Faculdade de Farmácia

IMPACT OF SUCCESSIVE POST-AUTHORISATION CHANGES ON THE DISSOLUTION PROFILE OF SOLID ORAL DOSAGE FORMS

Lorena Santos Pereira

Dissertation supervised by Professor Luis Filipe Pleno de Gouveia, Ph. D
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REGULATION AND EVALUATION OF MEDICINES AND HEALTH PRODUCTS

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Quando os ventos de mudança sopram, umas pessoas levantam barreiras, outras constroem moinhos de vento.

Érico Veríssimo

Agradecimentos

Meu agradecimento, ao Ike, por ter enfrentado comigo esse período, suportando minha ausência e me incentivando a não desistir.

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Resumo

A equivalência terapêutica de medicamentos genéricos (MG) é a principal premissa para a obtenção da autorização de introdução do medicamento no mercado (AIM). Aquando a apresentação de um pedido de AIM, a prova de equivalência do medicamento genérico em comparação com o seu medicamento de referência (MR) deve ser irrefutavél. A mesma é confirmada através de testes in-vitro, incluindo testes de desempenho, como por exemplo, o perfil de dissolução comparativo. Quando aplicável no âmbito do pedido de AIM, a confirmação da bioequivalência é confirmada através de testes in-vivo. Este tipo de ensaios permite a extrapolação tanto dos dados de eficácia (clínicos) como de segurança (pré-clínicos e farmacovigilância) do MR comparativamente ao produto genérico proposto.

Durante o ciclo de vida do produto, o desempenho do mesmo deve ser reavaliado a cada necessidade de alteração de qualquer condição aprovada na AIM, provando que o medicamento genérico continua a ser um equivalente terapêutico ao seu MR. Testes comparativos de desempenho, tais como a dissolução, são úteis na simulação do comportamento do medicamento no corpo humano, tornando possível a comparação da sua absorção com a de um MR. A necessidade de repetir o estudo alargado de bioequivalência (BE) pode ser substancialmente reduzida quando se estabelece uma relação entre dados de desempenho in-vitro e dados de desempenho in-vivo.

O controlo destas características é da responsabilidade dos titulares da AIM, e cada autoridade reguladora tem a sua própria regulamentação, o que permite avaliar o nível de impacto da alteração e apresentar as provas adequadas durante a gestão do ciclo de vida do medicamento.

Contudo, após sucessivas alterações menores ao medicamento genérico e medicamento de referência, devido a directrizes e regulamentos de testes não padronizados, é possível o surgimento de uma potencial bio-inequivalência do medicamento genérico após a sua aprovação inicial.

O presente trabalho pode ser dividido em três objectivos principais. Primeiramente, confirmar a presença de divergências de desempenho entre MR e MG, que potencialmente resultam em bio-inequivalencia, após mudanças pós-AIM sucessivas durante todo o ciclo de vida do medicamento. Simultaneamente, identificar lacunas no panorama regulamentar das autoridades reguladoras ANVISA (Agência Nacional de

Vigilância Sanitária) do Brasil, a EMA (Agência Europeia de Medicamentos) da Europa e a FDA (Food and Drug Administration) dos Estados Unidos da América, que potenciam possíveis divergências de desempenho e, portanto, bio-inequivalência. O último objectivo deste trabalho é sugerir e analisar possíveis alterações de regulação que atenuem este risco.

Para este efeito, foi realizada uma pesquisa bibliográfica aprofundada, analisando regulamentação local, directrizes, documentação e publicações oficiais, bases de dados públicas das autoridades de saúde com AIM aprovadas e teses académicas, utilizando termos, definições e linguagem adaptados para os efeitos desta pesquisa. Os principais instrumentos de pesquisa aplicados às publicações indexadas foram PubMed, Science.gov, Google books, Science Direct e Research Gate. Esta pesquisa permitiu a comparação dos critérios de aceitação de BE, perfil comparativo de dissolução (PCD), requisitos para o desenvolvimento do método de dissolução juntamente com a regulamentação da alteração dos termos do AIM no que respeita à sua classificação, provas a apresentar e forma de apresentação para a implementação de alterações.

Em termos de critérios de aceitação do perfil comparativo de dissolução e bioequivalência, não foram observadas diferenças entre as directrizes das autoridades reguladoras estudadas. Entre as principais semelhanças nos diferentes regulamentos para alterações aos termos da AIM estão: a necessidade de realizar o PCD entre a condição anterior aprovada e a condição proposta; e a exigência de factor de semelhança, f2, com um valor superior a 50. Estas conclusões estão de acordo com a hipótese proposta para este trabalho, isto é, após sucessivas pequenas alterações ao medicamento genérico e ao MR, para as quais apenas foram apresentadas provas comparativas in-vitro versus a condição previamente aprovada, o perfil de dissolução pode se tornar distinto do perfil do seu MR, o que pode levar à bio-inequivalência do medicamento genérico após a sua aprovação inicial.

Uma simulação de PCD foi proposta, considerando um aumento de 10 vezes no tamanho do lote do medicamento genérico em comparação com o bio-lote, concomitantemente com uma pequena alteração no processo de produção e uma mudança no equipamento. Neste cálculo, foram consideradas mesma classe e subclasse de um produto com principios activos de baixa solubilidade (classe II ou IV) do sistema de classificação biofarmacêutico, para o qual a dissolução é sempre um factor crítico. Este conjunto de alterações foi classificado como menor e moderado pelas autoridades de saúde avaliadas neste trabalho. Considerando que o critério de semelhança entre o PCD proposto e o aprovado se restringia ao valor f2 superior a 50,

através da simulação de uma única alteração, foi possível demonstrar que, quando comparado com a referência, a curva de dissolução proposta divergia da curva da mesma.

Numa tentativa de mitigação dos riscos encontrados, várias soluções foram estudadas e propostas, desde a simples realização do estudo contra o medicamento de referência no seu estado actual (assumindo todas as alterações) para qualquer tipo de alteração, até um programa de monitorização específico para avaliar uma possível bio-inequivalência dos medicamentos do mercado.

Atendendo à premissa desta obra de avaliar os requisitos regulamentares para a hipótese levantada de perda de bioequivalência, foi considerado confirmado que existe uma lacuna regulamentar para a prova de comparação necessária para alterações menores e moderadas na AIM de uma forma farmacêutica sólida genérica de libertação imediata.

Foi possível concluir que, tendo em consideração que a isenção da necessidade de bioequivalência utiliza principalmente o critério f2, genéricos das classes II e IV BCS, podem ser introduzidos no mercado com perfis de dissolução que diferem dos do seu medicamento de referência. Foi possível constatar, também, que os produtos de libertação imediata são mais vulneráveis do que os produtos de libertação modificada, tendo em vista um menor número de condicionantes para a classificação da mudança como menores e moderadas.

Palavras-chave: formas farmacêuticas orais; dissolução; bioequivalência; medicamento genérico

Abstract

Therapeutic equivalence is the main premise for obtaining Marketing Authorization (MA) for generic drugs. Proof of equivalence is presented in the submission of an MA application. Pharmaceutical equivalence is confirmed through in vitro testing, including performance tests such as comparative dissolution profile. When applicable in the scope of the MA application, bioequivalence confirmation is asserted by in vivo testing. This testing supports the extrapolation of both efficacy (clinical) and safety (pre-clinical and pharmacovigilance) data of the reference product (RP) to the proposed generic product.

During its life cycle, product performance must be re-evaluated at every need to change any condition approved in the MA, proving that the generic product continues to be a therapeutic equivalent to its RP. Comparative performance tests, such as dissolution, are useful in simulating the behaviour of the drug in the human body, making it possible to compare its absorption against a RP. The need to repeat the extended bioequivalence study (BE) can be substantially reduced when a relationship between in-vitro performance data and in-vivo performance data is established.

The monitoring of these characteristics is responsibility of the MA holders, and each regulatory agency has its own regulation, which allows the level of impact of the change to be assessed and the appropriate evidence to be submitted during the life cycle management of the drug.

However, after successive minor changes to the generic drug and RP, due to unstandardized guidelines and regulations of testing, a potential bio-inequivalence of the generic drug after its initial approval may arise.

The present work is axed in three main goals. The first to attest the presence of performance divergences between RP and generic solid oral products, after successive post-authorisation changes throughout their lifecycle, possibly resulting in bio-inequivalence. This while identifying gaps in the regulatory landscape of the regulatory authorities ANVISA (Agência Nacional de Vigilância Sanitária) from Brazil, the EMA (European Medicines Agency) from Europe and the FDA (Food and Drug Administration) from the United States of America that potentiate possible performance divergences and thus, bio-inequivalence. The last goal of this body of work is to suggest and analyse possible regulation changes that mitigate this risk.

A comprehensive literature search was performed by analysing local regulations,

guidelines, official documentation and publications, health authorities' public online databases of approved MAs, academic thesis, using adapted terms, definitions, and language for the research purpose. Main research tools applied to indexed publications were PubMed, Science.gov, Google books, Science Direct and Research Gate. This allowed for the comparison of the acceptance criteria of BE, comparative dissolution profile (CDP), requirements for development of the dissolution method along with the regulation of change to the terms of the MA regarding its classification, evidence to be presented and form of submission for the implementation of changes.

In terms of acceptance criteria for comparative dissolution profile and bioequivalence, no differences between regulatory authorities' guidelines were observed. Among the main similarities in the different regulations for changes to the terms of the MA researched are: the need to perform the CDP between the previous approved condition and the proposed condition; and requiring similarity factor, f2, with a value greater than 50. These findings are in line with the proposed hypothesis of this work, that is, after successive minor changes to the generic drug and RP, for which only in-vitro comparative evidence has been presented against the previously approved condition, this dissolution profile may no longer be similar to its reference drug, which may lead to bio-inequivalence of the generic drug after its initial approval.

A simulation of CDP was performed considering a 10-fold increase in the batch size of the generic drug compared to the bio-batch, concomitant with a minor change in the production process and a change in equipment. Same class and subclass of a product with low solubility assets (class II or IV) of the biopharmaceutical classification system, for which dissolution is always a critical factor was assumed. This set of changes was rated as minor and moderate by the health authorities subject in this work. Considering that the similarity criterion between proposed and approved CDP was restricted to f2 value greater than 50, by simulating a single change, it was possible to demonstrate that, when compared to the reference, the proposed dissolution curve diverged from the curve of the reference drug.

To mitigate the risks found, a number of solutions were studied and proposed, ranging from simply conducting the study against the RP in its current condition (assuming all changes) for all of the changes categories, to a specific monitoring program for possible bio-inequivalence.

As the aim of this research was to assess the regulatory requirements for the hypothesis raised, it was considered confirmed that there is a regulatory gap for the evidence of

comparison required for minor and moderate changes in the MA acceptance of an immediate release generic solid dosage form.

It was possible to conclude that, taking into consideration that the exemption of the need for bioequivalence uses mainly the f2 criterion, generics of classes II and IV BCS, may be available the market with dissolution profiles that differ from those of their reference product during its lifecycle. Immediate release products were found to be more vulnerable than modified release products, given fewer constraints on the classification of change as minor and moderate.

Keywords: solid dosage forms; dissolution; bioequivalence; generic product

List Of Abbreviations

ANDA – Abbreviated New Drug Application
ANVISA – Agência Nacional de Vigilância Sanitária (Brazilian Health Authority)
AS – Active Substance
BA – Bioavailability
BCS – Bio Classification System
BE – Bioequivalence
CDER – Center for Drug Evaluation
CI – Confidence Interval
CP – Centralized Procedure
CV – Coefficient Variation
DCP – Decentralized Procedure
EMA – European Medicine Agency
ER – Extended Release
FDA – Food and Drug Administration
FDC – Fixed Dose Combination
IR – Immediate Release
IVIVC – In-Vivo/In-Vivo Correlation
IVIVR – In-Vivo/In-Vivo Relationship
MA – Marketing Authorisation
MAA – Marketing Authorisation Application
MR – Modified Release
MRP – Mutual Recognition Procedure
NDA – New Drug Application
NP – National Procedure
PE – Pharmaceutical Equivalence
PK – Pharmacokinetic
QC – Quality Control
RMP – Reference Medicinal Product
SD – Standard Deviation
SMPC – Summary of Product Characteristics

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1. Introduction

In most regulatory agencies in the world, one of the premises for the approval of a generic drug for marketing authorisation is its proven therapeutic equivalence regarding the innovative drug or reference, enabling its interchangeability, and consequently, expanding the population's access to it.

Therapeutic equivalence evidence is obtained by in vitro tests (pharmaceutical equivalence), including performance tests and, when applicable, in vivo tests (bioequivalence), which are evaluated formerly at the Marketing Authorisation Application (MAA). These tests make it is possible to extrapolate the efficacy (clinical data) and safety (preclinical and pharmacovigilance) data from the innovative Reference Medicinal Product (RMP) to the proposed generic product.

During the lifecycle of the product, the principle of therapeutic equivalence must be maintained. Therefore, performance tests of the product are to be reassessed for each need of change in any condition approved in the marketing authorisation, proving that the generic product continues to be a therapeutic equivalent to the RMP.

The pharmaceutical equivalence (PE) study is carried out to all dosage forms, to assure the same quality criteria, and includes the physical, physical-chemical, and microbiological tests applicable to each dosage form.

Comparative performance tests, such as dissolution profile, skin permeation, and aerodynamic particle size are useful for simulating the drug's behaviour in the human body, thus, proving that generic product´s Active Substance(s) (AS) will be available for absorption under similar quantity(ies) and time as the RMP.

Also, In Vitro/ In Vivo Correlation (IVIVC) allows the assess of the impact of a proposed change, reducing the need for medicine testing on humans, avoiding unnecessary exposure to medicines in Bioequivalence (BE) studies every time a new modification emerges.

For oral dosage forms, it is important to evaluate the differences in the delivery form of the drug for absorption. In case of perfect solutions, the drug is already fully available for absorption, if the need to use formulations with excipients of similar functionality between the reference drug and the generic drug has been observed (especially regarding possible interferences in gastro-motility).

For medicinal products for oral use, but with local action (stomach, intestine, lungs) that

have no absorption, the concept of performance is limited to the release of the AS at the site of action.

In the case of oral suspensions and oral solids with systemic action, the necessity to determine and monitor the correlation between the in vitro performance test and BE study of the generic product are central for maintaining this extrapolation of clinical studies results of RMP, assuring the interchangeability during generic product's life cycle.

In this scientific thesis, the regulatory aspects and framework of important regulatory agencies, ANVISA (Agência Nacional de Vigilância Sanitária) from Brazil, EMA (European Medicines Agency) from Europe and FDA (Food and Drug Administration) from the United States will be discussed. Evaluating their requirements during the medicinal product lifecycle management to assure that the premise of therapeutic equivalence is maintained.

Hence, to enable a deep discussion of the variables, our focus will be on solid oral dosage forms and on a worst-case scenario simulation, that will be performed to consider the possibility of the interference of successive changes in the BE between generic and RMP in the market.

1.1 Generic products history and Current regulatory framework

1.1.1. ANVISA

To receive a MA approval from ANVISA, generic products must present the same active pharmaceutical ingredient, in the same concentration and dosage form as the RMP determined by them, being able to be launched to market after its approval and expiration of reference´s product patent.

The first legislation on generic products, Law 9787/1999 of February 11th of 1999, published 15 days after the creation of ANVISA, is still in force. The main goals are to promote competition in the market, improve the quality of medicinal products and improve the access of the population to medicinal treatments. It also establishes that it is ANVISA's responsibility to develop generic product's regulation for marketing authorisation, quality control, therapeutic equivalence, including the dispensing criteria.

Another crucial condition established by this law was that SUS (Sistema Único de Saúde), Brazilian public funded health care system, must favour generics (when

available) in pharmaceutical tendering. (1)

With the implementation of the generics policy, the market, which until then was dominated by multinational companies, began to make room for the growth of national industries. These industries started to invest heavily in the sector and leveraged a significant market expansion.

After that, to provide specific requirements for marketing authorisation of generic medicines, ANVISA published the Collegiate Board Resolution – RDC 391/1999, establishing the guides for stability study conduction, Bioavailability/Bioequivalence (BA/BE) studies, analytical method validation, pharmaceutical equivalence, documental proof to be provided in the MA application, and also the first list of RMPs.

