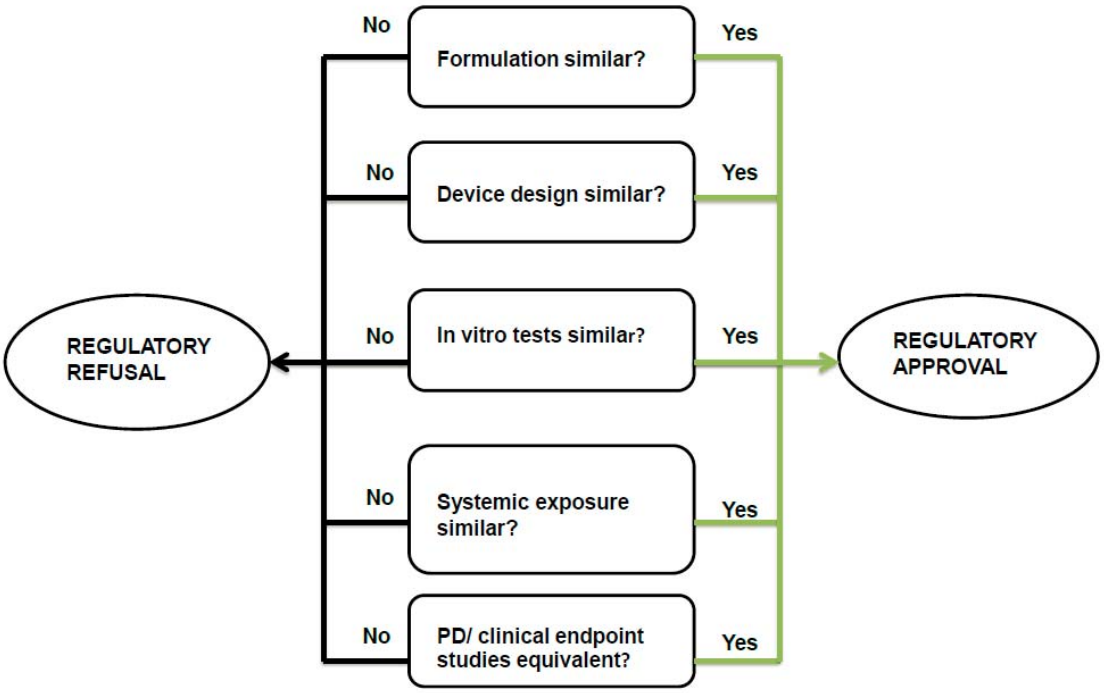

Figure 3 Schematic illustration of the US weight of evidence approach

As a result of GDUFA funded research projects, guidance documents tailored for specific drug products containing one or a combination of two drug substances, were published on FDA's homepage in the recent years [38]. These cover different

pulmonary dosage forms, such as metered dose inhalers (MDIs)[2], dry powder inhalers (DPIs) or solutions/ suspensions for nebulisation, which are still in the draft status.

The first product-specific guidance for OIPs was released in 2012, in particular for suspensions for inhalation (nebulisation) containing the ICS budesonide [39]. In 2013 further guidance documents followed, particularly for MDIs containing the SABA albuterol sulfate[3] [40] and for DPIs containing a combination of the ICS fluticasone propionate and LABA salmeterol xinafoate [41]. All product-specific guidances for OIPs have in common that they provide detailed recommendations on the study design of *in vitro* tests, PK studies, PD or clinical studies and further additional remarks concerning the inhalation device, where applicable.

The subsequent sections highlight the particular requirements for the study programs of various types of OIPs currently awaited by FDA.

5.1 *In vitro* studies

In the opinion of the FDA the implications of *in vitro* tests intended to detect differences in drug product performance for the product quality, safety and efficacy of the patient are still not well understood. On these grounds, there could be no clear *in vitro*/in vivo correlation established so far. Either no reliable laboratory techniques are available to directly determine the lung deposition of OIPs [37].

5.1.1 Particularities depending on the pharmaceutical dosage form

Based on the product-specific guidances published by FDA, *in vitro* tests and corresponding analytical procedures are outlined in the following abstracts as required for each dosage form.

General recommendations concerning choice of batches

Whenever approval is applied for DPIs or MDIs with several strengths, the comparative *in vitro* tests discussed below should be conducted for all strengths. In order to get meaningful results investigations for all OIPs should cover at least three batches of test product and the RLD with at least ten inhalers per batch.

[2] The US uses the term “metered dose inhalers” for inhalation aerosols, which are equivalent to “pressurised metered dose inhalers” in the EU.
[3] Albuterol sulfate is the US synonym for salbutamol sulfate, which is the commonly used term in the EU.

Dry powder inhalers

Up to now (status as of 31st July 2019), FDA published fourteen product-specific guidances for dry powder inhalers containing a single drug substance as well as a combination of ICS and LABA [38]. Further details concerning currently published draft product-specific guidance documents concerning dry powder inhalers are outlined in *Annex I* of this master thesis.

For demonstration of equivalence between the test product and the corresponding RLD *in vitro* tests should encompass the following product performance characteristics.

The **single actuation content (SAC)** of the test product and the RLD should be compared at the beginning, middle and end lifestages of the respective drug product[4] according to USP monograph <601> [54] using apparatus B (DUSA) or another validated method. The drug products should be tested at a specified range of flow rates (i.e. at 31.5 L/min, 63.0 L/min and 94.5 L/min or at 30 L/min, 60 L/min and 90 L/min) [41–53,55]. The population bioequivalence (PBE) approach should be used for statistical evaluation of SAC results, which assumes a log normal distribution [56].

The second required method is the comparison of the **aerodynamic particle size distribution** at the beginning and end of lifestage of the drug product. The procedure should be performed according to USP <601> [54] using apparatus 3 (Andersen Cascade Impactor), apparatus 5 or another validated method. The respective apparatus should be operated at a specified range of flow rates (i.e. at 28.3 L/min or 31.5 L/min, 63.0 L/min and 94.5 L/min or at 28.3 L/min or 30 L/min, 60 L/min and 90 L/min) [41–53,55].

The product-specific guidance documents do not recommend a specified minimum number of required actuations, but stipulates to analyse the minimum number of actuations, which is justified by the sensitivity of the method. For statistical evaluation FDA recommends to use PBE for the analysis of impactor-sized mass (ISM) defined as the sum of drug substance mass deposited at all cascade impactor stages except of the top stage, but including the terminal filter. With respect to the extent of APSD analysis FDA requires the determination of drug deposition of each single impactor stage including demonstration of mass balance. MMAD, GSD and FPM should be indicated as supporting evidence of comparable APSD profiles [41–53,55].

[4] According to the FDA definition, the beginning (B), middle (M) and end (E) lifestages of the drug product refer to the respective labelled number of actuations:
B = first actuation(s) following the respective priming actuations, M = corresponding to 50 % of actuations in the label and E= corresponding to labelled number of actuations [41–53].

Metered dose inhalers

Regarding metered dose inhalers, eleven draft product-specific guidances are available so far (status as of 31st July 2019) covering the subsequent mono- and fixed dose combination products (see *Annex I* for an overview*).*

The *in vitro* testing program for demonstration of bioequivalence of MDIs should cover the subsequent analytical procedures:

Like recommended for DPIs, the **SAC** as well as the **APSD** should be analysed and compared with the RLD. The analytical procedures are very similar to the ones of DPI analyses, but vary in the apparatus to be chosen and operating flow rates.

For SAC analysis USP <601> [54] apparatus A (or another validated method) should be used, which should run at a fixed flow rate of 28.3 L/min. The comparison of APSD of MDIs should be carried out according to USP <601> [54] using apparatus 1, apparatus 6 (Next Generation Impactor) or another validated method. A fixed flow rate of 28.3 L/min or 30 L/min should be applied for these investigations.

Statistical evaluation of the comparison of SAC and APSD is carried out on the basis of bioequivalence criteria applied for DPIs [40,57–66].

Furthermore, the **spray pattern**, a product performance test for the actuator and valve, should be compared with that of the RLD. The test procedure should be carried out at the beginning of lifestage of the drug product. FDA recommends characterisation of the spray pattern profile of one spray at a minimum of two determined distances from the actuator mouthpiece. Characterisation can be carried out by different analytical methods, such as impaction (thin-layer chromatography place impaction) or non-impaction (laser light sheet technology) methods.

Equivalence should be based on both qualitative comparison of the spray shape and quantitative results of "*PBE analysis of the ovality ratio and area within the perimeter of the true shape or ovality ratio and D_{max}*"[5] [40,57–66].

A further product performance test is the dimensional characterization of **plume geometry**, defined as the side view of the plume [67]. Characterisation of the test product and the RLD should be performed at the beginning of the lifestage of the

[5] The ovality ratio is defined as the ratio of the longest diameter (D_{max}) and the shortest diameter (D_{min}). Both of the aforementioned diameter units should "*pass through the center of mass or center of gravity"* [40,57–64]*.*

product using the "*time sequence sound-triggered flash photography method, laser light sheet technology"* [40,57–64] or another appropriate method.

Equivalence is confirmed in case the geometric mean of the three test product and RLD batches for the parameters plume angle and width lies within 90 – 111 % [40,56–[40,57–66].

The required numbers of actuations wasted for initial **priming and repriming** of the MDI after a defined time of non-use should be characterized based on the emitted dose (ex-actuator) generated from one single actuation. Corresponding test conditions should be based on information provided in the instructions for use of the RLD and should also take into account the storage of the product in the valve upright or valve inverted position. Characterisation of priming can be accepted by using SAC data at the beginning of lifestage of the drug product.

Equivalence should be based on the PBE analysis of the emitted dose of one SAC following the required number of priming or repriming actuations as per labelling of the RLD [40,57–66].

Solutions and suspensions for nebulisation

For generic products for nebulisation, including solutions and suspensions, only one guidance document was published so far (status as of 31st July 2019 [39]), namely for budesonide suspension for inhalation in three different dose strengths (0.25 mg/ 2mL, 0.5mg/ 2mL, 1mg/ 2mL).

Solely for generic suspensions for inhalation containing budesonide FDA might grant approval where bioequivalence is demonstrated based on *in vitro* data only. However, the basic prerequisite for this approach is the fulfilment of all subsequent listed characteristics exemplified for the highest dose strength of budesonide suspension for inhalation. The evaluation of equivalence concerning these *in vitro* tests should be based on PBE analysis [39].

- ✓ The drug substance exhibits the same polymorphic form.
- ✓ The drug substance provides the same crystalline shape.
- ✓ The content of the drug substance in the ampoule is comparable.
- ✓ The mean nebulisation time and mean delivered dose is comparable.
- ✓ The drug particle and agglomerate particle size distribution (PSD) of the suspension in the ampoules is comparable.

- ✓ The "*drug particle and agglomerate PSD*"[6] [39] in the aerosol is comparable. The tests should be based on the requirements of USP <1601> [68] by explicitly using the Pari LC Plus Nebulizer or Pari Master compressor system. For determination of the PSD USP <601> [54] apparatus 5 should be chosen operated at a fixed flow rate of 15 L/min. For the APSD profile, the drug deposition on the induction port, all singe stages cascade impactor stages, the sum of back-up filter and the micro-orifice collector should be measured.
- ✓ The nebulised aerosol exhibits a comparative droplet size distribution measured by a laser diffraction method.