Many updates have followed this first regulation. Now, the most recent version in force is RDC 200/2017(2). It consists in a technical regulation, determining the minimal requirements for MA and renewal of medicines classified as new, generic, and similar, with synthetic and semi-synthetic active ingredients.

During this period, the guides and specific regulations for technical requirements were separated from the main regulation, facilitating their revisions.

After the MA approval, the generic product must continue to be comparable to the RMP during its lifecycle. Furthermore, the regulation on post-registration changes (RDC 73/2016) defines what documents and evidence should be presented to allow any change in the conditions that already proven the equivalence to the RMP.

It is also possible to have branded generic medicines, named “similar medicines”, that nowadays are under the same regulations of generics for quality, efficacy, and safety requirements, differing only in the above-mentioned tenders’ priorities and price regulation. Considering this information, all the discussion on generics in this thesis includes “similar medicines” in the current requirements.

1.1.2 FDA

The USA are the largest market between the regions discussed in this thesis, and FDA, the most mature regulatory agency.

The most important regulations related to generic history in USA starts in 1938, when

the congress passed the Federal Food, Drug, and Cosmetic (FD&C) Act of 1938 and for the first time, manufacturers were required to show that a medicinal product was safe before it could be marketed.

The 1962 Kefauver-Harris Drug Amendments (KHDA) added the requirement that drugs should be proven effective for their intended use.

Until 1962, generic versions of post 1938 drugs were marketed based on a “general recognition” of safety. Classically, this labelling rested on a history of safe use of the innovator product. Such generic products were designated as “not new drugs”.(3)

In 1984, Drug price competition and patient term restoration act (Hatch-Waxman Act) passed, amending the FD&C Act to approve applications for generic versions of brand-name drugs released after 1962, aiming to facilitate low-cost copies of medicinal products after expiration of patents for the original products, while protecting the original drug developer in terms of patents and market exclusivities to encourage further drug development.

These drugs are comparable to a brand-name medicinal product in dosage form, strength, route of administration, quality, performance characteristics and intended use and have high quality, purity, and stability, just like the brand name drug.

A Bioequivalence Task Force was formed in 1986 to examine the FDA’s procedures for approving generic products. The respective report was released in January 1988, and several statistical issues were discussed.

In 1992, the FDA issued the guidance on statistical procedures for establishing BE. A revised guidance document was issued in 2001 and later in 2013.

In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) included the Generic Drug User Fee Act (GDUFA), and, for the first time, the industry was required to pay for a generic drug application.

The generic drug is filed as an Abbreviated New Drug Application (ANDA) under section 505(j) of the FD&C Act, consolidated in U.S. Code at title 21 § 355(j) and regulated in Code of Federal Regulations (CFR) title 21 §314.94.

The CFR title 21 is the legal basis for marketing application and is complemented with guidelines providing the details for the documents and proof required.

According to 21 CFR 320.24, different types of evidence may be used to establish BE for pharmaceutically equivalent medicinal products, including in vivo or in vitro testing, or both. The selection of the method used to demonstrate BE depends upon the purpose of the study, the analytical methods available, and the nature of the medicinal product. Under this regulation, applicants must conduct BE testing using the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24.

To further facilitate generic medicinal product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing medicinal products and generating evidence needed to support ANDA approval, FDA publishes product-specific guidance describing the Agency's current thinking and expectations on how to develop generic products therapeutically equivalent to specific RMPs.

After the approval of the ANDA, all post approval Chemistry Manufacturing and Control (CMC) changes are classified under CFR 21 §314.70 and the proof and evaluations needed to confirm that the therapeutic equivalency is maintained are provided in the guidelines.

1.1.3 EMA

The definition of generic medicine for the EMA is a medicinal product that has the same qualitative and quantitative composition in ASs and the same pharmaceutical form as the RMP, and whose BE with the RMP was demonstrated by appropriate Bioavailability (BA) studies.

Generic medicines can be submitted for MAA by a Centralized Procedure (CP), either when they are equivalent to a significant therapeutic, scientific, or technical innovation, or the granting of a Union authorisation for the medicinal product is in the interest of patients at the Union level. Otherwise, it can be submitted by the Decentralized (DCP), Mutual Recognition (MRP) or National procedures (NP).

Although many European countries have had previously their own regulations for medicines, the first harmonized European Union regulation was published in 1965, in the Council Directive 65/65/EEC. It came as an answer for the thalidomide tragedy and required that all medicines should have their quality, safety and efficacy proved beforehand to obtain a marketing authorisation. Therefore, technical details and tests must be presented in advance.

In its article 4, point 8 a), the directive also provides when pharmacological, toxicological, and clinical trials published literature can substitute new data for products with an established use, which was adequately tested on human beings so that its effects, including side-effects, are already known and are included in the published references. No more details for the similarity of the proposed medicinal product and the established use are provided.

In 1975, two directives were introduced. The first, Directive 75/318/EEC, referring to the quality, safety, and efficacy testing of medicines, required to be carried out by companies seeking a MA, explain, in its article 1, paragraph 2, that the directive is also applicable to products submitted with literature, according to article 4, point 8 (a) of Directive 65/65/EEC.

Directive 75/319/EEC established the procedure for MAA, request that the use of article 4, point 8 (a) of Directive 65/65/EEC in substitution of tests detailed in Council Directive 75/318/EE, be justified.

In 1983, Directive 83/570/CEE amends Directives 65/65/EEC, 75/318/EEC, and 75/319/EEC, bringing the concept and requirement of BA tests, when relevant, to patients and characteristics that could affect it.

The Directive 87/21/EEC, published in 1987, brought another amendment to the Council Directive 65/65/EEC, changing its article 4, point 8 (a), now including the intellectual property protection with minimum time to refer the pharmacological and toxicological tests from the RMP (named “proprietary medicinal product”) with no need of the Marketing Authorisation Holder (MAH) authorisation. The criteria were that the RMP having been authorized in the European Community, following the previously mentioned regulations, for not less than six years and commercialized in the member state for which the application is made. This minimum time changes to ten years in case of high-technology medicinal products listed in Directive 87/22/EEC. This was the first nearly concept for the current definition of generic medicines, even if no substitution rules were mentioned in the regulation.

Also in 1987, Directive 87/176/EEC updated Directive 75/318/EEC and was the first regulation to bring the BE criteria for applications that were not submitted with complete efficacy and clinical data. The exception was only for local action products, intravenous administration and oral formulations with ASs (AS’s) that are not absorbed by the gastrointestinal tract. It is also referenced the applicability of the concept for changes to the approved medicinal product formulation that could impact the BA.

Directive 91/507/EEC brings clear requirements for BE tests to confirm the same BA of the RMP, when pharmacokinetic properties are relevant for MAA, following Directive 65/65/EEC, article 4, point 8 (a).

In 1993, the European Medicine Agency is created by Regulation 93/2309/EEC. That also provided a protection period of ten years for other products to be able to use the clinical and preclinical tests on published bibliography based on efficacy and safety studies of the RMP (well established use submissions).

Directive 2001/83/EEC(4) is the one presently in force and, by the time of its publication, raised questions on the needed to stipulate more precisely when toxicological and pharmacological tests or clinical trials are not mandatory. These requirements, that did not demand complete data, remained the same of Directive 87/21/EEC.

In the regulation, only in article 10 of Directive 2004/27/EC (amending of Directive 2001/83/ECC), the actual concept of generic medicines was finally provided.

It should be noted that at the time of submission of the generic application, the protection period of the RMP should have expired to allow the applicant to rely on the safety and efficacy studies of the dossier of the RMP.

According to Article 10 (1) of Directive 2001/83/EC the applicant is not required to provide the results of pre-clinical tests and clinical trials if he can demonstrate that the medicinal product is a generic medicinal product of a RMP which is or was authorized under Article 6 of Directive 2001/83/EC for not less than 8 years in a Member State or in the Union. The period of 8 years from initial authorisation of the RMP, providing a period of so-called “data exclusivity”, applies only for RMPs for which the marketing authorisation application was submitted as of 30 October 2005 for MRP, DCP and national procedures and as of 20 November 2005 for centralized procedure according to the revised Union Legislation.

The possibility of using in vitro instead of in vivo studies is also addressed.

Test products in an application for a generic or hybrid product or an extension of a generic/hybrid product are normally compared with the corresponding dosage form of a RMP, if available on the market.

2. Objectives

Restricting to oral solids with systemic action, the need to maintain the BE should be the central point for ensuring the interchangeability between a generic product and its RMP during its life cycle. The purpose of this dissertation is to discuss the different aspects of regulations that ensure that the therapeutic equivalence premise is maintained, comparing these requirements in Brazil (ANVISA), Europe (EMA), and the United States (FDA).

The above agencies acceptance criteria of BE and Comparative Dissolution Profile (CDP) will be compared, with requirements for dissolution development together with their change's regulation regarding the classification and proofs required to maintain the therapeutic equivalence premise.

After evaluating these regulatory aspects, a simulation of results will be carried out considering a scale-up change up to 10 times of the biobatch concomitant with minor manufacturing and equipment (same design and operating principle) of a product of a product with an AS of Class II of Bio classification System (BCS), where the dissolution limits the absorption.

Finally, it will conclude on whether the current regulation of these regions and agencies brings sufficient requirements to maintain BE between solid generic products and their RMP during its life cycle.

In the case of identification of regulatory fragilities, possible adjustments will be suggested considering the viability and maintenance of the population's accessibility to generic products with the same safety and efficacy as their references, in addition to the quality that is already the main point of evaluation at MAA, and the change of procedures for these products.

3. Methodology

To study the regulatory scenario of the proposed Health Authorities (HA), it was adopted a comparative-descriptive approach based on extensive research on literature, local regulations, guidelines, official documentation and publications, HA public online databases of approved MA's, academic theses, using, for the research purpose, adapted terms, definitions, and language.

The selected terms were searched on each authority´s website and all the available results were checked for their applicability, being the pertinent categorized after assessment.

The mainly research tools for indexed publications were PubMed, science.gov, Google books, Science direct and Research gate.

The publications that already discussed the BE during medicinal product lifecycle and in vitro/in vivo levels of correlations highly collaborated with practical side and increased critical evaluation helping towards the applicability of the discussion.

After the confirmation of the possibility of divergent comparative dissolution profiles between Reference Medicinal Product and Generic Product after successive submissions, a case study has been proposed with a theoretical simulation of a post-approval change being f_2 the acceptance criteria, calculated in a validated Microsoft excel spreadsheet.

4. Main regulatory differences between ANVISA, EMA and FDA for therapeutic equivalence throughout medicinal products lifecycle

4.1 Reference Medicinal Product choice criteria

The definition of a reference product is the same for the HAs and its choice is based on the medicinal product that firstly proved its quality, safety and efficacy based on complete clinical and preclinical data for a starting quality condition, extrapolating these studies to a generic product.

To obtain a generic MA of a generic solid oral dosage form, the Holder should prove that the proposed formulation has comparable performance in vivo to the RMP by the BE study conduction.

For all regions that are being discussed in this document, the data protection period for the RMP use must be expired to put the generic product on the market.

The RMP List is chosen in an independent way for each of these agencies, and at different times. This allows differences between them when a global submission of a generic product is planned, especially if they are not submitted within a timeline near to the patent expiration.

Another important variable to be considered consists in the assumption that is common that, after some time after the patent's expiration, the RMP may be withdrawn from the market.

4.1.1 ANVISA

In 2012, ANVISA published RDC 35/2012, that establishes the criteria for referral, inclusion, and exclusion of medicinal products in the RMP List. At that moment, the list was completely reviewed, which resulted in a large exclusion of those RMPs that do not comply with the new regulation.

As a result, published lists are divided in medicines with 1 AS ingredient – List A – and fixed dose combinations (FDC) – List B, being available on ANVISA's website and updated frequently.

ANVISA defines a reference medicine as an innovator product, which efficacy, safety, and quality were scientifically assessed and approved by them. Thus, interchangeability between generic and RMP should be possible. This concept can be understood as the potential substitution of one medicinal product for another, based on the therapeutic equivalence between them, whose proof is essentially related to PE and relative BA studies.(5)

The concept of the RMP (and consequently, generic products) is applicable only for synthetic or semi-synthetic medicines. Therefore, it excludes biological, immunotherapeutic products, derived from human plasma and blood; herbal medicines; specific medications (ANVISA´s classification for vitamins, isolated phytochemicals, and other types of medicines); homeopathic medicines; low risk notification products; antiseptics for hospital use; products for diagnostic purposes and radiological contrasts; radiopharmaceuticals; medicinal gases; and other classes of medicinal products that may have specific legislation for their MA.

The recommendation of a RMP must be submitted by the company interested in submitting a new generic or branded generic, using a medicinal product that is not described in the RMPs List.

When the innovator RMP that performed all the preclinical /clinical studies is no longer marketed in the country, a generic or branded generic can replace it latter. The following parameters are considered:

- the medicinal product must be available in the market.

- the medicinal product was already compared to the RMP elected in the past.

- the medicinal product presented the most similar pharmacokinetic data comparing to the RMP. The pharmacokinetic data refers to the biostatistical confidence interval, ratio between the areas under the curve (AUC), maximum concentration (Cmax) of the evaluated drugs and overlapping of partial pharmacokinetic curves.

If there is more than one medicinal product that can be considered a reference, the following aspects will be evaluated by ANVISA:

- Product history in the Brazilian market related to quality specifications and pharmacovigilance notifications.

- MA approval date will be verified.

- the date of the MAA submission

4.1.2 FDA

As defined in CFR §314.3, a RMP (named as Reference Listed Drug – RLD) is the listed medicinal identified by FDA as the medicinal product upon which an applicant relies in seeking approval of its ANDA.

There is also the concept of Reference Standard (RS), that is the medicinal product selected by FDA which an applicant seeking approval of an ANDA must use when conducting an in vivo study, if required for approval.(6)

FDA generally selects a single RS to ensure the greatest level of consistency between a generic drug and its RMP and among generic drugs.

In general, a new RMP is elected when a New Drug Aplication (NDA) is approved based on safety and effectiveness by FDA under the FD&C Act and is included in the Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book, in the month following its approval.

The RMP is the listed drug to which the ANDA applicant must show its proposed generic drug is the same with respect to AS(s), dosage form, route of administration, strength, labeling, conditions of use, when comparing medicinal product formulations and inactive ingredients, among other characteristics.

If different from the RMP, the RS will be used just for the conduction of the BE studies.

Among other factors, FDA may select a new RS in the following cases: when the RMP that is also the RS is no longer marketed; to help prevent a shortage of a particular medicinal product or category of medicinal products; when the current reference standard in distribution is so limited that a potential ANDA applicant is not able to obtain enough for BE studies.

When not yet defined, the ANDA applicant should request FDA indication of the RMP and, if there is no product approved by a NDA available in the market to be selected as RMP, FDA can select a previously approved product already proven to be equivalent to the RMP in the past and, if there is more than one with this condition, it will be considered the generic market leader, based on commercial data.

The main criterion for the inclusion of any product is that it is the subject of an application with an approval that has not been withdrawn for safety or efficacy reasons.(7)

In the Orange Book, medicinal products are classified as either A (substitutable) or B (non- interchangeable) and can also present a second letter that indicates the type of study by which a product was determined to be bioequivalent. For example, AT corresponds to a product that the topical dosage of the generic drug is bioequivalent to the topical dosage form of the reference drug.

AB products are those that had their BE problems resolved with additional in vitro and/or in vivo evidence. This classification is a very important point to be considered as a possible control of the main discussion of this thesis and will be detailed in section 5 - discussion.

The medicinal products classified as not therapeutically equivalent are designated with the letter B, plus a second letter that indicates the dosage form.

The Orange Book is divided in Prescription only (RX) product list, Over the Counter (OTC) product list and Prescription and OTC medicinal product patent and Exclusivity List and is available on FDA's website.(8)

4.1.3 EMA

The definition of reference medicinal product, provided in article 10 paragraph 2 (a) of Directive 2001/83/EC, is a medicinal product authorized under article 6, that requires marketing authorisation issued by a Member State to be marketed, and in accordance with article 8, which provides the documents required for MA, including the results of preclinical tests and clinical trials requested in its paragraph 3(i).

The Notice to Applicants, that provide rules governing medicinal products in the European Union and contains a list of regulatory guidelines related to procedural and regulatory requirements, mentions in its chapter 1(9) – 5.3.1.1 – that the reference can be made to the dossier of a RMP for which a marketing authorisation was granted in the Union in accordance with articles 8(3), 10a (well established use), 10b (new fixed combination) or 10c (informed consent) of Directive 2001/83/EC.

The well-established use products are considered due to a jurisprudence of Case C-104-13, ECJ 23/10/2014(10), that contemplated the literature-based efficacy and safety

dossier. Those can also be referenced and used as a RMP. This decision set a precedent for how to perform BE studies with products that do not prove their relative BA with those medicines firstly used to prove safety and efficacy.

The generic application can be submitted through CP, DCP, MRP and National procedure.

The generic application of a reference medicine authorized through CP can be directly submitted through CP, being necessary only to submit, in the previous 6 to 18 months, a “Letter of intention to submit”, informing what RMP will be used in the generic application.

When the reference medicine is approved through DCP, MRP or NP, the submission through CP will only be accepted if the generic is a significant therapeutic, scientific, or technical innovation, or the granting of a Union authorisation for the medicinal product is in the interest of patients at Union level. EMA will inform the applicant of the outcome of the eligibility request for both cases.

When the submission is made through DCP, MRP or NP, and the reference medicine product has never been authorized in the Member state where the generic product is being submitted, this competent authority should request to the competent authority of the other Member State that approved the RMP a confirmation that the RMP is or has been authorized together with the full composition of the RMP and, if necessary, other relevant documentation. This request should be answered within a period of one month.

When the RMP is no longer marketed in the EU, demonstration of the BE to the RMP through BA studies should be done on batches which have been authorized within the Union.

4.2 Bioequivalence Criteria

Each HA BE requirements will be presented to verify if there are any differences of the study conduction and acceptance criteria.

Table 1 provides the standardize the terms used for BE regulations and references used.

Table 1 – General Definitions

AUC	Area under plasma, serum, or blood time curve.
AUC0-t	Area under concentration time curve from time 0 to time t.
t	relative time to the last measurable drug concentration determined experimentally, above the quantification limit (LoQ).
tau	Dosing interval length at steady state.
AUC0-inf or AUC0-∞	Area under the curve (AUC0-inf) from time 0 extrapolated to infinite. AUC0-inf = AUC0-t + Ct / k
AUC0-tau	Area under the concentration time curve for one dosing interval at steady state/equilibrium state
K_{el} or λz	Terminal or elimination rate constant calculated according to an appropriate method
Cmax	Maximum concentration peak of the drug and/or metabolite
Cmin	Minimum concentration peak of the drug and/or metabolite
CmaxSS	Maximum concentration peak of the drug and/or metabolite in Steady-State/Equilibrium State
CminSS	Minimum or trough concentrations at steady state
C* or CavSS	Average plasma concentration at steady state/during a dosing interval. C* or CavSS= AUC0-t /tau
Tmax	Time to reach the Cmax
Ct	Last measurable drug concentration determined experimentally (above LoQ)
t1/2	Elimination half-life of the drug and/or metabolite
Degree of fluctuation	(Cmax – Cmin)/CavSS
Swing	(CmaxSS-CminSS)/CminSS

4.2.1 ANVISA

For ANVISA, BE consists of the demonstration of PE between products presented under the same dosage form, containing identical qualitative and quantitative composition of AS(s), and which have comparable BA, when studied under the same experimental design.(11)

It is required that the BE is performed with the Brazilian RMP in a centre that is a national or international centre certified by ANVISA.

The PE study should be performed in a Brazilian Network of Laboratories (REBLAS), also certified by ANVISA, previously to the BE study with NMT 5% of content difference between the RMP and the generic.

According to the “Guideline to evidence relative BA/BE of medicinal products,” determined by RE 1170/2006(12), the relative BA/BE studies reports should present clinical, analytical, and statistical steps, complying with the requirements described below.

Clinical phase: In the clinical phase, both medicinal products, test, and reference, must be submitted to the study that will be evaluated based in the unchanged drug or its metabolite quantification in the blood or urine. The study can be evaluated using pharmacodynamics measures alternatively.

The conventional study is of the open, randomized, crossover type in a single or multiple dose schedule and the volunteers should receive the test and RMP on separate occasions with a standard water quantity of 200 ml. Different designs can be used, if justified.

Single-dose studies are preferrable than multiple-dose as they are more sensitive to differences in formulations. However, multiple dose studies may be used in cases where they reduce intra-individual variability in the drug absorption.

The research project, experimental protocol and informed consent form must be submitted, approved by the Ethics Committee in Research (CEP), and accredited by the National Research Ethics Committee (CONEP) of the National Health Department (MS).

The participants are volunteers, over 18, and able to provide their Informed Consent, and it is recommended that the number of men and women be distributed equally and varying ±15% of the weight considered normal for each gender. The number of participants should provide robust statistical results based on the variability of the drug.

For Immediate Release (IR) tablets, the study is performed in fasting conditions, except for drugs that have the absorption influenced by the presence of food, resulting in clinically significant changes. The recommended conditions are provided in list 1(13) available at ANVISA´s website being constantly updated by the agency.

The sample collection schedule must ensure proper plasma profile characterization of the drug or metabolite (concentration versus time), with a washout period equal to or greater than 3-5 times the elimination half-life of the drug.

Analytical phase: The analytical phase should be conducted according to international Good Laboratory Practices (GLP) to assure that the methods used for all analysis are adequate, reliable and with reproducible results, and the bioanalytical method used should be detailed in the protocol and fully validated according to RDC 27/2012(14), that provides the requirements for bioanalytical methods validation.

The stability of the analyte in biological fluids must be performed and the calibration curve of the bioanalytical method should have enough standard points and adequate reproducibility.

The analyte that should be dosed is provided in List 2(15) and when not the unchanged AS molecule, the metabolite or alternative analyte is also indicated there.

The sample analysis should be carried without replication, in duplicate or triplicate with the acceptance criteria described in the standard operation procedure of the method with any sample loss justified. All the analyses with less than the Limit of Quantification should be considered zero for statistical calculations.

The analytical protocol should provide sample reintegration criteria, and all the deviation from the protocol must be reported and justified.

In the last step, the statistical one, the pharmacokinetic parameters are obtained from the drug blood concentration curves versus time and analysed statistically to BE determination.

The following Pharmacokinetics (PK) parameters should be determined for single dose studies:

Table 2 - Pharmacokinetics (PK) parameters for single dose studies

AUC0-t	Calculated by the trapezoidal method
AUC0-inf	AUC0-t should be equal to or greater than 80% of AUC0-inf, except in cases where truncated AUC is used calculated according to an appropriate method
Cmax and Tmax	Without data interpolation.
t1/2	No statistical analysis is required

The following pharmacokinetic parameters should be determined for multiple dose studies:

Table 3 - PK parameters for multiple dose studies

AUC0-t	Calculated between the dose interval, in the steady state
Cmax and Tmax	Obtained without data interpolation
Cmin	Determined at the end of each dose interval of the steady state
C*	Average drug concentration at a steady state
-	Degree of fluctuation in the steady state

For multiple dose/steady state BE studies, it must be proved that the steady state was achieved after administration of the test and RMP.

It is not permitted the exclusion of more than 5% of volunteers who participated in the study until its conclusion, or the lack of more than 10% of the values of the blood concentrations of the drug from the administration of each medicine per volunteer.

Statistical phase: The statistical analysis should consider the confidence interval (CI) of 90% to the difference of the averages of the test and RMP data transformed in natural logarithm, for AUC0-t and Cmax parameters.

A table containing individual values, averages (arithmetic and geometric), Standard Deviation (SD) and Coefficient of Variance (CV) of all PK parameters related to the administration of test and RMP should be provided.

Using statistical software's, the variance analysis (ANOVA) of the PK parameters AUC0-t and Cmax should be performed and transformed to assess the effects of sequence, voluntary within the sequence, period, and treatment. In addition, an ANOVA table containing font, degree of freedom, sum of squares, square mean, F statistics, p-value and the intra and inter individual variation coefficients must be presented.

Based on the ANOVA results, the obtained antilogarithm of the CI constitutes the 90% CI for the ratio of the geometric means of the parameters: AUC0-t test/AUC0-t reference and Cmax test/ Cmax reference).

Tmax will be analysed as an individual difference (= test - reference), building 90% CI, using non-parametric tests.

When necessary, appropriate statistical models should be employed, *e.g.*, multiple dose studies.

Two medicinal products will be considered bioequivalents if the 90% CI extreme values of the geometric mean ratio (AUC0-t test / AUC0-t reference and Cmax test/ Cmax reference) are greater than 0.8 and less that 1.25. Other 90% CI limits for Cmax,

previously established in the protocol, may be accepted under scientific justification. When clinically relevant, Tmax should also be considered.

The exclusion of participants that present discrepant pharmacokinetic parameters should be justified, and the results considering the outliers should also be provided.

ANVISA also have published two guidelines with the detailed information that the BE protocol and report should present – RE 894/2003(16) and RE 895/2003(17), and a guideline for the planning and conduction of the statistical phase of the BE – RE 898/2003(18).

The results of the equivalence and BE studies are registered in ANVISA's system named SINEB, and its requirements are defined by RDC 34/2008(19).

4.2.2 FDA

FDA's regulations define BA in terms of rate and extent of absorption of the AS or moiety to the site of action and BE is the absence of significant difference in the BA between pharmaceutical equivalent products administered at the same molar dose and similar conditions in an appropriate designed study.(20)

BA or BE may be evidenced by in vitro and in vivo test methods. It will depend on the nature of the medicinal product, the analytical methods available and the purpose of the study and the following approaches are acceptable and are described in descending order of accuracy, sensitivity, and reproducibility:(21)

Table 4 – FDA BE Accepted approaches and their Applicability

Type	Description	Applicability
(1)	(i) In vivo test in humans in which the active ingredient or active moiety concentration and, when appropriate, its active metabolite is measured as a function of time in whole blood, plasma, serum, or other appropriate biological fluid	Dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution
	(ii) In vitro test that has been correlated with and is predictive of human in vivo BA data	-
(2)	In vivo test in humans in which the urinary excretion of the active moiety and, when appropriate, its active metabolite, are measured as a function of time	Dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution
(3)	In vivo test in humans in which an appropriate acute pharmacological effect of the active moiety and, when	This approach can be followed for dosage forms intended to deliver

	appropriate, its active metabolite, are measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility	the active moiety to the bloodstream for systemic distribution, only when an accurate, sensitive, and reproducible method is not available to follow items 1 or 2. This approach may be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution
(4)	Well-controlled clinical trials that establish the safety and effectiveness of the medicinal product, for purposes of measuring BA, or appropriately designed comparative clinical trials, for purposes of demonstrating BE	This approach may be considered acceptable only when previous methods are not applicable and may also be considered sufficiently accurate for measuring BA or demonstrating BE of dosage forms intended to deliver the active moiety locally
(5)	Currently available in vitro test acceptable to FDA that ensures human in vivo BA.	-
(6)	Any other approach deemed adequate by FDA to measure BA or establish BE.	-

Considering the main approaches presented in item 1 (i and ii), the study should be performed with a RMP selected by FDA (provided in the Orange Book) and should be conducted in a Bioresearch Monitoring (BIMO) Centre inspected by FDA.

For IR products, FDA recommends that the content difference between RMP and test product of less than 5%.

Unless other approach is more appropriate for valid scientific reasons, FDA recommends that BE studies design be a crossover, two-period, two-sequence, two-treatment, single-dose replicate study design in fasting conditions, with at least 3 times the half-life for the elimination period and decay of the acute pharmacological effect.

The highest strength of both test and RMP products, unless for safety reasons, but considering that the following conditions are met:

- Documented linear elimination kinetics over the therapeutic dose range.
- The higher strengths of both test and RMP products are proportionally like their respective lower strength.
- Acceptable results of the comparative dissolution testing on the higher strength

of both products are positive.

The collection of blood samples should be based on blood concentration x time curves in sufficient frequency to permit an estimate of the peak concentration and total area under the curve for at least 3 times the half-life measured, with identical sampling times in reference and test product.

Multiple dose should be used when the analyte is in a concentration that is not possible to be measured with sensible analytical methods.

The study should enroll enough participants to have adequate statistical power and considering participants with 18 years or older, representative of general population considering age, race and in similar proportions of males and females (for medicinal products intended for use in both sexes).

The RMP and test product can be administered with about 240 ml of water, with and adequate washout period of more than five half-lives time separating the treatments.

Analytical methods for an in vivo BA or BE study should be accurate, with sufficient sensitivity, precision to measure the analyte concentrations. The validations should follow FDA's guidance for industry on Bioanalytical Method Validation.

For in vivo studies, the regulations also provide for use of PK measures in an accessible biological matrix such as blood, plasma, and/or serum to indicate release of the AS from the medicinal product into body's systemic distribution.

Regarding rate of absorption, the Cmax should be assessed, without data interpolation and Tmax can also provide important information.

The following parameters should be determined for single-dose studies: $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and Cmax containing also the Tmax, Kel and t1/2 as supportive information.

The following parameters should be determined for multiple-dose studies: $AUC_{0\text{-}tau}$, and CmaxSS. It is also necessary to report the CminSS, CavSS, degree of fluctuation, swing and Tmax.

Statistical information for AUC0-t, AUC0-inf, and Cmax is recommended: standard deviation (or coefficient of variation), geometric means (antilog of the means of the logs), arithmetic means, geometric mean ratios, and 90% confidence intervals (CI) transformed in common (base 10) or natural logarithm with no round values.

To be considered BE, the results for CI should be between 80.00 and 125.00%.(21)

All the information used for the statistical analysis should be provided in the submission, such as: plasma concentrations and time points, subject, period, sequence, treatment, intersubject, intrasubject and/or total variability, if available.

The analysis of variance (ANOVA) should be used.

Statistical Analysis:

Analysis of variance appropriate for a crossover design on the pharmacokinetic parameters using the general linear model procedures of SAS or an equivalent program should be performed, with examination of period, sequence, and treatment effects. The 90% confidence intervals for the estimates of the difference between the test and reference least square means for the pharmacokinetic parameters (AUC0-t, AUC0-inf, Cmax) should be calculated, using the two one-sided t-test procedures.

4.2.3 EMA

According to EMA – Guideline on the investigation of BE, 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. The AUC reflects the extent of exposure, Cmax, the maximum plasma concentration or peak exposure, and tmax, the time to maximum plasma concentration.

In studies to determine BE after a single dose, the parameters to be analyzed are AUC(0-t), or, when relevant, AUC(0-72h), and Cmax. For these parameters, 90% CI for the ratio of the test and RMPs should be contained within the acceptance interval of 80.00-125.00%. To be inside the acceptance interval the lower bound should be ≥ 80.00% when rounded to two decimal places and the upper bound should be ≤ 125.00% when rounded to two decimal places.(22)

The standard design is a randomized, two-period, two-sequence, single dose crossover, with the treatment periods separated by a washout period of at least 5 times (in average).

If scientifically justified, parallel designs can be used for long half-life drugs.

It will only be accepted multiple dose studies conduction instead of single dose for limited

sensitivity of the bioanalytical method in exceptional cases, when the applicant can prove that a method improvement(22) is not possible, as multiple dose studies have limited sensitivity for Cmax.

A multiple dose study in patients is acceptable if a single dose study cannot be conducted in healthy volunteers due to tolerability reasons, and a single dose study is not feasible in patients.

For Narrow Therapeutic Index Drugs (NTID's) and for Highly Variable Drug Products (HVDP's), the acceptance interval is different.