With regard to the middle and lowest dose strength (0.5 mg/ 2mL or 0.25 mg/mL) FDA may also accept an "*in vitro* only approach" under the following circumstances:

In case the lower strength exhibits the same physicochemical characteristics, such as the particle size, PSD, polymorphic form and particle shape compared to the RLD, the investigation of the lower strength may be sufficient [39].

- ✓ The bioequivalence of the higher strength should be documented based on comparable *in vitro* data as listed above.
- ✓ The drug particle and agglomerate PSD in the suspension is comparable.
- ✓ The drug particle and agglomerate PSD in the aerosol is comparable.
- ✓ The content of the drug substance per ampoule is comparable between the respective lower strengths of test product and RLD.
- ✓ The mean nebulisation time and the mean delivered dose is comparable.
- ✓ The mean delivered dose ratio of the higher and lower strength of test product and RLD, respectively, resembled each other.

If not all criteria are met, equivalence should be substantiated by in vivo PK and PD or Clinical Endpoint (CE) studies [39].

5.2 Formulation and device design

FDA generally recommends for all pharmaceutical dosage forms that the test product should be both qualitatively (Q1) and quantitatively (Q2) the same as its RLD. This implies the use of the same drug substance (Q1) and a maximum deviation of 5 % concerning excipients (Q2) compared to the RLD. Any higher deviation in the

[6] This US term corresponds to the APSD commonly used in the EU.

quantitative composition should be adequately justified. Furthermore, the choice of composition should be substantiated by *in vitro* data of formulations with different ratios of drug substance and excipients [39–53,55,57–66,69].

With respect to the device design development, recent published DPI and MDI product-specific guidances from 2017 onwards require studies to identify and assess design differences between the generic device and the reference device. They also require to consider outcomes from comparative human factor studies, where applicable [45,46,48,50,53,55,61,65,66,69].

The main goal of these studies is to provide evidence that a potential switch of the RLD to the generic drug product does not interfere the safe and effective use by the user or rather patient [70]. In this regard, FDA provides further details on how deviations from the RLD's user interface should be evaluated on a risk-oriented basis [70]. Concerning both DPIs and MDIs user interface factors are defined by "*all components of the combination product with which the user interacts"* [70] and cover consequently external critical design attributes of the device, such as displays, the labelling information or feedback and control mechanisms [71].

FDA provides exact details on design factors for DPIs and MDIs, which an applicant needs to take into consideration in the development of a generic OIP. These aspects will be presented hereafter. By contrast, products for nebulisation are marketed separately from their recommended administration device just like in the EU. Consequently, there are no specific requirements related to the device design of a nebuliser system. However, FDA recommends to use the same nebuliser system as specified in the label of the RLD [39].

Considerations with respect to device design of DPIs

The development of a generic DPI including the metering device should take into consideration the overall design of the reference DPI. These requirements include design factors of the reference DPI such as

- the energy source, i.e. whether the device is actively actuated by a pressing an activating button on the device (active device) or triggered by the patient's inspiratory flow (breath-actuated, passive device) [42–53,55,69],
- the principle of dose metering (e.g. device-metered multi-dose format with a powder reservoir [41–47,51,53,55,69] or pre-metered single-dose format such as capsules) [48,49,52],

- the presence of a dose counting mechanism [41–47,51,53,69],
- the handling procedures or external operating principles including cleaning requirements [42–53,69],
- the physical appearance in terms of size and shape of the device [42–53,55,69] and
- the device resistance [42–53,55,69].

Furthermore, the recently published product-specific guidance for fluticasone propionate DPI requires the generic DPI to exhibit a comparable number of doses [55].

Considerations with respect to device design of MDIs

The requirements by FDA concerning device design of MDIs encompass the similarity of the shape and size and the presence of a dose counter [40,57–64]. Similarly as stipulated for specific DPI, the recently published product-specific guidances for fluticasone propionate MDI [61], beclomethasone dipropionate MDI [65] and fluticasone propionate/ salmeterol xinafoate MDI [66] require the generic versions to exhibit comparable number of doses.

5.3 Pharmacokinetic studies

Purpose of PK studies and study design

For the establishment of bioequivalence between two OIPs, PK studies should be conducted to demonstrate equivalent systemic exposure of the respective drug substance of the test product and the RLD. The study design of PK studies for OIPs resembles the one for conventional drug products, such as orally administered solid dosage forms [72]: According to the draft product-specific guidance documents for OIPs FDA advocates a single-dose, crossover PK study in fasting state carried out in healthy volunteers (males and non-pregnant females) [39–53,55,57–66,69].

Dose selection

The minimum number of inhalations of the test product and RLD should be selected such that the characterisation of an accurate PK profile is feasible measured by a sensitive validated bioanalytical procedure. In case the intended study dose exceeds the maximum single dose of the drug product label an investigational new drug application for bioequivalence studies (Bio-IND) must be filed according to 21 CFR 320.31(b) prior to the start of the PK study [42–46,48–51,53,55,59,61–66].

Bioequivalence parameters and criteria

Equivalence is demonstrated, if the 90 % CI of the geometric means of test product and RLD (T/R) ratio of AUC and C_{max} is within the range of 80.00 – 125.00 % [39–53,55,57–66,69].

Choice of suitable matrix and analyte

The draft product-specific guidance documents for OIPs recommend to measure the parent compound in plasma, which is in line with the general recommendations for generic products filed under ANDA [73].

However, there are exceptions, where the evaluation of bioequivalence should be based on the active metabolite: In case of beclomethasone dipropionate MDI [59,65], primarily the active metabolite beclomethasone 17-monopropionate should be measured. This seems comprehensible since it is known that beclomethasone dipropionate is metabolised rapidly in the liver, which aggravates the measurement of the parent compound [31]. As no equivalence criterion is specified for the parent compound it is concluded that these data serve as supportive data [59,65].

Other biological fluids are recommended for ciclesonide MDI [60], namely measuring of the parent compound as well as the active metabolite des-ciclesonide in serum. Equivalence criteria have been established solely for the active metabolite here as well [60].

High variability of reference product batches and high intra-subject variability

Concerning highly variable drugs in relation to the RLD, such as levalbuterol tartrate MDI [57], FDA highlights the possibility to apply the reference-scaled average bioequivalence approach, which is though not solely limited to OIPs. Prerequisite in support of this approach is a high variability in AUC and / or C_{max} whereby the “within-subject CV (%)” is at least 30 % [57]. Equivalence is evaluated by scaling to the variability of the RLD [74]. For detailed information on the statistical analysis of this alternative approach, reference is made to the draft product-specific guidance for progesterone capsules [75].

With respect to systemically acting drug products, FDA generally endorses a replicate study design in case of highly variable drugs [73]. However, no overall guidance on a consistent strategy addressing this issue associated with OIPs is available to date.

Therefore, it is advisable to discuss any alternative PK study design with the FDA in a product development meeting prior to conduct of the study [32,76].

5.3.1 Fixed dose combination products

Previously published product–specific guidance documents for ICS/LABA combinations, exhibit in general the same requirements concerning study design, choice of subjects, dose selection and choice of biological matrix and analyte as applicable for the mono formulations. However, equivalent systemic exposure must be demonstrated for both drug substances contained in the combination products [41,42,63,64,66].

5.3.2 Multiple strengths products

From the present FDA's point of view the relationship among dose proportionality across multiple strengths studied in vivo by PK and *in vitro* performance attributes as well as the link to formulation characteristics of the OIP is not (yet) well understood. Consequently, PK studies in the light of demonstration of bioequivalence of OIPs are mandatory across all dose strengths [72].

5.4 Pharmacodynamic or clinical endpoint studies

Additional PD studies or CE studies are required by the US to complement the evaluation on equivalence between two OIPs. These in vivo studies focus on the assessment of equivalence with regard to clinical effects (efficacy).

From the perspective of the FDA an adequate dose-response relationship of a biomarker is generally of high importance, particularly for PD studies. Consequently, the PD study should be designed in such a way that differences in drug delivery to the lungs of two OIPs can be detected. Historically speaking a PD study was thus preferred over a CE study due to a higher discriminating power concerning formulation differences [72]. Taking into account the aforementioned aspects the FDA is of the opinion that this approach is, however, not feasible for all therapeutic classes or rather drug substance classes [71,72].

Based on the information provided in the product-specific guidances for OIPs it cannot be generalised which type of in vivo study (PD study or CE study) is recommended for each drug substance class. Therefore, it was decided to present the recommendations

in view of the choice and design of the respective study by using examples for each drug substance class. For further information a tabulated overview of key aspects of these studies taken from recently published product-specific guidances for OIPs can be found in *Annex I*.

Along the stipulations concerning study design, primary endpoints and equivalence criteria, which will be specified in the following paragraphs, FDA's draft product-specific guidance documents provide further detailed information concerning the following aspects:

- inclusion and exclusion criteria concerning the choice of study subjects (commonly males and non-pregnant females with asthma or COPD),
- the recommended sampling schedule,
- suggested duration of the study and
- further recommendations important for study planning and evaluation for the respective drug product [39–53,57–65,69].

Due to extensive information behind the above listed aspects, they will not be discussed in more detail.

5.4.1 Bronchodilators

Short-acting beta-2-agonists

With respect to SABA (e.g. albuterol sulfate [40,69] or levalbuterol tartrate [57]) two PD study models are generally considered to provide an adequate dose-response relationship, i.e. bronchodilatation and bronchoprotection studies [72].

For both PD models FDA favours a single-dose, double-blind, double dummy, randomized cross-over study design with at least four arms (two arms for two different doses of the RLD, one dose of the test product and one dose of the placebo) and a minimum of a 24 hours washout period between treatments.

Primary endpoints for the bronchodilatation study should be pre-defined as the areas under the effect curve calculated from zero time to four hours ($AUEC_{0\text{-}4h}$) and from zero time to six hours ($AUEC_{0\text{-}6h}$). The maximum forced expiratory volume in one second or rather peak effect (FEV_{1max}) should also be measured as primary endpoint, which should generally be baseline adjusted. As primary endpoint of the bronchoprotection study should serve the determination $PC_{20}FEV_1$ *or* $PD_{20}FEV_1$ after administration of metacholine agent.

Based on a non-linear dose-response relationship of PD endpoints [71] equivalence should rest on the dose-scale analysis of study results (E_{max} model), which is applicable for both PD models [40,57,69].

Concerning details on the statistical model it is referred to the draft product-specific guidance document for orlistat oral capsules [77]. The 90 % CI for the relative bioavailability (*F)*, which *"is the ratio of the doses of test and reference formulations that produce an equivalent PD response"* [77], should lie within the range of 67.00 – 150.00 % [40,57,69].

Long-acting beta-2-agonists

For LABA (e.g. formoterol fumarate [52]) PD studies are accepted. A randomized, single-dose, placebo-controlled cross-over or parallel-group study design with three treatment arms (test product, RLD and placebo) should be envisaged. The area under the serial FEV_1 curve calculated from zero to 12 hours ($AUC_{0\text{-}12h}$ (27)) on the first day of treatment should be defined as primary endpoint, which also needs to be baseline adjusted. Equivalence is confirmed in case the 90 % CI for the T/R ratio for the primary endpoint lies within 80.00 – 125.00 % [52].

Long acting-muscarinergic antagonists

The recommendations concerning study design and equivalence evaluation of anticholinergics is in general similar to those of LABA. For aclidinium bromide [47], for example, a PD study is recommended with a single-dose cross-over or parallel group design. The study should be randomized, blinded where possible and placebo-controlled. Like stipulated for LABA the measurement of serial FEV_1 or rather the area under the serial FEV_1 time curve ($AUC_{0\text{-}6\ h}$) is recommended as primary endpoint. A necessary condition is again that FEV_1 baseline values are measured. Equivalence should be based on the same criteria as recommended for LABA [47].

5.4.2 Inhaled corticosteroids

The majority of the published draft product-specific guidance documents FDA recommends CE studies for demonstration of equivalence in terms of ICS. For fluticasone furoate MDI [44] for example, a randomized, multiple-dose, placebo-controlled parallel group design with three treatment arms (test product, placebo and RLD) should be adopted. Change of FEV_1 on the last day of treatment from the base-line should be measured and defined as primary endpoint. Test product and RLD are

considered equivalent in case the 90 % CI of the T/R ratio for the primary endpoint lies within 80.00 – 125.00 % [44].

5.4.3 Fixed dose combination products

FDA recommends the performance of CE studies for fixed dose combinations of ICS/LABA (status as of 31st July 2019) with the exception of the combination mometasone furoate/ formoterol fumarate MDI [64].

Exemplified for fluticasone propionate/salmeterol xinafoate DPI [41] a randomized multiple-dose, placebo-controlled, parallel group design with three treatment arms (test product, placebo and RLD) should be envisaged. Bioequivalence study endpoints and equivalence criteria are similar to those recommended for the salmeterol xinafoate DPI (22) and fluticasone propionate MDI or DPI [45,55,61] mono-formulations:

The 90 % CI T/R ratios for the area under the serial FEV_1-time curve calculated from time zero to 12 hours (AUC_{-0-12h}) on the first day of treatment [41,53] and FEV_1 measured in the morning prior to the application of the medication on last day of the treatment [41,45,55,61] should lie within 80.00 – 125.00 % [45,53,55,61].

5.4.4 Multiple strengths products

In case approval is applied for multiple strengths, it is acceptable to investigate the lowest strength as recommended in the product-specific guidance documents by FDA [39–53,55,57–66,69].

6 Summarized Overview of EU and US Requirements

Key characteristics of *in vitro*, PK and PD studies of both approaches are outlined in the subsequent tables for a simplified overview. A detailed discussion concerning these aspects will follow in the next chapter "**7 Similarities and Differences of EU and US Requirements.**"

With regard to the tabular summaries, the following comments are made.

Table 1 summarises the EU and US requirements with respect to *in vitro* studies to be conducted to demonstrate equivalence of two OIPs. There are additional tests, which are only required for MDIs in the US, namely the investigations of spray pattern, plume geometry and priming and repriming. Since these tests have already been specified in the previous chapter "**5.1.1 Particularities depending on the pharmaceutical dosage form,**" they will not be repeated at this point.

With respect to PD studies, it was decided to contrast solely characteristics of PD efficacy studies as outlined in **Table 4** since in the US demonstration of equivalent safety is not foreseen via this kind of in vivo study.

Table 1 Overview of key characteristics of *in vitro* studies - EU versus US

EU [13]	**US** [39–53,55,57–66,69]
DPIs and pMDIs/ MDIs	
Delivered dose (EU)/ Single actuation content (US)	
Acceptance criteria: Target delivered dose ± 15 % of R Analytical method: Ph. Eur. 0671 DUSA, at three different flow rates determined via PIFR studies (DPI) or apparatus A at one fixed flow rate (pMDI)	Acceptance criteria: at B, M and E life stages (by PBE analysis) Analytical method: USP <601> apparatus B (DUSA) at three predefined flow rates (DPI) or apparatus A at one fixed flow rate (MDI)
Aerodynamic particle size distribution (APSD) and fine particle mass (FPM)	
Acceptance criteria: DPI/ pMDI: Each single impactor stage or ≥ 4 justified grouped stages (including FPM): 90 % CI of T/R ± 15 % (85.00 – 117.65 %); comparison of MMAD and GSD (supportive) Analytical method: Ph. Eur. 2.9.18 [25], impinger or impactor operated at three different flow rates determined via PIFR studies (DPI) or at one fixed flow rate (pMDI)	Acceptance criteria: DPI/ MDI: PBE analysis of ISM; all single impactor stages to be tested at B and E lifestage of the drug product; comparison of MMAD, GSD and FPM (supportive) Analytical method: USP <601> [54], impinger or impactor operated at three predefined flow rates (DPI) or at one fixed flow rate (MDI)

Table 2 Comparison of the EU and US "*in vitro* only approach"

<table>
<tr><th>EU</th><th>US</th></tr>
<tr><td>Solutions for nebulisation [13,24]</td><td rowspan="4">Suspensions for nebulisation [39]
Comparable in vitro parameter
PBE analysis of the following in vitro characteristics:
✓ Same qualitative and quantitative formulation
✓ Same polymorphic form determined by X-ray diffraction
✓ Same shape in terms of crystalline structure
✓ Comparable unit dose content (ampoule)
✓ Comparable mean nebulisation time and mean delivered dose
✓ Comparable PSD of the drug substance in the suspension (ampoule)
✓ Comparable APSD of the nebulised aerosol by cascade impactor
✓ Comparable droplet size distribution by laser diffraction</td></tr>
<tr><td>Comparable in vitro parameter</td></tr>
<tr><td>✓ Same qualitative and quantitative formulation
✓ Droplet size distribution by laser diffraction (Ph. Eur. 2.9.13)
✓ Comparable physicochemical properties such as viscosity, pH
✓ Same output rate, total drug output</td></tr>
<tr><td>All dosage forms (except of suspensions for nebulisation) [13]
Comparable in vitro parameter</td></tr>
<tr><td>✓ Same drug substance (salt, ester, hydrate, solvate etc.)
✓ Identical pharmaceutical dosage form
✓ Solid drug substances: differences in crystalline structure or polymorphic forms have no impact on product performance
✓ Qualitative/ quantitative differences in composition have no impact on drug product performance or inhalation behaviour
✓ Qualitative/ quantitative differences in composition have no impact on safety
✓ Same inhaled volume ± 15 %
✓ Similar handling of the device
✓ Similar device resistance ± 15 %
✓ Target delivered dose ± 15 %
✓ Comparable APSD (stage wise/ justified pooled stages): 90 % CI within 85 – 117.68 % (after log transformation)</td></tr>
</table>

Table 3 Overview of key characteristics of PK studies - EU versus US

Criteria of PK studies	**EU** [13]	**US** [39–53,55,57–66,69]
Objective	Comparison of pulmonary deposition (surrogate for efficacy, with charcoal block) and systemic exposure (surrogate for safety, without charcoal block)	Comparison of systemic exposure (surrogate for safety)
Study design	Crossover, double blind, single-dose [13], in fasting state [12]	Crossover, single-dose in fasting state
Study subjects	Adults of intended patient population [13], healthy accepted [12]	Healthy male and non-pregnant healthy female subjects
Choice of dose	most sensitive or highest dose	Minimum number of inhalations, which is sufficient to characterise PK profile by using a sensitive analytical method
BE parameters	C_{max}, $AUC_{(0-t)}$, (secondary variable: t_{max})	C_{max}, AUC
Equivalence criteria	90 % CI of T/R ratio within geometric means of area under the curve (AUC) within 80.00 – 125.00 % Stricter limits for drugs with narrow therapeutic window: not yet specified in OIP guideline; 90.00 – 111.11% for AUC, and C_{max} according to BE guideline [12].	90% CI of T/R ratio within geometric means of area under the curve (AUC) and C_{max} within 80.00 – 125.00 %

Table 3 Overview of key characteristics of PK studies - EU versus US (continued)

Criteria of PK studies	**EU** [13]	**US** [39–53,55,57–66,69]
Matrix	Plasma (or urine)	Plasma (exception for ciclesonid MDI: serum [60])
Analyte	According to BE guideline parent drug should be analysed, but active metabolite could be accepted in certain circumstances [12].	Parent drug should be analysed with the following exceptions: beclomethasone dipropionate MDI [59], ciclesonid MDI (50) (No acceptance criteria established for parent compound)
Highly variable drugs (reference product)	Wider BE criteria (C_{max}): 90 % CI within 75 – 133 % (replicate study design and clinically justified)	Use of reference-scaled average bioequivalence approach

Table 4 Overview of key characteristics of PD efficacy studies – EU versus US

Criteria of PD studies	**EU** [13]	**US**
Objective	Comparison of safety and efficacy	Comparison of efficacy
Statistical approach	Relative potency analysis (dose-scale analysis) and response-scale analysis	**SABA** (albuterol sulfate [40,69]: dose-scale analysis (E_{max} model) No specific statistical approaches stipulated for LABA, LAMA and ICS
Study design	**Bronchodilators (SABA, LABA and LAMA)** Bronchodilatation and bronchoprotection study Single-dose, double blind, double dummy, cross over, two dose levels (four treatment arms) **ICS** Double-blind, randomized, parallel group design; alternatively: double-blind, randomized, cross-over design, two dose levels (four treatment arms), chronic dosing for at least 4 weeks (bronchoprotection study)	**Bronchodilators** **SABA** (e.g. albuterol sulfate [40,69]) Bronchodilatation study and bronchoprotection study Single-dose, double-blind, double dummy, randomized cross-over study design with at least four arms (two different doses of R, one dose of T and one dose of P) **LABA** (e.g. formoterol fumarate ([52])) Randomized, single-dose, placebo-controlled, cross-over or parallel-group study design with three treatment arms **LAMA** (e.g. aclidinium bromide [47]) Randomized, blinded where possible, placebo-controlled, single-dose cross-over or parallel group design with three treatment arms **ICS** (e.g. fluticasone furoate [44]) Randomized, multiple-dose, placebo-controlled, parallel group design with three treatment arms, 4 weeks

Table 4 Overview of key characteristics of PD efficacy studies – EU versus US (continued)

Criteria of PD studies	**EU** [13]	**US**
PD primary endpoints	**Bronchodilators (SABA, LABA and LAMA)** Bronchodilatation study change in FEV_1 or FEV_1 AUC (bronchodilatation over at least 80 % of duration of action after one single inhalation) Bronchoprotection study $PC_{20}FEV_1$ or $PD_{20}FEV_1$ **ICS** Bronchodilatation study FEV_1 measured on a regular basis daily at home, if not possible: morning PEF measured daily at home Bronchoprotection study $PC_{20}FEV_1AMP$ or $PD_{20}FEV_1AMP$	**Bronchodilators** **SABA** (albuterol sulphate [40,69]) Bronchodilatation study ($AUEC_{0\text{-}4h}$), ($AUEC_{0\text{-}6h}$), and FEV_{1max} Bronchoprotection study $PC_{20}FEV_1$ or $PD_{20}FEV_1$ **LABA** (e.g. formoterol fumarate [52]) $AUC_{0\text{-}12\ h}$ **LAMA** (e.g. aclidinium bromide [47]) $AUC_{0\text{-}6\ h}$ **ICS** (e.g. fluticasone furoate [44]) Change of FEV_1 on the last day of treatment from base-line
Equivalence criteria	**Applicable for all therapeutic classes** 90% CI within the range of 67 – 150 % (relative potency analysis)	**SABA** [40,69] 90 % CI for relative bioavailability within 67.00 – 150.00 % **LABA** [52], **LAMA** [47] and **ICS** [44] 90% CI for the T/R within 80.00 – 125.00 %

7 Similarities and Differences of EU and US Requirements

In many respects it is apparent that the EU and the US pursue distinctly different overall strategies for regulatory approvals of generic OIPs. However, both ICH regions share generally the same principle features, namely *in vitro* tests, PK, PD studies, device similarity and similarity of formulations.