HVDP's are those whose intra-subject variability for a parameter is larger than 30% and a replicate crossover design study can be carried out. Those HVDP's for which a wider difference in Cmax is considered clinically irrelevant based on a sound clinical justification can be assessed with a widened acceptance range. If this is the case, the acceptance criteria for Cmax can be widened to a maximum of 69.84 – 143.19%. For the acceptance interval to be widened, the BE study must be of a replicate design whit intra-subject variability for Cmax of >30%, according to the following table:

Table 5 – EMA Bioequivalence acceptable ranges within subjects' variation

Within-subject CV %	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

The acceptance range for AUC should remain at 80.00 – 125.00%, regardless of variability and it is acceptable to apply either a 3-period or a 4-period crossover scheme in the replicate design study.

For NTID, AUC should be tightened to 90.00 – 111.11%. Where Cmax is of particular importance for safety, efficacy or drug level monitoring the 90.00 – 111.11% acceptance interval should also be applied for this parameter.

The test and RMPs should be administered with a standardized volume of fluid of at least 150 ml, and it is recommended that water is allowed as desired except for a window of one hour before and one hour after drug administration, with food allowed only 4 hours post-dosing. Meals taken after dosing should have the composition and time

standardized during an adequate period.

Enough samples should be collected to adequately describe the plasma concentration-time profile, including frequent sampling around predicted tmax, to provide a reliable estimate of peak exposure avoiding having Cmax being the first point of the curve. The sampling schedule should have a long enough curve to provide a reliable estimate of exposure extension, achieved with an AUC(0-t) coverage of at least 80% of AUC (0-∞). In multiple-dose studies, the pre-dose sample should be taken immediately before dosing and the last within 10 minutes of the nominal time for the dosage interval ensuring an accurate determination of AUC(0-τ).

In general, a BE study should be conducted under fasting conditions. For products where the RMP SmPC recommends empty stomach, irrespective of food intake, then the BE study should be conducted under fasting conditions. For products where the RMP SmPC recommends the intake only in Fed conditions, then the BE study should be conducted under fed conditions.

For products with specific formulation characteristics, BE should be performed under both fasted and fed conditions, unless the product must be taken only in the fasted state or only in the fed state. When both studies are required, it is acceptable to conduct either two separate two-way crossover studies or a four-way crossover study.

In studies performed under fed conditions, the composition of the meal is recommended to be according to the SmPC of the originator product. If no specific recommendation is given, the meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, considering about 800-1000 kcal meal.

4.3 Dissolution method development requirements

4.3.1 ANVISA

A dissolution method is discriminative if it can evidence significant changes in formulations and in manufacturing processes of tested medicinal products that may impact the performance of the formulation.

According to ANVISA´s Resolution RDC 31/2010 - Guideline on performance of Pharmaceutical Equivalence and Comparative Dissolution Profile Studies, in case of absence of the dissolution method in an official compendium, it is the Sponsor responsibility the development and validation of dissolution method. These should comply with national and international guidelines, and the obtained data should demonstrate a discriminatory dissolution methods. (23)

When a compendia method is selected, it should also be proved that it is discriminatory for the product being developed.

The recommendation for conducting the tests required in RDC 31/2010(23) are provided in Guideline 14/2018, which brings cases illustration in a very didact way.

It describes what information and tests are expected to be presented in the dissolution development report, as provided in Table 6 bellow:

Table 6 - ANVISA´s Dissolution method development requirements

AS characteristics	AS characteristics	-Discussion of the AS characteristics that could interfere in the dissolution, such as: particle size, polymorphism, hygroscopicity, pKa or pKb.
	Solubility test	-Preferable to be experimentally determined using shake flask method -At least three different mediums between physiological pH (e.g.: 1,2; 4,5 and 6,8), -Performed in triplicate, calculating average, SD and CV of the results. -Use of stability indicative analytical method to detect possible degradation products, -Prove of the AS stability in the selected pH and condition tested. -Confirm the suitability of the filter used evaluating the need of sample centrifugation. -Register the initial and final pH of the saturated solution. -Justification of the use of surfactants and its respective quantities (lower possible concentration), if applicable
Dissolution conditions	Dissolution medium	-Based on AS solubility results, test of the drug product in all the satisfactory mediums. -Justification of the use of surfactants and its respective quantities (lower possible concentration), if applicable. -Water medium is recommended only if the AS dissolution is not pH dependent. -Confirmation of the maintenance of pH value throughout the dissolution
	Volume	-Determination of sink condition (3 x of the volume required for the AS saturation) considering the highest strength commercialized of the medicinal product (use of one pharmaceutical unit). -Use of volumes that do not satisfy the sink condition are acceptable if proved the discriminatory power of method.
	Deaeration	-When deaeration is needed, the presentation of the results without deaeration to justify its use.
	Enzymes	-Justification of the use of enzymes for cross-linking reduction, if applicable.
	Temperature	-Confirmation that the temperature of 37ºC±0,5ºC is maintained during the dissolution test.

	Apparatus and rotation speed	-Tests confirming that the apparatus and speed choice are the most suitable to confirm the discriminatory power of the method considering the AS and dosage form. -Justification for use of speeds different from 50 and 75 rpm for paddle and 50 and 100 rpm for basket, when applicable.
	Sinkers	-Justification of the use of sinkers and its format and size, if applicable.
	Filters	-Justification of the filter choice.
Discriminatory power	When reproved and approved In-vivo results are available	-Confirmation of the correlation between the PK profile and the dissolution method capability to differentiate the bioequivalent results from bioinequivalents.
	When only approved In-vivo results are available	-Correlation of the PK parameters and the dissolution profile result.
	Deliberate change in quality attributes of the product	-Manufacturing of pilot batches with subtle realistic changes in the quality attributes of the drug product, confirming that the method is capable of identifying the batches with quality deviation by reproving them at the quality control.
Determination of dissolution specification (Q)	% of dissolved AS	-Confirmation that the proposed Q % is suitable to the delivery proposal of the product to distinguish approved from reproved batches
	Collection points	-Justification of the selected points are suitable to confirm the delivery proposal of the dosage form

4.3.2 FDA

FDA does not present the conduction details for the development of dissolution procedures in guidelines, but it recommends(24) the applicants to refer to U.S. Pharmacopeia (USP) General Chapter <1092> - The dissolution procedure; Development and validation, which provides all the details for determining the more suitable dissolution conditions for the product, confirming or not the referred USP individual conditions presented in the monograph.

Regarding the dissolution specification definitions, other recommendations are provided in Guidelines for both, IR, and MR oral dosage forms.

For IR, FDA presents the requirements at SUPAC-IR, FDA – Guidance for Industry – Dissolution Testing of Immediate Release Solid Oral Dosage Forms(25) in its Appendix A and for MR, the requirements are presented in SUPAC-MR and at Guidance for Industry Extended-Release Oral Dosage Forms: Development, Evaluation, and Application of s, which provide more details for determination of dissolution specifications(26).

FDA website informs that in case a medicinal product does not have a dissolution test method in the USP, FDA Dissolution Methods Database provides information on dissolution methods presently recommended by the Division of Biopharmaceutics, Office of Pharmaceutical Quality.

This database was provided to aid industry personnel in developing generic products(27). Current knowledge about solubility, permeability, dissolution, and pharmacokinetics of a drug product should be considered in defining dissolution test specifications for the drug product approval process. This knowledge is also used to ensure continued equivalence of the product, as well as to ensure the uniformity of the product under certain scale-up and post-approval changes.

For generic products, the definition of the dissolution specification depends on three categories:

- USP medicinal dissolution test available: the Division of BE, Office of Generic Drugs, also recommends taking a dissolution profile at 15-minute intervals or less using the USP method for test and RMPs (12 units each). Also recommended submitting additional dissolution data when scientifically justified.

- USP medicinal dissolution test not available and dissolution test for RMP publicly available: a dissolution profile at 15-minute intervals of test and RMP (12 units each) using the method approved for the RMP is recommended.

- USP medicinal dissolution test not available and dissolution test for RMP not publicity available: recommended the comparative dissolution testing using different test conditions as different solution media (pH 1 to 6.8), addition of surfactant and use of apparatus 1 and 2 with varying agitation.

More details for the dissolution development method requirements are provided in table 7.

Table 7 - FDA´s Dissolution method development requirements

AS characteristics	**Solubility test**(28)	Detail the experimental procedure to verify the influence of buffers, pH, and if needed, different surfactants on the solubility and stability of the drug substance - Recommends using shake flask method <1236> *Solubility measures.* - In addition to buffers solutions, mixtures of HCl and NaOH are used to perform solubility investigations, to level out potential ion effects between the AS and the buffers used in the media. -The pH of the clear supernatant should be checked to determine whether the pH changes during the solubility test. -Typical media for dissolution: diluted hydrochloric acid, buffers (phosphate or acetate) in the pH range of 1.2-7.2, simulated gastric or intestinal fluid (with or without enzymes) and water. - Aqueous solutions may contain a surfactant to enhance the solubility of the AS. After identifying the more suitable one (list provided in table one of the chapter), the quantity should be tested to propose the lowest concentration that provides the better solubility. - The use of purified water as the dissolution medium is suitable for products with a dissolution behaviour independent of the pH of the medium. - Use of an aqueous–organic solvent mixture as a dissolution medium is discouraged. -The stability of the solution should be confirmed. -The suitability of the filter used should be confirmed.
Dissolution conditions(28)	**Dissolution medium**	-Sink condition is desirable but can be justified if not possible to be determined. -The selection of composition and volume should be guided by the AS characteristic and results obtained with the solubility test and being based on physicochemical characteristics of the AS and the environmental conditions the dosage form might be exposed to after oral administration (physiological conditions), if possible. -An aqueous medium with pH range 1.2 to 6.8 should be used. -Use of water as a dissolution medium also is discouraged. -For water insoluble or sparingly water-soluble products use of a surfactant such as sodium lauryl sulphate is recommended justifying its necessity and amount. -Use of a hydro alcoholic medium is discouraged.

	Biorelevant medium	-To simulate intestinal fluid (SIF), a dissolution medium of pH 6.8 with and without pancreatin may be employed to assess batch-to-batch product quality provided the BE is maintained. A higher pH should be justified on a case-by-case basis and, in general, should not exceed pH 8.0. -To simulate gastric fluid (SGF), a dissolution medium of pH 1.2, with and without pepsin may be employed to assess batch-to-batch product quality provided the BE is maintained.
	Volume	-The volume will be usually determined to maintain sinking condition. -For compendial Apparatus 1 (basket) and Apparatus 2 (paddle), the volume of the dissolution medium can vary from 500 to 1000 mL, but can be enlarger to 2-4 L depending on the sink condition of the AS.
	Deaeration	Certain drug products and formulations are sensitive to dissolved air in the dissolution medium and will need deaeration. In this case, its recommended to compare the results with and without dearation.
	Enzymes	Enzymes uses are acceptable for cross-linking reduction.
	Temperature	37±0.5°C
	Apparatus and agitation speed	-Apparatus 1 and Apparatus 2, unless showed not appropriate. In this case, another official apparatus may be used, such as a reciprocating cylinder (Apparatus 3), flow-through cell (Apparatus 4) or reciprocating holder (Apparatus 7). USP Apparatus 1 (rotating basket) – 50-100 rpm USP Apparatus 2 (rotating paddle) – 50 or 75 rpm USP Apparatus 3 (reciprocating cylinder) – 5 to 30 dips/min USP Apparatus 4 (flow-through cell) – 4, 8, and 16 mL/min If justified, 100 rpm may be used with Apparatus 2, especially for extended-release products. Rates outside 25–150 rpm for both the paddle and the basket are usually not appropriate because of mixing inconsistencies that can be generated by stirring too slow or too fast. Different experimental modifications may need to be carried out to obtain a suitable in vivo correlation with in vitro release data.
	Sinkers	When sinkers are used, a detailed description of the sinker must be provided in the written procedure. It may be useful to evaluate different sinker types, recognizing that sinkers can significantly influence the dissolution.

	Filters	The suitability of the filter used should be confirmed.
Discriminatory power **One of more of the following approaches**(25)*	**Mapping or Response Surface Methodology**	Mapping is defined as a process for determining the relationship between critical manufacturing variables (CMV) and a response surface derived from an in vitro dissolution profile and an in vivo BA data set. The CMV include changes in the formulation, process, equipment, materials, and methods for the drug product that can significantly affect in vitro dissolution. The goal is to develop product specifications that will ensure BE of future batches prepared within the limits of acceptable dissolution specifications. Experimental design suggestion: -Preparation of two or more dosage formulations using CMV to study their in vitro dissolution characteristics; Test of the products with fastest and slowest dissolution characteristics along with the standard or the to be marketed dosage form in small groups (e.g., n> 12) of human subjects; and determination of the BA of the products and in IVIVC/R. If the products with the extreme range of dissolution characteristics are found to be bioequivalent to the standard or the to be marketed dosage form, future batches with dissolution characteristics between these ranges should be equivalent to one another.
	In Vivo-In Vitro Correlations	For highly water soluble (BCS classes 1 and 3) immediate release products using currently available excipients and manufacturing technology, an IVIVC may not be possible, but for BCS class 2 may be. To achieve an in IVIVC, at least three batches that differ in the in vivo as well as the in vitro performance should be available. If the batches show differences in in vivo performance, then in vitro test conditions can be modified to correspond with the in vivo data to achieve an IVIVC. If no difference is found in the in vivo performance of the batches and if the in vitro performance is different, it may be possible to modify test conditions to achieve the same dissolution performance of the batches studied in vivo. Very often, the in vitro dissolution test is found to be more From a quality assurance point of view, a more discriminative dissolution method is preferred, because the test will indicate possible changes in the quality of the product before in vivo performance is affected.
	Validation and Verification of Specifications	Confirmation by in vivo studies may be needed for validation of an in vitro system. In this situation, the same formulation should be used but nonformulation CMV should be varied. Two batches with different in vitro profiles should be prepared (mapping approach) and tested in vivo. If the two products show different in vivo characteristics, then the system is validated. In contrast, if there is no difference in the in vivo performance, the results can be interpreted as verifying the dissolution specification limits as discussed under mapping. Thus, either validation or verification of dissolution specifications should be confirmed.

Determination of dissolution specification (Q)	**% of dissolved AS Collection points**	Immediate Release: A Q value of 80% is generally recommended, except when a justification with adequate data is provided to support a lower Q value (e.g., clinical or BA/BE data). Q values above 80% are not generally used. During product development, the collection of complete dissolution profile data is recommended from biobatches and stability batches at specified intervals, such as 10, 15, 20, 30, 40, 50, and 60 min or 15, 20, 30, 45, and 60 min, because these data are used to establish the dissolution acceptance criterion/criteria. From the dissolution profile data, a Q value of 80% should be set at the first time point where the average dissolution is at least 85%. However, this time point should not be less than 15 min. Extended Release: Acceptance criteria include at least 3 points. An early time point, usually 1–2 h, is chosen to show that dose dumping is not probable. An intermediate time point is chosen to define the in vitro release profile of the dosage form, and a final time point is chosen to show essentially complete release of the drug(28). Adequate sampling should be performed, for example at 1, 2, and 4 hours, and every two hours thereafter until either 80% of the drug is released or an asymptote is reached. If the maximum amount dissolved is less than 80%, the last time point should be the time when the plateau of the dissolution profile has been reached. When IVIVC was not established, the recommended range at any dissolution time point specification is ±10% deviation from the mean dissolution profile obtained from the clinical/BA lots. Specifications should be established on clinical/BA lots. Widening specifications based on scale-up, stability, or other lots for which BA data are unavailable is not recommended. Specifications should be established based on average dissolution data for each lot under study, equivalent to USP Stage 2 testing. Specifications allow that all lots to pass at Stage 1 of testing may result in lots with less-than-optimal in vivo performance passing these specifications at USP Stage 2 or Stage 3. (26) Delayed release: The medium used for an acid stage is usually 0.1 N hydrochloric acid (HCl), and the duration of this stage is typically 2 h. The dosage unit is then exposed to a buffer medium, usually 0.05 M phosphate buffer at pH 6.8, but other buffers and pH targets may be used if justified. The duration of the buffer stage will depend on whether the in vivo release of the drug substance in the intestinal tract is intended to be immediate or extended. When the release in the intestinal tract is immediate, the sampling in the buffer stage is usually 60 min for compendial tests. When the release in the intestinal tract is extended, the buffer stage time will depend on the extended-release characteristics. In general, sampling should be done at 30 min, 1 h, 2 h, and after that every 2 h until complete drug release. (28) Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug is released or an asymptote is reached.(29)

*IR dosage forms. For MR no discussion is presented

4.3.3 EMA

The dissolution specification is determined in terms of quantity (Q) of pharmaceutical active ingredient dissolved in a specified period. In this context, the immediate release of a drug product is determined as at least 75% (Q) dissolution of the AS within 45 minutes(30).