While the EU may grant approval at each development step (*in vitro* tests covering device similarity, PK and PD studies) provided certain equivalence criteria are fulfilled, the US only accepts the entire data set of these investigations. However, it should be noted that approval for most EU applications for generic OIPs have been granted based on PK studies [31].

These different evaluation strategies are not surprising taking into account the different review strategies of the EU and US: It is commonly known that FDA takes a so-called "bottom-up" approach to review extensive raw data in the course of a marketing authorisation application while in the EU the "top down" approach usually permits to rely on summarized data. This attitude is also reflected in the different guidance of both authorities: CHMP exhibits an overall leading guideline for all generic OIPs, which consequently leaves a margin for the applicant regarding the development of his product. On the other hand, FDA published specific drug product guidance documents, which precisely provide recommendations concerning all required studies to be conducted.

However, in principle similarities can be found amongst these overarching differences when contrasting both approaches. The main issues of this comparison focus primarily on the characteristics of *in vitro*, PK and PD studies, which have already summarized in tabular in the previous chapter "**6 Summarized Overview of EU and US requirements**."

7.1 Choice of reference product

Prerequisite of an EU marketing authorisation for a drug product submitted under article 10 (3) of the Directive 2001/83/EC [8] is the demonstration of equivalence to a reference product, which is or has been authorised in any EU country or EEA (including Norway and Iceland). This means this product needs to be authorised based on a complete dossier including the quality documentation and own clinical and pre-clinical

data. Similarly, a RLD chosen for an ANDA or an NDA under section 505(b)(2) of the FD & C Act [15] needs to be approved in the US based on a full dossier under section 505 (c) of the FD & C Act [15].

Comparable regulatory requirements apply to the choice of reference product used in the in clinical equivalence (in vivo bioequivalence) studies:

In the EU CHMP requires that a drug product intended to be used as reference product in the in vivo BE studies is part of the global marketing authorisation from a reference medicinal product as per Article 6(1) second subparagraph of Directive 2001/83/EC [8]. This in turn requires that this drug product is sourced from the European market [12].

In a similar manner, FDA only accepts reference products in the in vivo bioequivalence studies, which are designated as reference standard or rather RLD and consequently drug products, which are approved in the US [19].

7.2 *In vitro* studies

The main *in vitro* characteristics, which are required in the establishment of equivalence of two OIPs in the EU and US, have been summarized in chapter "**6 Summarized Overview of EU and US requirements**" for a simplified overview. These and other aspects of *in vitro* product performance characteristics of both ICH regions will be contrasted in the subsequent paragraphs:

Concerning the *in vitro* characteristics, which are crucial for drug product performance and consequently linked to the safety and efficacy of DPI and MDI, both authorities require the comparison of **APSD and the emitted dose**. Apparently there are differences concerning the European and US terminology for the emitted dose, namely delivered dose (EU) and single actuation content (US), though they refer to the same product characteristic [13,40–42,44–53,55,57–66,69].

However, with respect to the analysis of APSD the US seems to be stricter as pooling of stages is apparently not permitted in contrast to the EU. In the EU, FPM should be considered separately in the analysis of APSD, either presented in addition to the comparison of single stages or as part of justified grouped stages. Furthermore, the comparison of FPM is an integral part of the evaluation of *in vitro* equivalence characteristics. The US, on the other hand, only requires the comparison of FPM as supportive data [13,40–42,44–53,55,57–66,69].

The **analytical procedures** according to Ph. Eur. 2.9.18 [25] and USP <601> [68] are in principle similar – i.e. impactor or impinger methods are accepted. The required number of **flow rates** is also the same (i.e. three flow rates), which is required for DPI to demonstrate a consistent drug product quality over a flow rate range simulating use under intended patient populations. CHMP leaves a margin for the applicant as solely a range of clinically relevant flow rates is stipulated [13], whereas the FDA recommends fixed flow rates within their product-specific guidance documents, which might derive from the development experience of the approved reference listed drug [41–53,55,69].

Equivalence criteria differ in both jurisdictions: In the EU equivalence is based on numerical criteria or point estimates (i.e. for delivered dose) or 90 % CI for the log transformed means of T/R ratio [13]. However, in the US equivalence rests mainly upon PBE analysis of *in vitro* parameters [40–42,44–53,55,57–66,69].

Further tests are required by the FDA for demonstration of equivalent MDIs in particular comparison of spray pattern, plume geometry and specific requirements concerning priming/ repriming. These *in vitro* characteristics are generally not required in the EU in the context of demonstration of bioequivalence, but can serve as supportive data. CHMP could, however, require the comparison of plume geometry in case of abridged applications ("*in vitro* only approach"). In this context this specific *in vitro* characteristic could be utilised to confirm that differences in the composition of an MDI do not alter the behaviour of aerosol particles. Tests on priming/ repriming conditions of a pMDI container is an important product performance characteristic generally required in the EU to be tested within the pharmaceutical development [24] (just like for the US [78]), but is not necessarily used to determine bioequivalence of two products.

EU and US share a similar opinion concerning the challenge of an IVIVC used to predict lung deposition arising from the pharmaceutical and physiological properties of OIPs [13,37].

Nonetheless, EU allows waiving of in vivo PK and/ or PD studies in the following two cases:

Abridged applications based on *in vitro* data are accepted when the test product showed equivalence to the reference product by satisfying all *in vitro* characteristics according to chapter "5.2 Known active substance" of the OIP guideline [13], which is addressed in subparagraph "**4.1 Step1: *In vitro* studies**" of this master thesis. This is generally applicable for all orally inhaled products, except of suspensions for nebulisation for which in vivo studies are generally requested in the EU. Another option

of waiving studies in human subjects exists for solutions for nebulisation provided the test product has the same qualitative and quantitative composition compared to the reference product [13].

FDA, on the other hand, may accept the application for a generic OIP based solely on *in vitro* data in case of budesonide suspension for nebulisation [39]. The *in vitro* tests cover physicochemical properties of the drug substance, such as the polymorphic form, PSD of the drug substance or crystalline structure and typical product performance characteristics, such as the mean nebulisation time or APSD of the aerolised suspension for nebulisation, which resemble in principle criteria of the "*in vitro* only approach" of the EU [13,39].

7.3 Pharmacokinetic studies

Unlike in the US, PK studies in the EU are accepted to compare pulmonary deposition as surrogate for efficacy by preventing gastrointestinal absorption through the use of charcoal block. The investigation of equivalent systemic exposure as surrogate for safety is required in both ICH regions.

A crossover, double blind study in healthy volunteers [31], originally the target patient population [13], is envisaged by CHMP. Similarly, US requires a single-dose, two-way crossover PK study in healthy volunteers [39–53,55,57–66,69].

Concerning the **choice of dose** it is generally accepted to conduct the study at supra-therapeutic doses to enhance assay sensitivity [12], whereas the US product-specific guidance documents do not specify a concrete dose. Instead a minimum number of inhalations of both products is recommended which enables the characterisation of the PK profile by using a sensitive validated analytical method [39–53,55,57–66,69].

In the EU and US equivalence is based on the same **parameters**, i.e. C_{max} and AUC , and the same equivalence criteria: the 90 % CI of test product to reference product (T/R) ratio within geometric means of the AUC and C_{max} should fall within 80.00 – 125.00 % [39–53,55,57–66,69].

CHMP may accept wider limits in the event of **high intra-subject variability** of the reference product (90 % CI for C_{max} should fall within a maximum range of 69.84 – 143.19 %), in case of a clinical justification, but requires in this case a replicate study

design. The current version of the OIP guideline [13] in contrast recommends a maximum range of 75 – 133 %.

To overcome a potential variability within reference product batches due to aging effects, CHMP recommends the use of representative batches during *in vitro* tests and in vivo studies. For this purpose five or six batches from different EU markets should be tested for APSD and FPD with a maximum deviation of 15 % [28]. Likewise stipulated in the EU, FDA endorses a replicate study design in case of highly variable drugs which act systemically [73]. Instead of varying the acceptance limits the use of a reference-scaled average bioequivalence approach is recommended [57]. Alternative PK designs might be accepted, which should be discussed with the FDA in the course of a pre-ANDA meeting prior to the conduct of the PK study [32,76].

Stricter limits might be appropriate for drug products with a narrow therapeutic window in view of the European OIP guideline [13], which are, however, not specified for OIPs. It is therefore assumed that limits of the BE guideline [12] are applicable (90.00 - 111.11 % for AUC, and C_{max}). In contrary, on the US side no deviations of the stipulated bioequivalence margins are specified in any published product-specific guidance for OIPs [39–53,55,57–66,69]. In case of high variable drugs the use of the reference-scaled average bioequivalence approach is recommended [57].

As usually required for PK studies for traditional orally administered dosage forms, the determination of the **parent drug** in plasma is required for OIPs in the EU [12]. In exceptional circumstances as indicated in the BE guideline [12] the determination of the active metabolite might also be accepted. Similarly, as already discussed in paragraph "**6.3 Comparative Pharmacokinetic Studies**" FDA recommends the analysis of the parent drug in most cases.

7.4 Pharmacodynamic or clinical endpoint studies

PD studies are accepted in the EU to demonstrate equivalent efficacy as well as safety in the event of failed *in vitro* tests and PK studies [13]. On the other hand, FDA only requires PD studies or CE studies to compare efficacy of two drug products [39–53,55,57–66,69]. For this reason, it was decided to only proceed on similarities and differences concerning efficacy PD studies or CE studies:

For demonstration of efficacy of **bronchodilators** the European OIP guideline [13] generally recommends one study design that may be adapted to the pharmacological

properties of the drug substance. In the course of a bronchodilatation study or bronchoprotection study a single-dose, double blind, double dummy, crossover PD study with four treatment arms (two dose levels) should be envisaged [13].

A similar design should be envisaged in the US for SABA [40,69]. For long acting bronchodilators (LABA and LAMA) a slightly different study design should be chosen: The PD study or CE study should be carried out with a single-dose, placebo-controlled, randomized, crossover or parallel group study design with three treatment arms (test product, reference product and placebo). A corresponding efficacy PD or CE study for LAMA should additionally be blinded where feasible [47–51,58].

In the EU, a PD study for **ICS** should be double-blind, randomized in a parallel group design or crossover design with four treatment arms (two dose levels) [13]. In contrast, FDA accepts a placebo-controlled, randomized, multiple-dose parallel group design with three treatment arms (test product, reference product, placebo) [39,43–46,59–62]. The inclusion of placebo-control allows the evaluation whether the treatment with the test product and reference product is effective, i.e. statistical superior over placebo ($p<0.05$). In turn, this ensures the sensitivity of the method and provides evidence in support of assessment of efficacy between test product and reference product [23]. In contrast to that, the European regulatory approach aims to verify assay sensitivity in that sense that differences in dose levels should be detectable [13].

It should be emphasized, that the EU accepts bronchodilatation and bronchoprotection studies also for ICS [13] in contrast to FDA [39,43–46,55,59–62,65,66]. However, the study designs in terms of dosing, study duration and objective vary to that of bronchodilating agents due to their different pharmacological and pharmacodynamic properties.

Despite the differences in study designs and the strategies to improve the sensitivity of the studies, it becomes apparent that both ICH regions share the opinion that the demonstration of bioequivalence through PD or CE studies is rather difficult for ICS:

FDA considers the demonstration of an adequate dose-response relationship for ICS as challenging due to a typically flat dose-response profile and a lack of sufficient sensitivity [72]. On the other hand, CHMP seems to be aware of this issue since in the current version of the OIP guideline [13] it is emphasised on the need to study doses on the steep part of the dose-response curve and to have a significant dose-response relationship [13].

The comparison of primary endpoints per therapeutic class as outlined in **Table 4** "**Overview of key characteristics of PD efficacy studies in the EU and US**" shows that commonly the **airway function indicator FEV_1** is measured as primary efficacy variable, either as serial or as single lung function. The corresponding FEV_1 versus time profile is computed based on the respective time of onset, duration of action of the drug substance and thus the corresponding clinical dosing regimen.

Concerning **statistical approaches** utilised to evaluate the equivalence of both products EU requires the relative potency analysis and response-scale analysis [13]. FDA solely specifies a favoured statistical approach for SABA, namely the dose-scale analysis based on the E_{max} model [40,69].

Finally, **equivalence** should be based in the EU on the 90 % CI of the relative potency or rather dose-scale analysis, which should fall within 67 – 150 %. [13]. In the US similar limits are stipulated for SABA, where the 90 % CI for the relative bioavailability (F) should be within of 67.00 – 150.00 % [40,69]. For the remaining therapeutic classes of drug substances LABA, LAMA and ICS, FDA requires the 90 % CI for the ratio of test product and reference product to lie within 80.00 – 125.00 %, similarly as required for PK studies [39,41–48,50–53,55,57–66].

7.5 Device similarity

Equivalent functioning in view of the product performance as well as similar handling of an inhalation device is a crucial factor considering the potential switch of an originator product to a generic one [79].

In this respect, CHMP requires in its OIP guideline [13] that the newly developed drug product exhibits a similar inhaled volume through the device ($\pm$ 15 %), a similar resistance airflow ($\pm$ 15 %) and a similar handling, which is, however, not further specified [13]. As a consequence, the absence of specific requirements concerning this investigation offers the applicant a certain degree of flexibility.

FDA, on the other hand, clearly specifies in its published product-specific guidance documents for MDIs and DPIs in which terms the generic inhaler should resemble the originator inhaler. Key design factors, such as a dose counting mechanism, physical appearance (size and shape of device), the energy source, internal device resistance or operating principles should be considered in the development of the respective OIPs [40–42,44–53,55,57–66,69]. In addition, the more recent published draft specific

guidance documents for OIPs require the conduct of human factor studies to proof the effectiveness of the device [45,46,48,50,53,55,61,65,66,69].

On the side of the EU human factor studies are not stipulated in the OIP guideline [13] as such, but should generally be involved in the development of medicinal products administered through a device to mitigate the risk for use errors [80].

7.6 Formulation recommendations related to bioequivalence of OIP

With respect to the composition of the test product compared to its reference product, EU may accept qualitative or quantitative differences in excipients provided proven by data that product performance, efficacy and safety of the OIPs are not affected. With respect to the drug substance, the test product should contain the same form of drug substance in terms of the salt, ester, hydrate or solvate. For the drug substance in solid state any differences in physicochemical properties, such as the crystalline structure or the polymorphic form, should not have an impact on the dissolution characteristics, the drug product performance or the aerosol behaviour. Concerning the claim of a biowaiver, which is possible for solutions for nebulisation, both products should have the same qualitative and quantitative composition [13].

The US, in turn, requires the test product formulations to be both qualitatively (Q1) and quantitatively (Q2) the same compared to the RLD. Quantitatively the same is defined by a maximum deviation of 5 % with respect to the excipients. Higher quantitative deviations may be accepted by FDA provided justified by supportive *in vitro* data [39–53,57–64,69].

7.7 Requirements related to multiple strengths products

For an OIP to be marketed in multiple strengths in the EU it is not absolutely essential to carry out in vivo PK or PD studies across all dose strengths in case *in vitro* dose linearity can be demonstrated over clinically relevant flow rates [13]. This requires a similar APSD across all dose strengths of both drug products by comparable single impactor stages that deviate not more than 15 % [28].

In case in vivo data (PK or PD) are required according to the stepwise approach to demonstrate bioequivalence, it is sufficient to investigate only one dose strength [13,28]:

As previously discussed in sections "**4.1.3 Investigation of multiple strengths products"** and "**4.2.1 Pharmacokinetik studies"**, it is commonly accepted to conduct the PK study with the highest dose strength provided of a linear pharmacokinetic. In case of in vitro non-linearity a bracketing approach may be accepted using the most similar and most different strengths according to the results obtained at *in vitro* level [28].

Based on the outcome of the PK study, the PD study only needs to be performed with the dose strength that failed to demonstrate equivalence through PK data [13].

On the contrary, dose linearity in the US is considered more critically since from the FDA's perspective the link between *in vitro* performance and PK outcomes is not fully explored and understood in detail. Consequently, the evaluation of equivalence is required through *in vitro* studies and PK studies across all strengths of the test product and reference product [72]. However, for PD studies a partial waiver of in vivo studies is possible for the higher strengths. These studies only need to be performed with the lowest strength due to safety reasons [39–53,55,57–66,69].

8 Summary and Conclusion

The regulatory approval of generic or rather hybrid orally inhaled products stands out by an intricate relationship of different regulatory and scientific key aspects in contrast to traditional pharmaceutical dosage forms, such as orally administered drug products.

With focus on the ICH regions EU and US the detailed comparison of their rather complex approaches is striking that they share basic principles for demonstration of bioequivalence of two OIPs. Both regulatory approaches generally require *in vitro* tests covering device similarity and in vivo PK and PD studies. However, acceptance criteria, on which bioequivalence is established, or the study designs of in vivo studies may vary in some respect.

CHMP advocates a stepwise approach with *in vitro* studies as starting point, which enables the demonstration of equivalence at each level (*in vitro*, PK studies, PD studies). Consequently, in case of insufficient *in vitro* data in vivo PK or PD studies have a higher priority in the bioequivalence decision making. This strategy leaves a certain margin for the applicant with respect to timing and costs of each OIP individually based on the outcome at each “step” for demonstration of bioequivalence. On the other hand, FDA requires by its weight of evidence approach the entire “study program”, i.e. *in vitro* studies including device similarity and in vivo PK, and PD studies, right from the start. This leads to the conclusion that in contrast to the EU all acceptance criteria have to be fulfilled, which covers *in vitro* data as well as in vivo study results. Otherwise regulatory approval in the US is rather unlikely.

Despite the different approaches, both CHMP and FDA may accept the claim for a biowaiver. In the EU no in vivo data are required in case certain criteria are satisfied at *in vitro* level. In addition, equivalence for solutions for nebulisation may rely on *in vitro* data only in case of the same qualitatively and quantitatively composition of the drug product. The US on the other hand supports a similar approval strategy for suspensions for nebulisation containing budesonide.

Partial biowaiver claims for multiple strengths products are feasible in the EU in the event of *in vitro* dose linearity and linear PK, so that PK or PD studies, if required, need to be conducted with one dose strength only.

FDA in turn accepts reduced investigations in this respect only for PD studies, where the lowest dose strength should be chosen.

With respect to available guidance documents, CHMP provides one universal guideline applicable for all “generic” OIPs, in particular for drug products for the treatment of asthma and COPD. In contrast, FDA published very detailed product-specific guidance documents that should lead the applicant through the pharmaceutical and clinical development of the respective OIP.

Eventually, it seems from the outside that the approach envisaged by the US is more conservative towards the approval of those rather complex drug products. This might stem from the different scientific and regulatory views concerning the previous absence of an adequate IVIVC, though EU as well as the US acknowledges this issue as an overall challenge. Therefore, it could be advisable for an applicant who intends to file in the EU and US in parallel to seek close dialogue with both authorities already during early development.

Harmonisation of both regulatory approaches towards global consistency is a desirable objective. However, different attitudes towards the relevance of data required for the demonstration of bioequivalence of two OIPs make this a major challenge. Consequently, this will call for separate development plans for each ICH region at the present time. That is already evident with regard to the choice of originator product as both authorities require the reference product to be authorised in their own region. Furthermore, bridging *in vitro* or in vivo data generated with a reference product, e.g. from the EU with the one of the US, is not foreseen in either jurisdictions.

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2019 Main Report. [cited 2019 Jul 1]. Available from: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf

2. Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. 2017 Sep [cited 2019 Jul 1]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S221326001730293X

3. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy For The Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. 2019. [cited 2019 Jul 1]. Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf

4. European Federation of Pharmaceutical Industries and Associations (EFPIA). The Pharmaceutical Industry in Figures. Key Data 2018. [cited 2019 Jul 1]. Available from: https://www.efpia.eu/media/361960/efpia-pharmafigures2018_v07-hq.pdf

5. Hochhaus G, Davis-Cutting C, Oliver M, Lee SL, Lyapustina S. Current Scientific and Regulatory Approaches for Development of Orally Inhaled and Nasal Drug Products: Overview of the IPAC-RS/University of Florida Orlando Inhalation Conference. 2015 [cited 2019 Jun 30]. Available from: http://link.springer.com/10.1208/s12248-015-9791-z

6. Forbes B, Bäckman P, Christopher D, Dolovich M, Li BV, Morgan B. In Vitro Testing for Orally Inhaled Products: Developments in Science-Based Regulatory Approaches. AAPS J. 2015 Jul [cited 2019 Jul 15];17(4):837–52. Available from: http://link.springer.com/10.1208/s12248-015-9763-3

7. Guideline on process validation for finished products - information and data to be provided in regulatory submissions, EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1. 21 November 2016.

8. Directive 2001/83/EC of the European Parliament and Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67), as amended.

9. Regulation (EU) 2017/ 745 of the European Parliament and of the Council - of 5 April 2017 - on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/ 2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p.1-175).