For EMA, the test must present discriminatory power, i.e., the ability to discriminate between batches manufactured with different critical process parameters and/or critical material attributes that may impact on BA.

For the dissolution method development, the selection of dissolution medium should be based on the physic-chemical characteristics of the AS and intended dose range of the drug product. The use of surfactants should be avoided but, if used, should be justified and the selection of the dissolution apparatus should be discussed.

Not always the in vitro dissolution tests are predictive because they are over-discriminative. So, it is considered acceptable because if the dissolution profiles are not changed, the in vivo equivalence can be successful. As the dissolution test conditions are developed with the objective to detect differences between different quality attributes batches, the affirmative that these conditions are in vivo discriminative cannot be claimed.

The discriminatory power of the dissolution test can be estimated by the in vivo data of the BE study evaluation.

Furthermore, in certain instances a dissolution test can be used to waive a BE study. Therefore, dissolution studies can serve several purposes, as presented in the table below:

Table 8 – Objectives of Dissolution test

Testing on product quality:	- to get information on the test batches used in BA/BE studies and pivotal clinical studies to support specifications for quality control. - to be used as a tool in quality control to demonstrate consistency in manufacture. - to get information on the RMP used in BA/BE studies and pivotal clinical studies.
Bioequivalence surrogate inference:	- to demonstrate in certain cases similarity between different formulations of an AS and the RMP. - to investigate batch to batch consistency of the products (test and reference). - to be used as basis for the selection of appropriate batches for the in vivo study.

Regarding the dissolution testing on the guideline and on Reflection Paper, the dissolution specification for generic solid oral immediate release products with systemic action that discusses the suitability of the dissolution method and the specifications for in vitro dissolution of orally administered generic drug products with immediate release characteristics, the development of a dissolution procedure should consider the following (table 9):

Table 9 – EMA Guideline and EMA Reflection Paper summary

Dissolution testing:	
EMA Guideline	Based on general and/or specific pharmacopoeial requirements. In case those are shown to be unsatisfactory and/or do not reflect the in vivo dissolution (i.e., biorelevance) alternative methods can be considered when justified that these are discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the product in vivo. Current state-of-the-art information including the interplay of characteristics derived from the BCS classification and the dosage form must always be considered. Sampling time points should be sufficient to obtain meaningful dissolution profiles, and at least every 15 minutes. More frequent sampling during the period of greatest change in the dissolution profile is recommended. For rapidly dissolving products, where complete dissolution is within 30 minutes, generation of an adequate profile by sampling at 5- or 10-minute intervals may be necessary. If an AS is considered highly soluble, it is reasonable to expect that it will not cause any BA problems if, in addition, the dosage system is rapidly dissolved in the physiological pH range and the excipients are known not to affect BA. If an AS is considered to have a limited or low solubility, the rate limiting step for absorption may be dosage form dissolution. This is also the case when excipients are controlling the release and subsequent dissolution of the AS. In those cases, a variety of test conditions is recommended, and adequate sampling should be performed.
EMA Reflection paper	The selection of a suitable dissolution medium (composition, volume) should be based on the physico-chemical characteristics of the AS(s) and the intended dose range of the drug product and the formulation to be tested. Sink conditions should be attained but are not mandatory. In general, an aqueous medium should be used, and the pH should first be evaluated in the physiological pH range. The addition of surfactants should be avoided. When used, for instance to achieve adequate release for poorly aqueous-soluble ASs, the type of surfactant should be justified, the concentration should be as low as possible and be justified by relevant solubility and dissolution data and an accompanying scientific discussion. The selection of the dissolution apparatus is up to the applicant and should be sufficiently justified. The development of methods using the paddle apparatus should start with a stirring speed of 50 rpm; the development of methods using the basket apparatus should start with a stirring speed of 100 rpm. Higher stirring speeds or different basket mesh sizes may be applied with an appropriate justification. A higher stirring speed may be justified by high variability of the results (e.g. > 20% RSD at time-points ≤ 10 minutes, > 10% RSD in the later phase for a sample size of 12) observed at lower speed rates due to hydrodynamic effects (e.g. coning) or other factors (e.g. tablet sticking). However, it is known that methods with increased stirring speeds may be less discriminatory. Increasing the stirring

	speed at the expense of the discriminatory power simply to reduce variability of the results or to obtain complete dissolution in a shorter time should be avoided. An increase of the stirring speed may be considered in case of over-discriminatory conditions towards in vivo performance. In all cases, dissolution profiles at increased stirring speeds should have sufficient discriminatory power for drug product quality control. During development, the contribution of method parameters to the variability of the results should be investigated and reduced to a minimum. The discriminatory power should be discussed. Considering Test conditions and discriminatory power, the quality control tests must be chosen to allow extrapolation of the results of a BE study from the biobatch to commercial batches. So, it is necessary to have a suitable specification of the amount of the AS released at a specified time-point. The test conditions should enable discrimination between batches manufactured with different critical process parameters and /or critical material attributes which may have an impact on the BA. Ideally all non-bioequivalent batches should be detected.

The dissolution results, under different test conditions during development, should be compared with the pharmacokinetic data generated to select the most suitable test conditions for routine testing. Due to limited amount of in vivo data in most generic applications, mathematical correlations may not be possible; however, all the relevant in vivo data available should be taken into consideration in choosing the most suitable in vitro dissolution test conditions.

The suitability of the test conditions for routine batch testing should be demonstrated using batches with different quality attributes. To achieve this, batches with meaningful changes compared to the applied finished product should be manufactured. Such changes may relate to the quantitative formulation, material specifications and/or using slightly modified process parameters. Current knowledge of both the characteristics derived from the Biopharmaceutics Classification System (BCS) and the finished product must be considered when choosing the quality attributes to change. For instance, for a finished product where the in vivo absorption (rate and/or extent) is expected to be limited by solubility / intrinsic dissolution of the AS, i.e., BCS II and IV, suitable quality attributes may be particle size of the AS or other attributes that would have an impact on the in vivo dissolution. For a finished product where the in vivo absorption is expected to be limited by gastric emptying or intestinal permeability, i.e., containing BCS I or III class AS with rapid or very rapid dissolution, suitable quality attributes may be factors in the formulation and/or manufacturing process that will have an impact on the disintegration of the finished product and significantly affect the rate of in vitro dissolution.

Changes to the composition of the drug product to create a “bad batch” should be covered by the proposed qualitative batch formula and only the proportions of the

employed excipients might be changed. The complete omission of one or more specific excipients from the formulation (e.g. binder, disintegrant) is not supported. The dissolution test conditions should be able to detect these changes by setting a suitable specification. Ideally, the in vitro dissolution test should predict the in vivo outcome, but sometimes in vitro dissolution tests are not predictive because they are over-discriminative. This is also acceptable because if dissolution profiles are not altered, in vivo equivalence can be assumed. Usually, in vivo data for batches with different quality attributes is not available. As dissolution test conditions are defined based on their ability to detect differences between batches with different quality attributes, and as these changes are of unknown in vivo relevance, it cannot be claimed that these dissolution test conditions are in vivo discriminative.

Regarding the specification settings, the dissolution specification limit is defined by a Q value (mean value at a given time point) which allows discrimination between acceptable and non-acceptable batches. Batch results showing compliance with stage S1, S2 and S3 (Ph. Eur. 2.9.3.) are acceptable. The specification should be set in such a way so that during routine manufacture and testing it would be expected that compliance with S2 is attained.

Before setting the Q value, the time range allowing discrimination should be considered from the dissolution profile of the biobatch. Sampling time points should be sufficient to obtain a meaningful dissolution profile.

To ensure that the results of the BE study may be extrapolated to the drug product administered to the patient, all commercial batches should show similar behaviour compared to the biobatch. The dissolution profile of the biobatch, using test conditions providing discriminatory power should be used to set a suitable specification. Similar dissolution of two batches may be assumed in case of differences of less than 10% of the label claim in their mean results. Therefore, the Q value is recommended to be set based on the biobatch dissolution result (mean value of 12 units) minus 10%.

According to EMAs reflection paper, the acceptance criterion Q value is usually set in the range between 75-85% (5% intervals) to demonstrate discriminatory power and satisfactory dissolution. A limit greater than 85% is not relevant. Usually the time points 15, 30 or 45 minutes would be sufficient, but other time points may be used if justified. It is not considered relevant to choose a time point before 15 minutes.

The Annex of the Reflection Paper presents the Decision tree for the principles for setting

specifications based on the dissolution results of the biobatch. The recommendations are meant as guidance for setting the specification **(table 10).** The discriminatory power is closely linked to the time point and Q value chosen. If time points/Q values other than proposed in the decision tree would lead to discriminatory power, this is also acceptable.

Table 10 – EMA proposed dissolution acceptance criteria

Dissolution of the biobatch is larger than or equal to 95% in 15 minutes:	(Q) may be set to Q=85% after 15 minutes;
Dissolution of the biobatch is less than 95% but larger than or equal to 85% in 15 minutes:	(Q) may be set to 75%, 80% or 85% whichever is closer to Q=biobatch result -10% at 15 minutes;
Dissolution of the biobatch is larger than or equal to 85% only after 30 minutes:	(Q) may be set to 75%, 80% or 85% whichever is closer to Q=biobatch result -10% at 30 minutes;
Dissolution of the biobatch is larger than or equal to 85% only after 45 minutes:	(Q) may be set to 75%, 80% or 85% after 45 minutes.
Dissolution of the biobatch is less than or equal to 85% after 45 minutes	a minimum of 75% at 45 minutes should be specified if possible. Otherwise, if the dissolution specification (Q) is less than 75% after 45 minutes, the dissolution specification should be based on more than one time point (see Annex: Decision tree for the principles for setting specifications).
There is no biobatch.	Specification limit with a fixed Q value within 15 min (for BCS class I and III) or 30 minutes (applicable only for human BCS class I products) can be established. Q value should be at least 80% using discriminatory test conditions (i.e., the QC method applied for), irrespective of the dissolution results of the test batch observed in the study used to claim the BCS biowaiver.

The conditions for the dissolution test in the specification should be chosen as the most discriminatory between those used in the comparative dissolution study.

4.4 Comparative Dissolution Profile criteria

4.4.1 ANVISA

RDC n° 31/2010 provides criteria to perform a CDP study, defined as an analytical test with sampling at multiple points for the evaluation of a given AS dissolution by comparing two formulations.(23)

The Comparative Dissolution Profile Study must be performed considering:

-An Anvisa duly qualified Laboratory for this purpose, prior to the performance of the Relative BA/BE Study, when applicable.

-Using the same dissolution method as in the PE Study, when applicable.

-Using the same batches of Test and RMP as used for the PE and Relative BA/BE Studies, when applicable, simultaneously between the Test Drug and the Reference/Comparator drug product.

For post-approval cases, the Comparative Dissolution Profile Study may be performed by preferably using the dissolution method as described in the Brazilian Pharmacopoeia or other official compendia, standards or regulations approved/accepted by ANVISA, or in its absence, a dissolution method development report confirming the discriminatory power of the method should be presented

The discriminative power of the compendium method should also be confirmed for the drug product formulation.

For the comparison of dissolution profiles, the curve is evaluated by using the Simple Independent Model Method (table 11), and the other models are unforeseen in the actual regulation.

When the result of the Comparative Dissolution Profile Study is not similar, the proof of therapeutic equivalence between the Test and Reference/Comparator products may, at ANVISA's discretion, be based only the result of the Relative BA/BE Study.

Table 11 - Simple Independent Model Method

Conditions	Test and RMP/Comparator Drug products shall show corresponding dissolution types.
	Study conduction with 12 units of each product
	Collection times shall be the same for the two formulations.

	The number of collection points shall be representative of the dissolution process until a curve plateau is reached, with sample quantification for not less than 5 collection points. Extended-release products: Sampling shall be representative of the dissolution process, e.g., 1, 2, and 4 hours and every two-hour thereafter until both drugs show dissolution of 80% of the active ingredient or the plateau is reached. Delayed release products: Dissolution in 0.1N HCl medium must be carried out for 2 hours (acid step), followed by dissolution in buffer medium. After the moment the drug is placed in the buffer medium, the sample collection must be representative of the dissolution process in, for example, 15, 30, 45, 60 and 120 minutes until both products present a dissolution of 80% of the AS or plateau is reached.
	CV for the first collection points shall not exceed 20%. For the remaining points, a maximum of 10% is considered. The first collection points are considered as the ones corresponding to 40% of the total collected points.
	When the AS shows high solubility and is an IR product, showing very fast dissolution for both products, the f_2 factor loses its discriminative power being therefore not required to be calculated. If so, very fast dissolution of the products shall be evidenced by means of a curve plotting, by making collections, for instance, at 5, 10, 15, 20, and 30 minutes. The CV at 15-minute point shall not exceed 10%.
f_2 calculation	Factor f_2 corresponds to the measurement of the similarity between the percent dissolved for both profiles: $$F2 = 50 \times \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n}(Rt-Tt)^2\right]^{-0,5}\times 100\right\}$$ where: n = number of collection times considered for f_2 calculation purposes. Rt = percent dissolved value at time t, obtained with the RMP or Comparator Drug product. Tt = percent dissolved value of the Test Drug or the changed formulation, at time t.
	For f_2 calculation, use at least the three first points, excluding time zero;
	For f_2 calculation, include one curve point only after both drugs reach an average 85% dissolution:
Specification	Similarity factor value must be between 50 to 100, with all the conditions met.

4.4.2 FDA

FDA presents the discussion of CDP in different guidelines, separating them between IR and MR solid oral dosage forms.

When related to changes, in complement of the dissolution guidelines, other details are provided in the SUPAC Guidelines. Depending on the level of change and the BCS of the AS, different levels of in vitro dissolution test and/or in vivo BE studies are recommended, what vary depending on solubility and permeability factors of the drug substance for IR, and additional separated requirements between Narrow Therapeutic Index (NTI) drugs for MR oral solid dosage forms.

In the presence of certain minor changes, the single-point dissolution test may be adequate to ensure unchanged product quality and performance. For major changes, a dissolution profile comparison performed under identical conditions for the product before and after the change(s) is recommended in a case of a NDA and against the RMP in case of an ANDA.(25)

For formulation changes beyond those listed in the guidance, additional dissolution profile determinations in several media are recommended.

For manufacturing site changes, scale-up equipment changes, and minor process changes, only dissolution testing should be sufficient to ensure unchanged product quality and performance. The SUPAC guidelines recommends dissolution profile comparisons for approving different levels of changes and documenting product sameness between the test (post-change) and RMP or pre-change product. It recommends dissolution profile comparisons using a model independent approach and the similarity factor (f_2), but the Guidance for industry – Dissolution Testing of IR solid Oral Dosage Forms, also brings possibility of multivariate model independent and model dependent approaches, as presented in table 12.

SUPAC-MR provides specific requirements for extended and delayed release and, request the f_2 test only in the absence of an established IVIVC, referencing the IR Dissolution Guideline for description of multivariate model independent and model dependent approaches. (25)

It is also informed in SUPAC-MR guideline that, an f_2 value less than 50 does not necessarily indicate lack of similarity, and justifications may be accepted in case of Prior Approval Supplements, which should include additional data to support the claim of similarity, with supporting statistical analysis (e.g., 90% CI analysis).

For both IR and MR, when the comparative dissolution profile is not similar between the test and RMPs, the therapeutic equivalence may be evaluated based by the BE study.