10. CFR - Code of Federal Regulations,Title 21 - Food and Drugs. Chapter I - Food and Drug Administration, Department of Health and Human Services, Subchapter A - General, Part 3 Product Jurisdiction. [cited 2019 Jul 7]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=3.2

11. Strong P, Ito K, Murray J, Rapeport G. Current approaches to the discovery of novel inhaled medicines. Drug Discov Today. 2018 Oct [cited 2019 Jul

3];23(10):1705–17. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1359644617305822

12. Guideline on the investigation of bioequivalence. CPMP/EWP/QWP/1401/98 Rev. 1/ Corr. 20 January 2010.

13. Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents. CPMP/EWP/4151/00 Rev. 1. 22 January 2009.

14. CFR - Code of Federal Regulations, Title 21, Food and Drugs, Chapter I - Food and Drug Administration Department of Health and Human Services, Subchapter D - Drugs for Human Use, Part 320 - Bioavailability and Bioequivalence Requirements. [cited 2019 April 1]. Available from: https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=410e0ba236404e824fc80e5236c060c4&mc=true&n=pt21.5.320&r=PART&ty=HTML#se21.5.320_11

15. FD&C Act - Federal Food, Drug, and Cosmetic Act - Chapter V: Drugs and Devices. FDA. 2018 [cited 2019 Jul 7]. Available from: http://www.fda.gov/regulatory-information/federal-food-drug-and-cosmetic-act-fdc-act/fdc-act-chapter-v-drugs-and-devices

16. US Food and Drug Administration. Federal Food, Drug and Cosmetic Act. Section 505 (21 USC § 355: New Drugs). as amended. [cited 2019 March 3].

17. Notice to Applicants - Volume 2A Procedures for marketing authorisation. Chapter 1 Marketing Authorisation. December 2016. Revision 6. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/vol2a_chap1_rev6_201612.pdf

18. US Food and Drug Administration. Guidance for Industry. Applications covered by section 505(b)(2). Draft Guidance. October 1999.

19. US Food and Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. [cited 2019 Jul 25]. Available from: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm

20. US Food and Drug Administration. Referencing Approved Drug Products in ANDA Submissions. Guidance for Industry. January 2017.

21. Concept paper on revision of 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 for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the treatment of asthma in children and adolescents. EMA/CHMP/267194/2016. 23 February 2017.

22. Evans C, Cipolla D, Chesworth T, Agurell E, Ahrens R, Conner D, et al. Equivalence Considerations for Orally Inhaled Products for Local Action—ISAM/IPAC-RS European Workshop Report. J Aerosol Med Pulm Drug Deliv. 2012 Jun [cited 2019 Jul 9];25(3):117–39. Available from: http://www.liebertpub.com/doi/10.1089/jamp.2011.0968

23. Lu D, Lee SL, Lionberger RA, Choi S, Adams W, Caramenico HN, et al. International Guidelines for Bioequivalence of Locally Acting Orally Inhaled Drug Products: Similarities and Differences. AAPS J. 2015 May [cited 2019 Jun 21];17(3):546–57. Available from: http://link.springer.com/10.1208/s12248-015-9733-9

24. Guideline on the pharmaceutical quality of inhalation and nasal products. EMEA/CHMP/QWP/49313/2005 Corr. 21 June 2006.

25. European Pharmacopoeia Edition 9.8. 2.9.18 - Preparations for inhalation: aerodynamic assessment of fine particles. 01/2008:20918.

26. European Pharmacopoeia Edition 9.8. 2.9.44 - Preparations for nebulisation: Characterisation. 01/2012:20944.

27. European Pharmacopoeia Edition 9.8. Preparations for inhalation. 04/2018:0671.

28. European Medicines Agency. Quality of medicines. Questions and answers: Part 2. [cited 2019 Jul 20]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/qa-quality/quality-medicines-questions-answers-part-2#specific-types-of-product---orally-inhaled-products-section

29. Adams WP, Ahrens RC, Chen M-L, Christopher D, Chowdhury BA, Conner DP, et al. Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products (OIPs): Workshop Summary Report. J Aerosol Med Pulm Drug Deliv. 2010 Feb [cited 2019 Jun 29];23(1):1–29. Available from: http://www.liebertpub.com/doi/10.1089/jamp.2009.0803

30. Dissanayake S. Application of the EU Guidelines for Pharmacokinetic Studies of Locally Acting Orally Inhaled Drug Products. Respiratory Drug Delivery 2010. 2010.

31. European Medicines Agency. Questions and Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP). EMA/618604/2008 Rev. 13. 19 November 2015.

32. Hochhaus G, Horhota S, Hendeles L, Suarez S, Rebello J. Pharmacokinetics of Orally Inhaled Drug Products. AAPS J. 2015 Mar 12 [cited 2019 Jul 1];17(3):769–75. Available from: http://link.springer.com/10.1208/s12248-015-9736-6

33. O'Connor D, Adams WP, Chen M-L, Daley-Yates P, Davis J, Derendorf H, et al. Role of Pharmacokinetics in Establishing Bioequivalence for Orally Inhaled Drug Products: Workshop Summary Report. J Aerosol Med Pulm Drug Deliv. 2011 Jun [cited 2019 Jan 4];24(3):119–35. Available from: http://www.liebertpub.com/doi/10.1089/jamp.2011.0878

34. International Conference on Harmonisation. Choice of control group and related issues in clinical trials E10. Current Step 4 version dated 20 July 2000.

35. Guideline on the choice of the non-inferiority margin. EMEA/CPMP/EWP/2158/99. 27 July 2005. 2006 [cited 2019 Jul 22]. Available from: http://doi.wiley.com/10.1002/sim.2584

36. Usmani OS, Molimard M, Gaur V, Gogtay J, Singh GJP, Malhotra G, et al. Scientific Rationale for Determining the Bioequivalence of Inhaled Drugs. Clin Pharmacokinet. 2017 Oct [cited 2019 Jun 19];56(10):1139–54. Available from: http://link.springer.com/10.1007/s40262-017-0524-6

37. US Food and Drug Administration. Generic Drugs. FYs 2013-2017 Regulatory Science Report: Locally Acting Orally Inhaled and Nasal Drug Products [cited 2019 Apr 27]. Available from: https://www.fda.gov/media/111304/download.

38. US Food and Drug Administration. Product-Specific Guidances for Generic Drug Development. [cited 2019 Jul 31]. Available from: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm?event=Home.Letter&searchLetter=L#letterSearchBar

39. US Food and Drug Administration. Draft guidance on budesonide - Suspension for inhalation. September 2012. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Budesonide_Inhalation_Sus_20929_RC_09-12.pdf.

40. US Food and Drug Administration. Draft guidance on albuterol sulfate - MDI. December 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Albuterol%20sulfate_metered%20inhalation%20aerosol_RLD%2020503;%2020983;%2021457_RV12-16.pdf.

41. US Food and Drug Administration. Draft guidance on fluticasone propionate/ salmeterol xinafoate - DPI. September 2013. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Fluticasone%20Proprionate_Salmeterol%20Xinafoate_21077_RC09-13.pdf.

42. US Food and Drug Administration. Draft guidance on fluticasone furoate/ vilanterol trifenatate - DPI. April 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Fluticasone%20furoate;%20Vilanterol%20trif_inhal_%20pow_204275_RC04-16.pdf.

43. US Food and Drug Administration. Draft guidance on budesonide - DPI. December 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Budesonide_inhalation%20powder_RLD%2021949_RC12-16.pdf.

44. US Food and Drug Administration. Draft guidance on fluticasone furoate - DPI. April 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Fluticasone%20furoate_inhalation%20powder_RLD%20205625_RC04-16.pdf.

45. US Food and Drug Administration. Draft guidance on fluticasone propionate - DPI. October 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Fluticasone%20proprionate_inhalation%20powder_NDA%20020833_RC10-17.pdf.

46. US Food and Drug Administration. Draft guidance on mometasone furoate - DPI. October 2017. Available from https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mometasone%20furoate_inhalation%20powder_NDA%20021067_RC08-17.pdf.

47. US Food and Drug Administration. Draft guidance on aclidinium bromide - DPI. September 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Aclidinium%20bromide_inhalation%20powder_202450_RC09-15.pdf.

48. US Food and Drug Administration. Draft guidance on glycopyrrolate - DPI. July 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Glycopyrrolate_Inhalation%20Powder_NDA%20207923_RC05-17.pdf.

49. US Food and Drug Administration. Draft guidance on indacaterol maleate - DPI. April 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Indacaterol%20maleate_inhalation%20powder_RLD%2022383_RC04-16.pdf.

50. US Food and Drug Administration. Draft guidance on tiotropium bromide - DPI. October 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Tiotropium%20bromide_inhalation%20powder_NDA%20021395_RC10-17.pdf.

51. US Food and Drug Administration. Draft guidance on umeclidinium bromide - DPI. October 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Umeclidinium%20bromide_inhalation%20powder_RLD%20205382_RC09-16.pdf.

52. US Food and Drug Administration. Draft guidance on formoterol fumarate - DPI. September 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Formoterol%20fumarate_Inhalation%20powder_020831_RC09-15.pdf.

53. US Food and Drug Administration. Draft guidance on salmeterol xinafoate - DPI. October 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Salmeterol%20xinafoate_inhalation%20powder_NDA%20020692_RC10-17.pdf.

54. United States Pharmacopoeia. USP 42 (2019). General chapter <601>Inhalation and nasal products: Aerosols, sprays and powders - Performance quality tests.

55. US Food and Drug Administration. Draft guidance on fluticasone propionate - DPI. May 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Fluticasone%20Propionate%20Inhalation%20Powder%20NDA%20208798%20PSG%20Page%20RC%20May%202019.pdf.

56. Morgan B, Strickland H. Performance Properties of the Population Bioequivalence Approach for In Vitro Delivered Dose for Orally Inhaled Respiratory Products [Internet]. 2014 [cited 2019 Jun 23]. Available from: http://link.springer.com/10.1208/s12248-013-9543-x

57. US Food and Drug Administration. Draft guidance on levalbuterol tartrate - MDI. June 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Levalbuterol%20tartrate_draft_Inhalation%20aerosol%20metered_RLD%2021730_RC06-15.pdf.

58. US Food and Drug Administration. Draft guidance on ipratropium bromide - MDI. March 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Ipratropium%20bromide_MDI_021527_RC03-15.pdf.

59. US Food and Drug Administration. Draft guidance on beclomethasone dipropionate - MDI. January 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Beclomethasone%20dipropioate_inhalation%20aerosol_RLD%20020911_RC01-16.pdf.

60. US Food and Drug Administration. Draft guidance on ciclesonide - MDI. January 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Ciclesonide%20Inhalation%20aerosol_RLD%20021658_RC01-16.pdf.

61. US Food and Drug Administration. Draft guidance on fluticasone propionate - MDI. July 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Fluticasone%20propionate%20metered%20inhalation%20aerosol%20NDA%20021433%20RV%2007-2018.pdf.

62. US Food and Drug Administration. Draft guidance on mometasone furoate - MDI. April 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mometasone%20furoate_Metered%20aerosol%20inhalation_RLD%20205641_RC04-16.pdf.

63. US Food and Drug Administration. Draft guidance on budesonide/ formoterol fumarate dihydrate - MDI. June 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Budesonide%20and%20Formoterol%20fumarate%20dihydrate_MDI_021929_RC06-15.pdf.

64. US Food and Drug Administration. Draft guidance on formoterol fumarate/ mometasone furoate - MDI. January 2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Formoterol%20fumarate_Mometasone%20furoate_inhalation%20aerosol_RLD%20022518_RC01-16.pdf.

65. US Food and Drug Administration. Draft guidance on beclomethasone dipropionate - MDI. May 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Beclomethasone%20dipropionate%20Inhalation%20Aerosol%20Metered%20NDA%20207921%20PSG%20Page%20RC%20May%202019.pdf.

66. US Food and Drug Administration. Draft guidance on fluticasone propionate/ salmeterol xinafoate - MDI. May 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Fluticasone%20Propionate;%20Salmeterol%20Xinafoate%20Inhalation%20Aerosol%20Metered%20NDA%20021254%20PSG%20Page%20RC%20May%202019.pdf.

67. US Food and Drug Administration. Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers. October 1993.

68. United States Pharmacopoeia. USP 42 (2019). General chapter <1601> Products for nebulization - characterization tests.

69. US Food and Drug Administration. Draft guidance on albuterol sulfate - DPI. December 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Albuterol%20sulfate_draft_Inhalation%20powder%20metered_RLD%20205636_RC09-18.pdf.

70. US Food and Drug Administration. Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry. 2017.

71. Saluja B, Li BV, Lee SL. Bioequivalence for Orally Inhaled and Nasal Drug Products. In: Yu LX, Li BV, editors. FDA Bioequivalence Standards. New York, NY: Springer New York; 2014 [cited 2019 May 5]. p. 369–94. Available from: http://link.springer.com/10.1007/978-1-4939-1252-0_14

72. Lee SL, Saluja B, García-Arieta A, Santos GML, Li Y, Lu S, et al. Regulatory Considerations for Approval of Generic Inhalation Drug Products in the US, EU, Brazil, China, and India. AAPS J. 2015 Sep [cited 2019 Jun 27];17(5):1285–304. Available from: http://link.springer.com/10.1208/s12248-015-9787-8

73. US Food and Drug Administration. Guidance for Industry. Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA. December 2013. [cited 2019 May 07]. Available from: https://www.fda.gov/media/87219/download.

74. Davit BM, Chen M-L, Conner DP, Haidar SH, Kim S, Lee CH, et al. Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration. 2012 [cited 2019 May 11]. Available from: http://link.springer.com/10.1208/s12248-012-9406-x

75. US Food and Drug Administration. Draft guidance on progesterone capsules. Revised February 2011. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Progesterone_caps_19781_RC02-11.pdf.

76. Lionberger R. Interpreting Pharmacokinetics for Inhalation Bioequivalence. IPAC-RS/UF Orlando Inhalation Conference. 19 March 2014. [cited 2019 Jun 15]. Available from: https://ipacrs.org/assets/uploads/outputs/06_Day_2_OIC_Lionberger.pdf

77. US Food and Drug Administration. Draft guidance on orlistat capsules. Revised August 2010. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Orlistat_cap_21887_20766_RC2-10.pdf.

78. US Food and Drug Administration. Guidance for Industry. Metered dose inhaler (MDI) and dry powder inhaler (DPI) products. Draft Guidance. April 2018 Revision 1.

79. Leiner S, Parkins D, Lastow O. Inhalation Devices and Patient Interface: Human Factors. AAPS J. 2015 Mar [cited 2019 May 24];17(2):457–61. Available from: http://link.springer.com/10.1208/s12248-015-9717-9

80. European Medicines Agency. Good practice guide on risk minimisation and prevention of medication errors. EMA/606103/2014. 18 November 2015. [cited

2019 Jun 9]. Available from:
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/good-practice-guide-risk-minimisation-prevention-medication-errors_en.pdf

Annex I – US Product-Specific Guidance Documents for Orally Inhaled Products (status as of 31st July 2019)

Table 5 Overview of product-specific guidance documents for dry powder inhalers

Drug substance	Dose strength	Metering principle/ format
SABA/LABA		
Albuterol sulfate [69]	0.090 mg base/ inhalation	Device-metered multi-dose
Formoterol fumarate [52]	No specific dose strength stipulated	Single-unit dose capsule-based
Indacaterol maleate [49]	0.075 mg base/ inhalation	Single-unit dose capsule-based
Salmeterol xinafoate [53]	0.05 mg base/ inhalation	Device-metered multi-dose
LAMA		
Aclidinium bromide [47]	No specific dose strength stipulated	Device-metered multi-dose
Glycopyrrolate [48]	No specific dose strength stipulated	Single-unit dose capsule-based
Umeclidinium bromide [51]	0.0625 mg base/inhalation	Device-metered multi-dose
ICS		
Budesonide [43]	0.09 mg/ inhalation, 0.180 mg/ inhalation	Device-metered multi-dose
Fluticasone furoate [44]	0.1 mg/ inhalation, 0.2 mg/ inhalation	Device-metered multi-dose
Fluticasone propionate [45]	0.05 mg/ inhalation, 0.1 mg/ inhalation, 0.25 mg/ inhalation	Device-metered multi-dose
Fluticasone propionate [55]	0.055 mg/ inhalation, 0.113 mg/ inhalation, 0.232 mg/ inhalation	Device-metered multi-dose
Mometasone furoate [46]	0.110 mg/ inhalation, 0.220 mg/ inhalation	Device-metered multi-dose
Fixed dose combination of ICS/LABA		
Fluticasone furoate/ vilanterol trifenatate [42]	0.1 mg/ 0.025 mg base per inhalation, 0.2 mg/ 0.025 mg base per inhalation	Device-metered multi-dose
Fluticasone propionate/ salmeterol xinafoate [41]	No specific dose strength stipulated	Device-metered multi-dose

Table 6 Overview of product-specific guidance documents for metered dose inhalers

Drug substance	Dose strength
SABA/LABA	
Albuterol sulfate [40]	0.09 mg base/ inhalation
Levoalbuterol tartrate [57]	0.045 mg base/ inhalation
LAMA	
Ipatropium bromide [58]	No specific dose strength stipulated
ICS	
Beclomethasone dipropionate [59]	0.04 mg/ inhalation, 0.08 mg/ inhalation
Beclomethasone dipropionate [65]	0.04 mg/ inhalation, 0.08 mg/ inhalation
Ciclesonide [60]	0.08 mg/ inhalation, 0.16 mg/ inhalation
Fluticasone propionate [61]	0.044 mg/ inhalation, 0.11 mg/ inhalation, 0.22 mg/ inhalation
Mometasone furoate [62]	0.10 mg/ inhalation, 0.20 mg/ inhalation
Fixed dose combination of ICS/LABA	
Budesonide/ formoterol fumarate dihydrate [63]	0.08 mg/ 0.0045 mg per inhalation, 0.160 mg/ 0.0045 mg per inhalation
Formoterol fumarate/ momentasone furoate [64]	0.005 mg/ 0.1 mg per inhalation, 0.005 mg/ 0.2 mg per inhalation
Fluticasone propionate/ salmeterol xinafoate [66]	0.045 mg/ 0.021 mg (base) per inhalation, 0.115 mg/ 0.021 mg (base) per inhalation, 0.230 mg/ 0.021 mg (base) per inhalation

Table 7 Exemplary overview of product-specific FDA recommendations for pharmacodynamic or clinical endpoint studies for OIPs

General note: The change from baseline should be recorded (adjustment of baseline) for each BE primary endpoint.

ICS			
Drug substance	**Indication**	**Dosage form**	**Study recommendations**
Fluticasone furoate [44]	Asthma	DPI	**Comparative clinical endpoint Study** Type: comparative clinical endpoint BE study; Design: randomized, multiple-dose, placebo-controlled, parallel group design at a minimum that consists of a run-in period of 2 weeks followed by a 4-week treatment period of P, T or R[7]; Dose: 0.10 mg/ inhalation, two inhalations twice daily; BE study endpoints: FEV_1 measured in the morning prior to dosing of medication on last day of the 4-week treatment; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Fluticasone propionate [61]	Asthma	MDI	**Comparative clinical endpoint BE Study** Type: comparative clinical endpoint BE study; Design: randomized, multiple-dose, placebo-controlled, parallel group design, at minimum consisting of a 2-week run-in period followed by a 4-week treatment period of the P, T or R[7]; Dose: 0.044 mg/ inhalation, two inhalations twice daily; BE study endpoints: FEV_1 measured in the morning prior to dosing of medication on last day of the 4-week treatment, Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.

[7] P = placebo, T = test product, R= reference product

ICS			
Drug substance	**Indication**	**Dosage form**	**Study recommendations**
Fluticasone propionate [45]	Asthma	DPI	**Comparative clinical endpoint BE Study** Type: comparative clinical endpoint BE study; Design: randomized, multiple-dose, placebo-controlled, parallel group design, at minimum consisting of a 2 week run-in period followed by a 4-week treatment period of the P, T or R^7; Dose: 0.05 mg/ inhalation, two inhalations twice daily; BE study endpoints: FEV_1 measured in the morning prior to dosing of medication on last day of the 4-week treatment; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Fluticasone propionate [55]	Asthma	DPI	**Comparative clinical endpoint BE Study** Type: comparative clinical endpoint BE study; Design: randomized, multiple-dose, placebo-controlled, parallel group design, at minimum consisting of a 2 week run-in period followed by a 4-week treatment period of the P, T or R7; Dose: 0.055 mg/ inhalation, two inhalations twice daily; BE study endpoints: FEV_1 measured in the morning prior to dosing of medication on last day of the 4-week treatment; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Budesonide [43]	Asthma	DPI	**Comparative clinical endpoint study** Type: comparative clinical endpoint BE study Design: randomized, multiple-dose, placebo-controlled, parallel group design at a minimum that consists of a run-in period of 2 weeks followed by a 4-week treatment period of P, T or R^7; Dose: 0.09 mg/ inhalation, four inhalations twice daily;

ICS			
Drug substance	**Indication**	**Dosage form**	**Study recommendations**
			BE study endpoints: FEV_1 measured in the morning prior to dosing of medication on last day of the 4-week treatment; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Budesonide [39]	Asthma	Inhalation suspension	**Highest strength (1mg/2ml**) and **lower strengths (0.5 mg/2ml or 0.25mg/2ml)** ***Option B. Combination of in vitro and in vivo BE studies*** **Clinical endpoint BE study** No specific recommendations regarding study design; acceptable dose-response for T and R^7 required to assure sensitivity of study.
Beclomethasone dipropionate [59]	Asthma	MDI	**Clinical pharmacodynamic BE Study** Type: BE study; Design: randomized, multiple-dose, placebo-controlled, parallel group design at a minimum that consists of a run-in period of 2 weeks followed by a 4-week treatment period of P, T or R^7; Dose: 0.04 mg/ inhalation; one inhalation twice daily; BE study endpoints: FEV_1 measured in the morning prior to dosing of medication on last day of the 4-week treatment; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Beclomethasone dipropionate [65]	Asthma	MDI	**Comparative clinical endpoint BE study** Type: Comparative clinical endpoint BE study; Design: randomized, multiple-dose, placebo-controlled, parallel group design at a minimum that consists of a run-in period of 2 weeks followed by a 4-week treatment period of P, T or R7; Dose: 0.04 mg/ inhalation; one inhalation twice daily;

ICS			
Drug substance	**Indication**	**Dosage form**	**Study recommendations**
			BE study endpoints: FEV_1 measured in the morning prior to dosing of medication on last day of the 4-week treatment; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Ciclesonid [60]	Asthma	MDI	**Clinical PD BE study** Type: BE study; Design: randomized multiple-dose, placebo-controlled parallel group design, at minimum consisting of a 2 week run-in period followed by a 8-week treatment period of P, T or R^7; Dose: 0.08 mg/ inhalation, one inhalation twice daily; BE study endpoint: FEV_1 measured in the morning prior to the dosing of inhaled medications on the last day of the 8-week treatment period; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Mometasone furoate [62]	Asthma	MDI	**Comparative clinical endpoint study** Type: BE study; Design: randomized, multiple-dose, placebo-controlled, parallel group design at a minimum that consists of a run-in period of 2 weeks followed by a 4-week treatment period of P, T or R^7; Dose: 0.10 mg/ inhalation, two inhalations twice daily; BE study endpoints: FEV_1 measured in the morning prior to dosing of medication on last day of the 4-week treatment; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.