Table 12 - FDA Comparative Dissolution Profile approaches

Model Independent Approach Using a Similarity Factor (simple model independent approach)	**Model Independent Multivariate Confidence Region Procedure**	**Model Dependent Approaches**
Uses a difference factor (f1) and a similarity factor (f_2) to compare dissolution profiles. Most suitable for dissolution profile comparison when three to four or more dissolution time points are available. Guidance suggestions: - Performed in 12 individual dosage of both products. - The dissolution measurements of the test and reference batches should be made under the same conditions. Dissolution time points for both the profiles should be the same (e.g., 15, 30, 45, 60 minutes). The reference batch used should be the most recently manufactured pre-change product. - Only one measurement should be considered after 85% dissolution of both the products - To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%. - The mean dissolution values for R can be derived either from (1) last t prechange/RMP batch or (2) last two or more consecutively manufactured prechange batches. Similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. $f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \bullet 100\}$ Where: n is the number of time points, Rt is the dissolution value of the reference (prechange/RMP) batch at time t, and	In instances where within batch variation is more than 15% CV. Suggested: 1. Determine the similarity limits in terms of multivariate statistical distance (MSD) based on inter batch differences in dissolution from reference (standard approved) batches. 2. Estimate the MSD between the test and reference mean dissolutions. 3. Estimate 90% confidence interval of true MSD between test and reference batches. 4. Compare the upper limit of the confidence interval with the similarity limit. The test batch is considered similar to the reference batch if the upper limit of the confidence interval is less than or equal to the similarity limit.	To allow application of mathematical models described in the literature. -Suggested: 1. Select the most appropriate model for the dissolution profiles from the standard, pre-change, approved batches. A model with no more than three parameters (such as linear, quadratic, logistic, probit, and Weibull models) is recommended. 2. Using data for the profile generated for each unit, fit the data to the most appropriate model. 3. A similarity region is set based on variation of parameters of the fitted model for test units (e.g., capsules or tablets) from the standard approved batches. 4. Calculate the MSD in model parameters between test and reference batches. 5. Estimate the 90% confidence region of the true difference between the two batches. 6. Compare the limits of the confidence region with the similarity region. If the confidence region is within the limits of the similarity

Tt is the dissolution value of the test (postchange) batch at time t. To show difference and similarity factors: 1. Dissolution profile of two products (12 units each) of the test (post change) and reference (pre change) products. 2. Using the mean dissolution values from both curves at each time interval, calculate the difference factor (f1) and similarity factor (f_2) using the above equations. 3. For curves to be considered similar, f1 values should be close to 0, and f_2 values should be close to 100. Generally, f1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test (postchange) and RMP/prechange products. 4. the average difference at any dissolution sampling time point should not be greater than 15% between the postchange and RMP/prechange products dissolution profiles. *		region, the test batch is considered to have a similar dissolution profile to the reference batch.

*Requirement presented only in the SUPAC-MR guideline.

4.4.3 EMA

The requirements for comparative dissolution profile and possible approaches are provided in Guideline on the investigation of BE from EMA and a similar dissolution profile is necessary to demonstrate that the proposed change do not impact in the BA of the product.

When it's not possible to confirm similar dissolution profiles, a BE is required, unless a biowaiver is possible due to the BCS characteristic or whether an acceptable level IVIVC has been established.

In cases where the BA of the product undergoing change has been investigated and an acceptable level correlation between in vivo performance and in vitro dissolution has been established, the requirements for in vivo demonstration of BE can be waived if the dissolution profile in vitro of the new product is similar to that of the already approved medicinal product under the same test conditions that proved the correlation.

Dissolution profile similarity testing, and any conclusions drawn from the results (e.g., justification for a biowaiver) can be considered valid only if the dissolution profile has been satisfactorily characterized using enough time points. (22)

We can consider the characteristics for the similarity of the dissolution profile as presented in table 13.

Table 13 – EMA Comparative Dissolution Profile approaches

Conditions	Twelve individual values for every time point for each formulation
	The time points should be the same for the two formulations
	In case more than 85% is not dissolved at 15 minutes but within 30 minutes, at least three time points are required: the first time point before 15 minutes, the second one at 15 minutes and the third time point when the release is close to 85%.
	Where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation.
	Sampling time points should be sufficient to obtain meaningful dissolution profiles, and at least every 15 minutes. More frequent sampling during the period of greatest change in the dissolution profile is recommended. For rapidly dissolving products, where complete dissolution is within 30 minutes, generation of an adequate profile by sampling at 5- or 10-minute intervals may be necessary.
	Test methods should be developed product related based on general and/or specific pharmacopoeial requirements. In case those requirements are shown to be unsatisfactory and/or do not reflect the in vivo dissolution (i.e., biorelevance) alternative methods can be considered when justified that these are discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the

	product in vivo. Usual experimental conditions are e.g.: Apparatus: paddle or basket -Volume of dissolution medium: 900 ml or less -Temperature of the dissolution medium: 37±1 °C -Agitation: paddle apparatus - usually 50 rpm/ basket apparatus - usually 100 rpm -Sampling schedule: e.g., 10, 15, 20, 30 and 45 min -Buffer: pH 1.0 – 1.2 (usually 0.1 N HCl or SGF without enzymes), pH 4.5, and pH 6.8 (or SIF without enzymes); (pH should be ensured throughout the experiment; Ph.Eur. buffers recommended) -Other conditions: no surfactant; in case of gelatin capsules or tablets with gelatin coatings the use of enzymes may be acceptable.
f_2 calculation	$f_2 = 50 \cdot \log\left[\frac{100}{\sqrt{1+\frac{\sum_{t=1}^{t=n}[\bar{R}(t)-\bar{T}(t)]^2}{n}}}\right]$ where: $f2$ is the similarity factor. n is the number of time points. R(t) is the mean percent reference API dissolved at time t after initiation of the study. T(t) is the mean percent test drug dissolved at time t after initiation of the study. Percent dissolution should be determined for reference and test formulations.
	For f_2 calculation, use a minimum of three time points (zero excluded)
	For f_2 calculation, not more than one mean value of > 85% dissolved for any of the formulations.
	RSD% of any product should be less than 20% for the first point and less than 10% from second to last time point.
Specification	f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.
Mahalanobis Distance (MD)(31)	Not accepted to be used for similarity determination
Bootstrap methodology (31)	Bootstrap methodology could be used to derive confidence intervals for f_2 based on quantiles of re-sampling distributions, and this approach could be considered the preferred method over f_2 and MD.
Other models accepted	When the $f2$ statistic is not suitable, the similarity may be compared using model dependent (statistical multivariate comparison of the parameters of the Weibull function) or model-independent methods (% dissolved at different time points).
	Alternative methods to the $f2$ statistic to demonstrate dissolution similarity are considered acceptable, if statistically valid and satisfactorily justified.
	Evidence that the statistical software was validated should also be provided.
	The similarity acceptance limits should be pre-defined and justified and not be greater than a 10% difference. In addition, the dissolution variability of the test and RMP data should also be similar, however, a lower variability of the test product may be acceptable.
	A clear description and explanation of the steps taken in the application of the procedure should be provided, with appropriate summary tables.

4.5 Changes to the approved condition

After the MA, post-approval changes are usually necessary during drug product lifecycle and are expected to be done, as for manufacturing improvements and demand changes, as for knowledge and regulatory evolution.

The control of this changes and its impact evaluation is part of Good Manufacturing Practices. Maintenance of the MA is also required to confirm that the product preserves or improves the characteristics evaluated by the HA for initial approval.

The potential impact level of the change is the guide for its classification that also determines the autonomy of the holder for its implementation provided in regulations issued by HA.

There is no regulatory convergence between HA for this topic, and for drug products authorized in multiple countries, the differences between each region/country need to be cautiously managed.

The common factor regarding regulatory lifecycle management is the possibility of a Post-Approval Change Management Protocol (PACMP) submission and the Product Lifecycle Management (PLCM) document concept being introduced in these regions by the implementation of ICH Q12 Guideline, that provides for Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management.

The main classification factors and the requirements for changes, that could have direct impact in the dissolution profile of solid oral dosage forms, will be compared between ANVISA, EMA and FDA, considering their classification (level), type, criteria, proofs, and documents. The objective is to evaluate the risk of bioinequivalence due to successive minor changes from reference drugs and generic drugs.

The changing variables chosen to be evaluated are API physical characteristics, process parameters, composition of the FDF, excipients specifications, shape/dimensions of tablets, batch size, dissolution method/specification, equipment, and manufacturing site as presented in a more visual form in figure 1.

The tables and classifications will be presented in Annex I, II and III and the discussion of the results will be discussed in chapter 5.

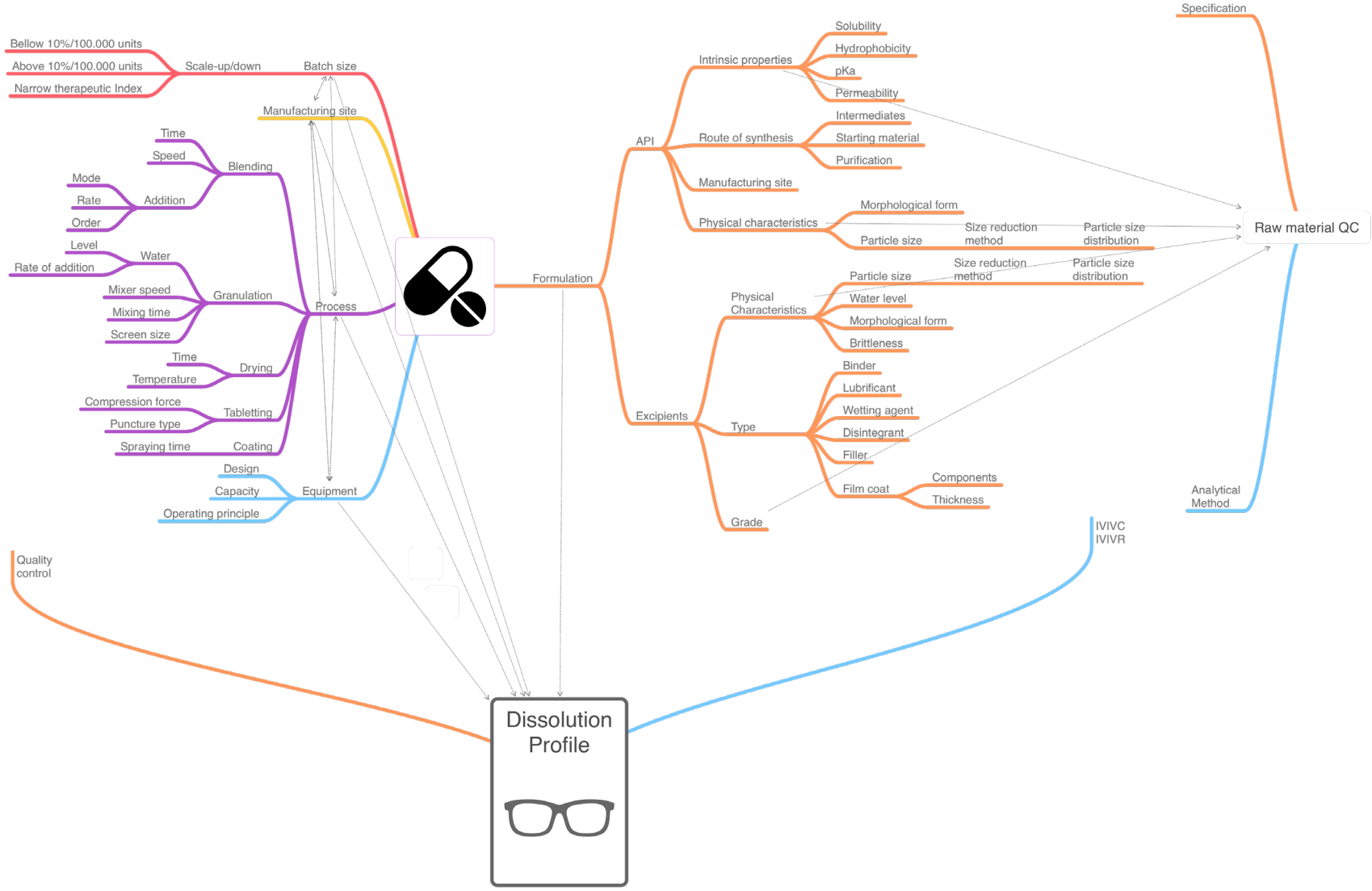

Figure 1 – Possible variables that could impact the In-Vitro performance of a solid oral dosage form

4.5.1 ANVISA

In Brazil, RDC 73/2016(32) provides the requirements for changes in drug products containing semi-synthetic and synthetic API's, classified as new drugs, generic and branded generics. This regulation is in force since November 2017 and is considered a regulatory mark in the country.

Among many important changes, a new document known as PATE (Technical Analysis Conclusion) started to be required. It stipulates that the applicant discusses all the impacts of the proposed change in the approved condition, linking all the tests and studies' results obtained, providing the company's conclusions on the change application. This document reinforces the shared responsibility between the HA and the regulated sector, as it enforces a deep assessment of those that own the knowledge on product's, which must be presented in all post-approval changes submissions.

RDC 73/2016 also provides 2 types of variation procedures:

- Ordinary procedure: the company submits the variation application and awaits ANVISA's assessment and decision.

- Simplified procedure: the variation is classified by ANVISA as an immediate implementation candidate, without waiting for ANVISA's assessment and decision.

It is important to mention that the confirmation of the classification of the change will be possible following the evaluation of its impact, and the product will be accepted for use only after the confirmation that the proposed change does not affect its quality, safety, and efficacy. When facing a change proven to significantly impact on these characteristics, even if classified as immediate implementation, the company should follow the ordinary procedure.

Regarding the classification of changes, they are divided into the following categories:

Ordinary procedure (major):

- Change submission. Must await ANVISA's approval for implementation.
- Change submission. Must await ANVISA's approval for implementation within 180 days after submission for the first manifestation.

Simplified procedure (moderate and minor):

- Change submission. Immediate implementation.

- Annual report submission. Immediate implementation.

For multiple submissions, if different classification is required between them, the higher risk level should be considered for all changes.

Except for the Annual Report Submission Classification, all changes submitted for all the authorized products are public in ANVISA's consultation system.

The RDC 73/2016 is divided in tables that group alike types of post-approval changes, where the type of submission classification, the supporting documents required and the conditionals to typification are described.

For generic drugs, PATE does not require a critical evaluation of their comparison to reference drugs and the discussion on the BE results is not developed. The previous approved condition is always the base for the comparison.

RDC 359/2020(33) is the regulatory mark that defined the API manufacturer's responsibility/possibility of its registration on ANVISA. This procedure, named CADIFA (like CEP procedure of EDQM), provides all the requirements for the submission and maintenance of the API lifecycle with the change classifications.

RDC 361/2020 is also part of API's regulatory mark that adequate to the FDF resolutions, RDC 200/2017 and RDC 73/2016, establishing, in Annex I, the new requirements for FDF MA, and maintaining, in Annex II, the previous requirements that can be used by the MAH for the transition period until August 2023, considering FDF test batches manufactured until February 1, 2022.

Find below the description of post-approval changes that require comparative dissolution profile according to RDC 73/2016.

Table 1 of RDC 73/2016 describes the changes related to Active Pharmaceutical Ingredient (API), with or without CADIFA, that needs to be submitted by the FDF MAH.

Considering that the initial point for the observation proposed in this thesis – variations that require CDP, for API change types, the difference between minor and major changes is conditioned upon the maintenance of the impurity profile and no change in FDF specification. Nevertheless, the maintenance of the dissolution specification does not guarantee the absence of impact on CDP, as QC uses only the Q specification to

approve the batches.

The CDP will be required in document 5, with the following description: "*The impact of the change on the drug should be assessed and determine what evidence should be presented. If the equivalence of the physical properties and the impurities profile of the API is not demonstrated, tests should be carried out with the drug, proportionally to the potential impact of the change. Factors to be considered include characteristics of the API (e.g., SCB classification, occurrence of polymorphism, particle size distribution, morphology) and the relevance of these properties to drug performance (e.g., pharmaceutical form, release system, manufacturing process). When the technical report of the drug relative bioavailability/bioequivalence study is submitted, change "1e", "1h" or "1k" should be filed."*

This will lead to the need of proof of discriminative method, especially relevant for low solubility drugs, and will be required to be provided when submitting a CDP to the REBLAS. As it does not describe whether it is against the reference or the approved condition, there is a possibility in practice of divergence due to an alteration against the RMP. For minor variations, the study is performed between previously approved and a proposed condition of the generic drug product.

The criteria for this discussion on the impact will be the actual requirement that considers the CDP similar between the previous and proposed condition, that is, when f_2 is above 50, that will not confirm that the in vitro performance against the RMP is maintained.

In this case, the possibility of divergence in BE is present and the risk is considered existent for 1d, 1g and 1j changes' submissions.

For major changes, the only (low) risk identified for changes in the API, is provided in table 1 of RDC 73/2016, as the decision to demand a new BE study will base itself on the analysis of the API change impact on the drug product. Even if not expressly informed in the table, a well based discussion to waive the BE could not be based only on the proof comparing the previous and proposed condition of the generic drug. It will also be necessary to include the RMP if not yet provided, as ANVISA requires its evaluation.

It has been considered a residual risk for API major changes from types 1e, 1f, 1h and 1k, because of the absence of clear information its definition in document 5. In worst case scenario, the MAH uses the previously approved condition in the CDP instead of RMP, based on the conclusion that the generic shares a similar profile. The BE can be waived and RDC 219/2018 (conditional approval) may be used to implement the change

after 180 days if no feedback from ANVISA is received.

In Brazil, due to confidentiality regarding regulatory information of products and companies, the publicity of the changes is exclusively about the classification of the change (e.g.: g. major inclusion of batch size). No additional information is published, which is an issue when a change is approved for the reference drug and may impact on the generic drug.

Also, there is no visibility for minor changes to be reported on the annual report because, as it is a periodic submission, there are only two options: with or without changes. In this type of post-approval submission, the changes are included directly in the annual report at ANVISA´s system, with all evidence required attached.

4.5.2 FDA

According to the U.S. Code of Federal Regulations(20) and the FDA Guidance for Industry - Changes to an Approved NDA or ANDA(34), the applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The applicant must describe each change fully and, depending on the type of change, through a supplement or an annual report.

Variation types, reporting categories and changes classifications are also described in the CFR(20) and in the guideline, as summarized below:

The reporting categories are related to the potential of the proposed change to cause adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. They are divided into Major, Moderate and Minor changes.

The variation types of regard to the need of previous approval from FDA or not to implementing that change and is also related to the risk.

For each change, the supplement must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change. They are divided in Prior approval, Changes being affected in 30 days, Changes being affected supplements and changes that are included in the annual report.

1) Major change:

As it is the change with higher probability of impacting the drug product, it is required a submission of a supplement (Prior Approval Supplement) and its approval by FDA prior to distribution of the drug product with the change implemented.

2) Moderate change:

For changes of moderate probability of impacting the drug product, there are two types of submissions, also divided according to potential risk:

Supplement - Changes Being Affected in 30 Days

Submission of a supplement to FDA at least 30 days before the distribution of the drug

product where the change was implemented. The drug product made using a moderate change cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required.

Supplement - Changes Being Effected in 30 Days

If, after review, FDA disapproves a changes-beingeffected-in-30-days supplement or changes-being-effected supplement, FDA may order the manufacturer to cease distribution of the drug products made using the disapproved change.

3) Minor change:

They represent the changes that have a minimal potential of impacting the drug product characteristics.

The applicant must describe minor changes in its next Annual Report(35).

The classification examples and expected documents are described considering the following situations: Manufacturing sites, manufacturing process, specifications, container closure system, labelling and miscellaneous changes.

Now focusing on oral solid dosage forms, the SUPAC (Scale-up and Post approval Changes) guidelines provides specific recommendations with the general cases for immediate(36) and modified release(29) dosage forms.

The changes are classified in 3 levels, according to the definitions described below:

- Level 1: Changes that are unlikely to have any detectable impact on formulation quality and performance.
- Level 2: Changes that could have a significant impact on formulation quality and performance.
- Level 3: Changes that are likely to have any detectable impact on formulation quality and performance.

The documents and proofs to be presented follows 2 factors: Therapeutic range, solubility, and permeability.

The dissolution details are provided in each exemplified situation considering the impact of the change in the product performance.

For immediate release components and composition changes, the dissolution documentation is described in three different cases as described below:

- Case A: High Permeability, High Solubility Drugs
- Case B: Low Permeability, High Solubility Drugs
- Case C: High Permeability, Low Solubility Drugs

Figure 2 correlates the cases and the dissolution tests that should be provided, as per SUPA-IR guideline.

A list of narrow therapeutic range drugs is provided in Appendix A. Drug solubility and drug permeability are defined as either low or high. Solubility is calculated based on the minimum concentration of drug, milligram/millilitre (mg/mL), in the largest dosage strength, determined in the physiological pH range (pH 1 to 8) and temperature (37± 0.5ºC). High solubility drugs are those with a dose/solubility volume of less than or equal to 250 mL (Example: Compound A has as its lowest solubility at 37± 0.5ºC, 1.0 mg/mL at pH 7, and is available in 100 mg, 200 mg and 400 mg strengths.

This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL=400 mL).

Permeability (Pe, centimetre per second) is defined as the effective human jejunal wall permeability of a drug and includes an apparent resistance to mass transport to the intestinal membrane. High permeability drugs are generally those with an extent of absorption greater than 90% in the absence of documented instability in the gastrointestinal tract, or those whose permeability attributes were determined experimentally).

The cases and rational for documents to be presented for the following situations: Components and compositions, site changes, changes in batch size and manufacturing.

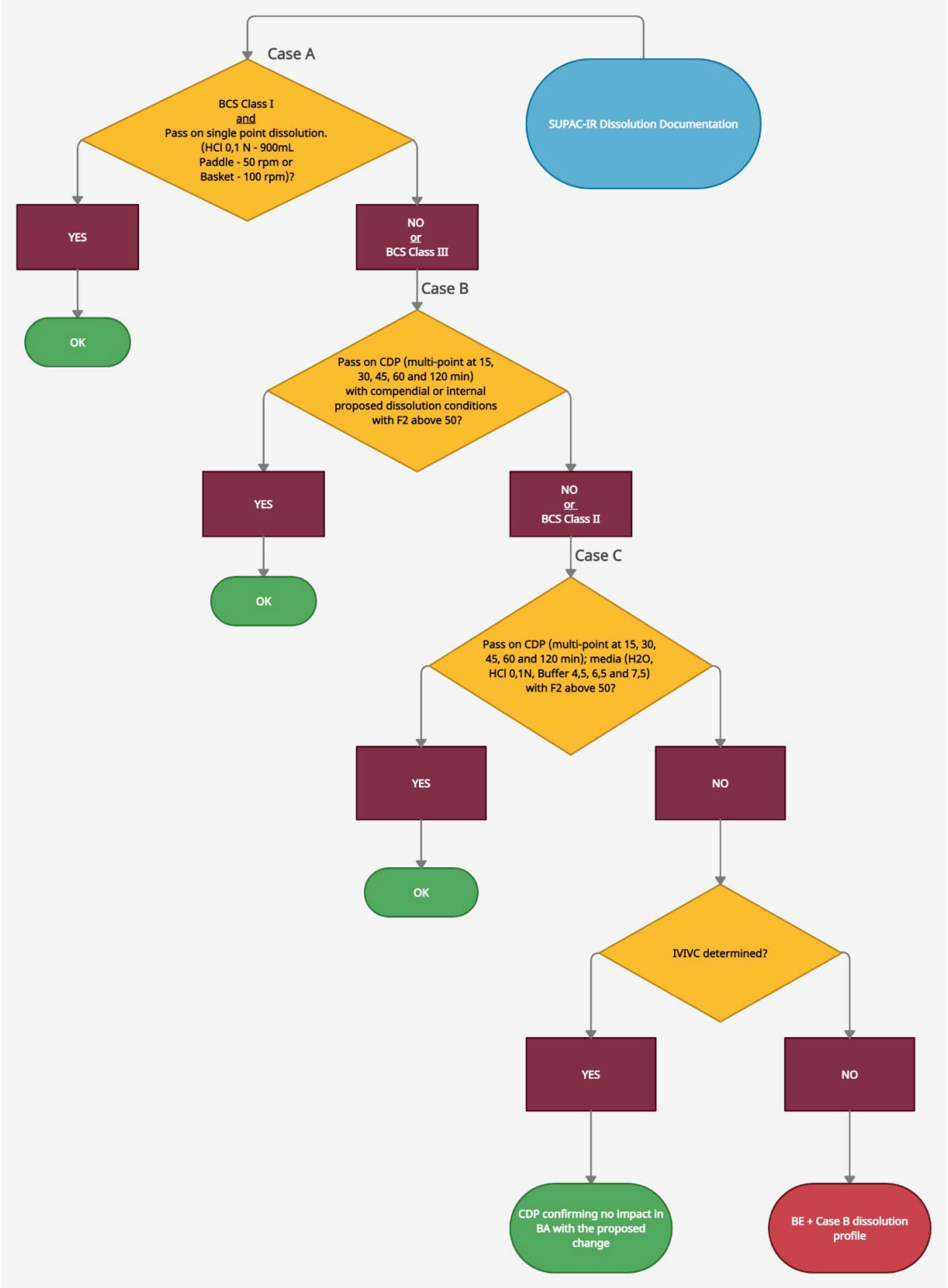

Figure 2 – Decision tree for dissolution proofs to be presented according to BCS class based on SUPAC-IR requirements.

For modified release changes, the cases and rational for documents to be presented for the following situations: Components and compositions – nonrelease controlling excipient and release controlling excipients, site changes, changes in batch size, manufacturing equipment changes and manufacturing process changes.

The description of the level of changes and their type of submission are provided in Appendix A-1 for the MR SUPAC guideline.

4.5.3 EMA

The main principle underlying Union pharmaceutical legislation is the protection of public health. Marketing authorizations for medicinal products are dynamic and not static and the dossier underlying a marketing authorization must be regularly updated in order to ensure that scientific progress and new regulatory requirements are respected, in accordance with Article 23 of Directive 2001/83/EC, Annex I to Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004. Any information which may influence the evaluation of the benefits and the risks of the medicinal product must be promptly supplied. In this regard, marketing authorization holders of marketing authorizations granted in accordance with Article 10 or 10c of Directive 2001/83/EC should introduce variations swiftly whenever the marketing authorization of the reference medicinal product or of the "original" medicinal product is changed to address a safety or efficacy concern.

In Europe, the post approval changes requirements are described in EC 2013/C 223/01. They are classified in minor variations of Type IA, minor variations of Type IB and major variations of Type II and there are specific requirements for each type of procedure (CP, MRP, NP).

Find below the description of each Type main characteristics:

Table 14 – EMA variations classification

Type	Submission and implementation procedure
IA	Minor variations of Type IA do not require prior examination by the authorities before they can be implemented by the holder. However, at the latest within 12 months from the date of the implementation, the holder must submit simultaneously to all Member States concerned, to the national competent authority, or to the Agency (as appropriate) a notification of the relevant variation(s).
IB	Such minor variations must be notified before implementation. The holder must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change (‘Tell, Wait and Do procedure).
II	Such major variations require approval of the relevant competent authority before implementation.

For some changes to the marketing authorization (other than extensions of indication), EMA publishes a summary of opinion in the CHMP (Meeting highlights from the Committee for Medicinal Products). Changes to the marketing authorization is of major public health importance, EMA may also publish in the CHMP meeting.

For variations that result in an updated product information, the medicine's EPAR is updated after the European Commission's decision. In addition to the updated product information, the EPAR update may include an updated medicine overview (if needed). The procedural steps taken and scientific information after authorization is published or updated in all cases.

Finally, the EPAR update also includes the publication of the public assessment report for those changes that are of particular importance. Public assessment reports are published for line extension applications when they contain new non-clinical or clinical data and for conditional marketing authorizations when they are switched to full authorizations.

Public assessment reports are also published for paediatric studies submitted under Article 46 of paediatric regulation (Regulation (EC) No 1901/2006).

All assessment reports are published in the section 'Assessment history' of the medicine's page with commercially confidential information redacted.

As with extension of indication applications, a CHMP evaluation of applications for other variations or line extensions may not result in a change to the marketing authorization, either because the CHMP decided no change was needed (negative opinion) or the applicant withdrew its application. In these situations, EMA may publish the assessment report for the evaluation if the application or the outcome of the evaluation is of particular importance. However, in most cases, the EPAR update only involves an update of the procedural steps taken and scientific information after authorization. In all cases where the only change to the EPAR concerns the document procedural steps taken and scientific information after authorization, this updated document is published with the next EPAR update.

5. Discussion

Table 155 – Comparative table for Submissions level and types between ANVISA, FDA and EMA.

Level	ANVISA	EMA	FDA
Minor	Annual Report Immediate implementation	IA Do and tell	Annual report
Minor/moderate	Change submission. Immediate implementation	IAIN Do and tell	Supplements being effected
Major	Change submission. Should wait for ANVISA´s approval for implementation. Possible to be implemented in 180 days if no manifestation from ANVISA.	IB	Supplements being effected 30 days
Major	Change application. Should wait for ANVISA´s approval for implementation	II	Prior approval Supplement

All these variables were assessed in the regulations of the 3 HA, and to facilitate the classification of the fragilities observed the following combinations were selected.

The classifications are presented in Annexes I, II and II.

Table 166 – Levels of proofs x risks

Risk considering BCS class II and IV	Description
Risk 1	Major variation, which already consider a new BE or a CDP between proposed condition and RMP
Risk 2	The conditionals already eliminate the applicability.
Risk 3	3 media CDP requirement.
Risk 4	Explicit definition for the responsibility of the MAH of presenting the relevant dissolution documents or explicit requirement of justifying the absence of BE, but not defining if between RMP or previous conditions.
Risk 5	Requirement of similar CDP in 1 media between previous and proposed conditions.
Risk 6	One point dissolution profile required (CoA of the drug product)
Risk 7	No CDP is required for the submission and just one point dissolution.
Risk 8	No proof of submission related to the drug product

Whenever a case fitted in more the 1 risk classification, the higher was maintained.

To illustrate the possibility of having a divergent dissolution profile when comparing the product with the proposed change against its previously approved condition, the following simulation was constructed, considering a generic product (BSC II or IV), approved without IVIVC definition, and submitted to a scale-up with concomitant minor and moderate changes after its approval, being classified in the researched regions as follows:

Table 177 – Scale-Up change with concomitant minor/moderate changes in the manufacturing process and equipment

Immediate release	ANVISA	EMA	FDA
Proposed change classification	6.a. Minor change in the manufacture process	B.II.b.3 a) Minor change in the manufacturing process*	VI.B.2.a - Changes being effected in 30 days**
	6.d. Minor change of equipment		VI.A.1.a - Change to alternative equipment of the same design and operating principles of the same or of a different capacity
	6.f. Minor inclusion of batch size	B.II.b.4 a) Up to 10-fold compared to the originally approved batch size	VI.A.1.a. Change in batch size, up to and including a factor of 10 times the size of the pilot/biobatch
Type	Immediate implementation. It does not require individual protocol. Annual report.	IA	Changes being effected in 30 days
Visibility of the change for public	No visibility	No visibility	The CMC supplement will be linked in history in Drugs@FDA Database, with no description of the change
Proof of performance maintenance (higher level)	5. Dissolution profile against the previous condition	3. Dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process 4. Justification for not submitting a new BE study according to the relevant (Human or Veterinary) guidance on Bioavailability	Case B - Multi-point dissolution profile in the application/compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached for the proposed and currently accepted formulation

* Equipment changes included in conditional 3. Any changes to the manufacturing method and/or to the in-process

controls are only those necessitated by the change in batch-size, e.g., use of different sized equipment.(37)

**Reporting category adjusted by guideline VII.C.c(34)

Below is presented a Comparative dissolution profile between generic product x RMP approved for marketing authorization, also the same batches of the BE study:

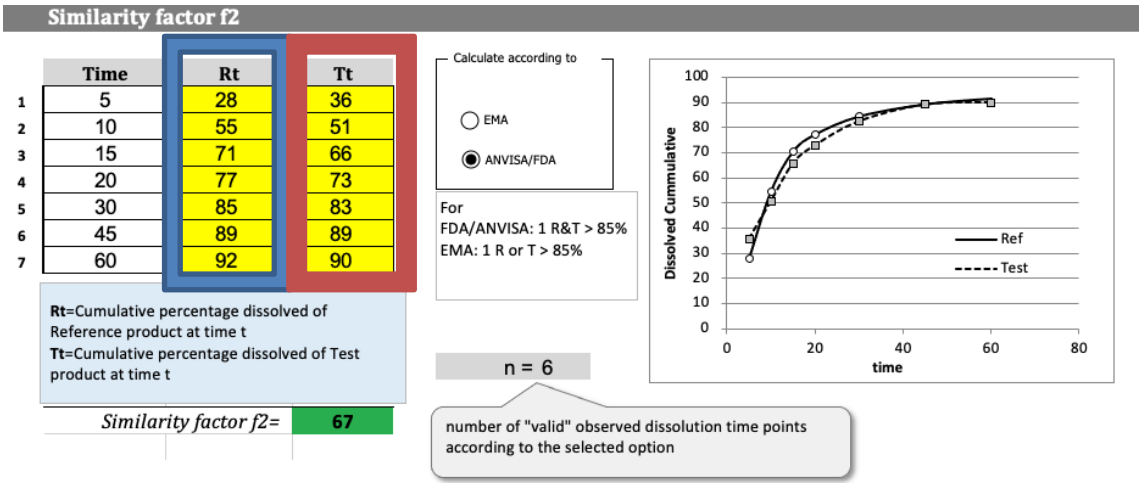

Figure 3 – Simulation of comparative profile for RMP (Rt) x generic biobatch (Tt)

After the approval for MA, the generic manufacturer has performed a scale-up change from 100.000 to 1.000.000 units, using equipment with the same design and manufacturing principle, and minor adjustments in the manufacture process.