ICS			
Drug substance	**Indication**	**Dosage form**	**Study recommendations**
Mometasone furoate [46]	Asthma	DPI	**Comparative clinical endpoint study** Type: comparative clinical endpoint BE study; Design: randomized, multiple-dose, placebo-controlled, parallel group design at a minimum that consists of a run-in period of 2 weeks followed by a 4-week treatment period of P, T or R[7]; Dose: 0.110 mg/ inhalation, two inhalations once daily in the evening; BE study endpoints: Trough FEV_1 measured in the evening prior to the dosing of inhaled medications on the last day of a 4-week treatment period; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.

LAMA			
Drug substance	**Indication**	**Dosage form**	**Study recommendations**
Umeclidinium bromide [51]	COPD	DPI	**Clinical PD BE study** Type: BE study Design: crossover or parallel-group design, randomized, single-dose, placebo-controlled; Minimum 2-week run-in period, one-day treatment of P, T or R[7]; Dose: 0.0625 mg/ inhalation, single-dose; BE study primary endpoints: AUC_{0-24h}; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.0 %.
Ipatropium bromide [58]	COPD	MDI	**Clinical PD study** Type: BE study; Design: crossover or parallel-group design, randomized, single-dose, double-blind, placebo-controlled; minimum run-in period, one-day treatment of P, T or R[7]; Dose: 42 mcg, single dose (i.e. two inhalations of 21 mcg); BE study primary endpoints: AUC_{0-6h}; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Indacaterol maleate [49]	COPD	DPI	**Comparative clinical endpoint study** Type: BE study Design: crossover or parallel-group design, randomized, single-dose, double-blind, placebo-controlled; minimum 2-week run-in period, one-day treatment of P, T or R[7]; Dose: 0.075 mg/ inhalation, single-dose; BE study primary endpoints: AUC_{0-24h}; Equivalence: 90% CI for T/R for primary endpoint within 80.00 - 125.00%

LAMA			
Drug substance	**Indication**	**Dosage form**	**Study recommendations**
Glycopyrrolate [48]	COPD	DPI	**Comparative clinical pharmacodynamic study** Type: comparative clinical PD BE study; Design: crossover or parallel-group design, randomized, single-dose, *blinded (where possible),* placebo-controlled; minimum 2-week run-in period, one-day treatment of placebo, T or R7; Dose: 15.6 mcg/ inhalation, single-dose (inhalation from one capsule); BE study primary endpoints: $AUC_{0\text{-}12h}$; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Tiotropium bromide [50]	COPD	DPI	**Comparative clinical pharmacodynamic study** Type: comparative clinical PD BE study; Design: crossover or parallel-group design, randomized, single-dose, blinded where possible, placebo-controlled; minimum 2-week run-in period, one-day treatment of P, T or R^7; Dose: 0.018 mg/ inhalation, single-dose (two inhalations from the same capsule); BE study primary endpoints: $AUC_{0\text{-}24h}$; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Aclidinium bromide [47]	COPD	DPI	**Clinical pharmacodynamic (PD) study** Type: BE study; Design: crossover or parallel-group design, randomized, single-dose, placebo-controlled; minimum run-in period, one-day treatment of P, T or R^7; Dose: 375 mcg aclidinium bromide/inhalation, single dose; BE study primary endpoints: $AUC_{0\text{-}6h}$; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.

LABA/SABA			
Drug substance	**Indication**	**Dosage form**	**Study recommendations**
Formoterol fumarate [52]	Asthma	DPI	**Clinical pharmacodynamic (PD) study** Type: BE study; Design: crossover or parallel-group design, randomized, single-dose, placebo-controlled; minimum 2-week run-in period, one-day treatment of P, T or R^7; Dose: 0.012 mg/ inhalation, single dose; BE study primary endpoints: $AUC_{0\text{-}12h}$; Equivalence: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Albuterol sulphate [40]	Asthma	MDI	**Pharmacodynamic (PD) BE study** 1.Type:Bronchoprovocation study Design: single-dose, double-blind, double dummy, randomized, crossover study; Dose: zero dose (placebo R and placebo T), 0.09 mg of R, 0.18 mg of R and 0.09 mg of T^7; PD endpoints: Post-dose PC20 or PD20 (use of methacholine agent); Equivalence criteria: dose-scale analysis of PD data, 90 % CI within 67.00 – 150.00 %. 2.Type: Bronchodilatation study Design: single-dose, double-blind, double dummy, randomized, crossover study; Dose: zero dose (placebo R and placebo T), 0.09 mg of R, 0.18 mg of R and 0.09 mg of T^7; PD endpoints: $AUEC_{0\text{-}4h}$, $AUEC_{0\text{-}6h}$ and FEV_{1max}; Equivalence criteria: dose scale analysis of PD data, CI 90 % for F within 67.00 – 150.00 %.

LABA/SABA			
Drug substance	**Indication**	**Dosage form**	**Study recommendations**
Levalbuterol tartrate [57]	Asthma	MDI	**Pharmacodynamic (PD) BE study** 1.Type: Bronchoprovocation study Design: single-dose, double-blind, double-dummy, randomized, crossover study; Dose: zero dose (placebo R and placebo T), 0.045 mg of R, 0.90 mg of R, 0.045 mg of T7; PD endpoints: post-dose PC_{20} or PD_{20} (use of methacholine agent); Equivalence criteria: dose-scale analysis of PD data (reference is made to the product-specific guidance document for Orlistat oral capsule [77]), 90 % CI within 67.00 – 150.00 %. 2.Type: Bronchodilatation study Design: single-dose, double-blind, double dummy, randomized, crossover study; Dose: zero dose (placebo R and placebo T), 0.045 mg of R, 0.90 mg of R, 0.045 mg of T^7; PD endpoints: AUEC $_{0\text{-}4h}$, AUEC $_{0\text{-}6h}$ and FEV_{1max}; Equivalence criteria: dose scale analysis of PD data, CI 90% for F within 67.00 – 150.00 %.
Salmeterol xinafoate [53]	Asthma	DPI	**Comparative clinical pharmacodynamic study** Type: comparative clinical pharmacodynamic study; Design: crossover or parallel-group design, randomized, single-dose, placebo-controlled; minimum 2-week run-in period, one-day treatment of P, T or R^7; Dose: 0.05 mg/ inhalation, single-dose of one inhalation; BE study endpoints: $AUC_{0\text{-}12h}$; Equivalence criteria: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.

Combination products ICS/LABA			
Drug substance	**Indication**	**Dosage form**	**Study recommendations**
Mometasone furoate, formoterol fumarate, [64]	Asthma	MDI	**Pharmacodynamic (PD) BE study** Type: BE study; Design: randomized multiple-dose, placebo-controlled, parallel group design, at a minimum consisting of a 2-week run-in period followed by a 4-week treatment period of P, T or R^7; Dose: 100/ 5 mcg (mometasone furoate 100 mcg and formoterol fumarate 5 mcg), two inhalations twice daily; BE study endpoints: $AUC_{0\text{-}12\ h}$ on first day of treatment and FEV_1 measured in the morning prior to the dosing of inhaled medications on last day of 4-week treatment; Equivalence criteria: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Budesonide, formoterol dihydrate [63]	Asthma	MDI	**Clinical endpoint study** Type: clinical endpoint study; Design: randomized multiple-dose, placebo-controlled, parallel group design consisting of a 2-week run-in period followed by a 6-week treatment period of P, T or R^7; Dose: 80/ 4.5 mcg (budesonide 80 mcg and formoterol 4.5 mcg), two inhalations twice daily; BE study endpoints: $AUC_{0\text{-}12\ h}$ on first day of treatment and FEV_1 measured in the morning prior to the dosing of inhaled medications on last day of 6-week treatment; Equivalence criteria: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.
Fluticasone propionate, salmeterol xinafoate [41]	Asthma	DPI	**Clinical endpoint study** Type: clinical endpoint study; Design: randomized, multiple-dose, placebo-controlled, parallel group design consisting of a 2 week run-in period followed by a 4-week treatment period of the placebo, T or R^7; Dose: 100/ 50 mcg (fluticasone propionate 100 mcg and salmeterol 50 mcg powder for inhalation),

Combination products ICS/LABA			
Drug substance	**Indication**	**Dosage form**	**Study recommendations**
			twice daily; BE study endpoints: $AUC_{0\text{-}12\ h}$ on first day of treatment and FEV_1 measured in the morning prior to the dosing of inhaled medications on last day of 4-week treatment; Equivalence criteria: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %
Fluticasone propionate/ salmeterol xinafoate [66]	Asthma	MDI	**Comparative clinical endpoint BE study** Type: comparative clinical endpoint BE study; Design: randomized, multiple-dose, placebo-controlled, parallel group design consisting of a 2 week run-in period followed by a 4-week treatment period of the placebo, T or R^7 Dose: 0.045 mg/ inhalation, 0.021 mg (base)/ inhalation, two inhalations twice daily; BE study endpoints: $AUC_{0\text{-}12\ h}$ on first day of treatment and FEV_1 measured in the morning prior to the dosing of inhaled medications on last day of 4-week treatment; Equivalence criteria: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %
Fluticasone furoate, vilanterol trifenatate [42]	Asthma	DPI	**Comparative clinical endpoint study** Type: comparative clinical endpoint BE study; Design: randomized, multiple-dose, placebo-controlled, parallel group design consisting of a 2 week run-in period followed by a 4-week treatment period of the P, T or R^7; Dose: 100/ 50 mcg (fluticasone propionate 100 mcg and salmeterol 50 mcg), twice daily; BE study endpoints: $AUC_{0\text{-}12}$ on first day of treatment and FEV_1 measured in the morning prior to the dosing of inhaled medications on last day of 4-week treatment; Equivalence criteria: 90 % CI for T/R for primary endpoint within 80.00 - 125.00 %.

Eidesstattliche Versicherung

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

_____ _____

Ort, Datum Unterschrift