For this variation, the MAH performed the comparative dissolution profile of a batch with the proposed change between the previous approved condition (Biobatch) with the following results:

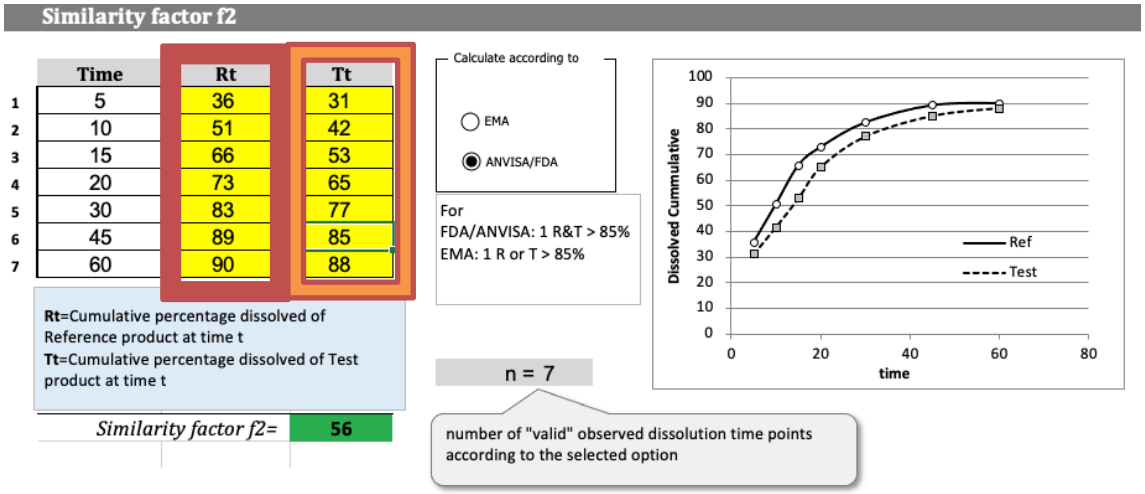

Figure 4 - Simulation of comparative profile for previous approved condition (biobatch) (Rt) x batch with the propose scale-up change (Tt)

As the f_2 result of 56, the batches dissolution profiles would be considered similar and the change would be correctly informed to the HA and implemented.

The comparative profile against the actual RMP would not be performed, as it is not required in the regulation.

Considering that this product had not been developed through quality by design approach, and no further discussion and research has been performed for establishment of the IVIVC between these products, the only data that would be required for the variation would be based on in vitro results between the biobatch that proved BE against the reference drug for MA or other batches with other minor variations (if considered multiple minor variations throughout lifecycle), and the proposed new batch size/process/equipment.

When compared the scale-up batch with the RMP, the f_2 results demonstrated that the profiles were not similar, as follows:

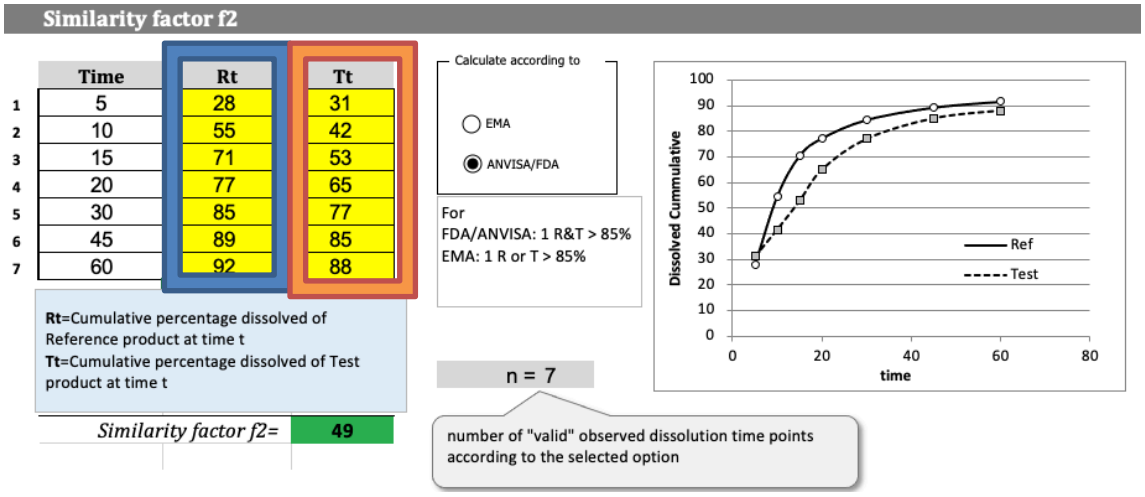

Figure 5 - Simulation of comparative profile for previous approved condition (biobatch) (Rt) x batch with the proposed scale-up change (Tt)

Considering this worst-case scenario for dissolution profiles in this minor/moderate variation (depending on the region where they will be submitted), the possibility of different profiles already exists, and would be possible upon a unique variation submission, and the probability increases when it is considered multiple minor submissions during the product lifecycle, that is a common industry behaviour.

This scenario only considered that the generic MAH proposed changes in the product as

these profiles could diverge (±) if the possibility of minor/moderate variations of the RMP, that can also impact the dissolution profile, is considered.

The need for comparing the dissolution profile against the RMP after the MA will only be required if the generic manufacturer needs to perform a major variation, or if the reference drug product has a major variation approved.

Despite the many updates concerning the process validations and comparative protocols for products' lifecycle management, the main consideration regarding the comparison with the previous formulation remains the most concerning point of minor/moderate variations, as they do not have to be compared again with the RMP, unless the company has a demand for a major variation, which is not possible to be predicted. This possibility starts with the scale up of the generic product, which is common to be submitted in the early stage of launch and will continue throughout both generic and RMP lifecycle.

A combination of factors regarding the RMP minor variations, changes in the dissolution methodology, and removal of the reference from the market also increase the possibility of the bioinequivalence of this type of products on the market.

The absence of requirements for IVIVC in the guidelines is also a variable to be considered in this scenario, as it is not mandatory that the MAH develops or discusses this correlation on the marketing authorization or in the variations.

Some other factors to be considered, that could collaborate in this divergence, are:

- Being possible to receive MA approval with non-comparative dissolution profile between RMP and generic as long as the BE is approved. This point would evidence fragilities to surrogate future changes with BE surrogate.

- Withdrawn of the RMP from the market, with election of a generic product previously compared to it.

- Changes of dissolution methods throughout the lifecycle, losing referential between initial biobatch obtained profile

A study performed in Saudi Arabia(38), funded by an autonomous government organization, performed BE (four-sequence, randomized, crossover studies) between 14 immediate release RMPs and 3 randomized selected generic studies for amlodipine, amoxicillin, atenolol, cephalexin, ciprofloxacin, clarithromycin, diclofenac, ibuprofen, fluconazole, metformin, metronidazole, paracetamol, omeprazole, and ranitidine,

presenting results of with the reference drug product and between 3 generics tested for each product presented the following results: 2 generics of diclofenac (class II), 1 generic of clarithromycin and 1 generic of omeprazole presented extreme values for Cmax outside 80% – 125% compared to their reference and also 1 generic x generic of ibuprofen study was out to Cmax. The relevance of Tmax was not discussed individually, but on average, 60% of generic/reference and 58% of generic/generic individual Tmax ratios were outside the ±25% range. The discussion of the irrelevance of Tmax was based on other studies, not individually considered, but on average between the products that participated in the BE.

The study also considered all the products that participated as bioequivalents, based on the average of results, not considering the failing results for Cmax described. So, in case of regulatory purpose, the 2 generics of diclofenac, 1 generic of clarithromycin and 1 generic of omeprazole would be considered as not bioequivalents to their RMP, in the 3 HA discussed in this thesis. In this context, ibuprofen results would be accepted in Europe, justified by the lower limits obtained (78%), being a highly variable drug with intra-subject variability of 37,1%.

During the writing period of this thesis, a recent article funded by Japan Agency for Medical Research and Development (AMED)(39) also collaborate with the discussion brought by the thesis scope. The article reinforces the importance of monitoring products on the market regarding their performance throughout their lifecycle, focusing on a periodical dissolution-monitoring program using four media (acidic, intermediate, neutral, and water) that has being conducted in Japan since 2007. The monitoring identified several brand products that show dissolution profiles markedly different from the original and/or with large variation between batches. Dissolution profiles of 67 products (approximately 5.3%) were out of the similarity range relative to the reference profiles in at least one of the media in 1261 formulations evaluated in a decade (between FY 2008 to 2017). The RMP dissolution profile monitoring also started to be discussed due to a case of a RMP with out-of-range BE result between batches in a post-marketed human study. Similar dissolution profiles between products were observed in many formulations, while some showed varied profiles in certain media. The article also reinforces the need of combining the GMP monitoring of the product regarding CQA's, ICH Q12 change managements. Monitoring programs should help avoiding these cases to happen and minimizing the regulatory burden.

A research performed by the University of Florida Centre for Pharmacometrics and Systems Pharmacology, in partnership with FDA, had the main objective of investigating

possible reasons for pharmacovigilance signals of inefficacy of metoprolol extended release (class I), used the same rationale proposed in the beginning of this research that is to use information of the marketing authorization dossier to compare the profiles throughout the product lifecycle using pharmacovigilance data to prioritize the products.

Using PB/PK modelling, the study confirmed the possibility of the signal (inefficacy) be caused by interference in BE and was able to conclude that in vitro dissolution determined only by the cut off of 50 for f_2, did not fully translated into in vivo BE, especially in Cmax. (40)

The study also brings the importance of the pharmacodynamic endpoint used in the clinical study, which can also be a discussion point for therapeutic equivalence, where the Heart Rate Variability used as endpoint in the clinical study could lead also to further PK/PD studies, to discuss if the bioinequivalence of drugs can also impact on the therapeutic inequivalence.

The porosity and tortuosity of hydroxypropyl methylcellulose, excipient responsible for the modified release of the metoprolol studied were considered critical to the release rate. Although changes in excipients responsible for release are major variations in the three HA discussed, these characteristics are not usually investigated in empiric drug product developments.
The outcomes published for this case could be obtained for other products, confirming, therefore, if the complete methodology applies to other BCS classes.

6 Regulatory proposals for risk mitigation

Based on the discussion and research of all the resources to conduct a CDP and all the data available from the HA and updated guidelines, a discussion of possible proposals for mitigating the fragilities found in the regulation are detailed bellow.

Table 188 – Considerations about possible solutions

Possible solutions	Pros	Cons
Always performing the CDP against actual RMP also for minor and moderate	Would permit the need for comparation in each change demand, regardless of type The cost of this scenario would be minimum, as the only difference would be to buy the RMP units for the conduction of the CDP.	Not evidenced.
Public access to the dissolution profile of the batch of pivotal clinical studies	Keeping this information public would define the target, committing the RMP MAH and the generic MAH to maintain this profile. A common dissolution method would be necessary.	For more complex products, the change in dissolution profile from the RMP could turn into a strategy for demanding extra pharmaceutical development from generic competitors. Barriers for data confidentiality between HA and MAH of RMP.
HA control of the CDP of the RMP, notifying generic products MAH's	More confidentiality for the RMP documents and less publicity regarding this topic that could generate improper doubts of the generic efficacy for users.	Augmentation in regulatory demand to assess the previous history of both reference and generic drug, that could lead to regulatory burden.
Use of CDP substituting BE only when IV/IVC have been determined (for class II and IV BCS)	Much more assurance in the maintenance of the BE as would be required a deep knowledge on the product. The use of modelling that could result in less future BE studies and more flexibility for holders	Large impact for industries growth as it will lower the flow of changes and the immense difficulty of reaching the IV/IVC. For products that do not have enough in vivo data to determine the IVIVC, increasement of BE studies and more exposure of subjects.
Internal risk analysis and internal CDP against RMP for products with no major variation during lifecycle and Q12 PLMC implementation	More information obtained with a simple investigation performed by the MAH in its portfolio, prioritizing the class IV and II BSC products, evaluating the historical changes submitted/implemented through ICH Q12 PLMC, comparing with actual RMP in the market.	Not evidenced.
Monitoring programs for conducting CDP of most critical products performed by the HAs	Signal driven monitoring program based on pharmacovigilance inefficacy reports and by randomly selected higher risk RMPs and the respective generics, will bring much more in-vitro data to discuss possible solutions.	Reactional model instead of a preventive one.

Monitoring programs conducting BE of most critical products.	Conduction of BE studies for the most critical products reproved in CDP monitoring against reference and other generics on market, will permit conclusions for this theoric discussion.	Reactional model instead of a preventive one. More exposure of healthy subjects and high costs of the project.
Database of BE studies shared between HA with list of products with higher risk classification	The Database would provide a better use of the already existing information of products submitted between these agencies, being also a good source of data for further IVIVC determination.	Not evidenced
Different approach on process validations including dissolution profile assessment	Will use the process validation that are already a routine study performed by the Pharmaceutical Industries, linking the Critical Quality Attributes performing multi-point dissolution profiles.	Not evidenced

The evolution of Biopharmaceutics research, that provides scientific base for regulatory improvements, is a masterpiece in terms of achieving the target of having more efficiency in IVIVC and relationship. Less BE studies being conducted for products that could safely be substituted by robust in vitro studies and more confidence of the maintenance of the BE in the post-marketing phase are just some of the benefits of this area growth. A lot of funding has already been directed for this research.

Some examples of projects are:

- The 21st century BA/BE project(41), funded by FDA, headed by Professor Amidon and his team of University of Michigan counts on several contributors, including Faculty of Pharmacy, Universidade de Lisboa, which includes Faculty Research Institute for Medicines (iMed.ULisboa), with the goal of measuring the impact of gastrointestinal (GI) physiology on the oral drug product behaviour throughout the different segments of the GI tract;

- OrBiTo project, finished in 2018, in a successful collaboration between the academic, regulated and regulators parties, funded by the Innovative Medicines Initiative (IMI) and the European Federation of Pharmaceutical Industries and Associations (EFPIA), which achieved step change in informed drug product development by significantly improving the use of, and confidence in, in vivo predictive in vitro/in silico tools.(42)

- The PEARRL (Pharmaceutical Education and Research with Regulatory Links)

project also counted on European Pharma industry, academia, and regulatory agency funding by the European Commission – Horizon 2020 under the Marie Skłodowska-Curie Program. The main research objectives of the PEARRL are to deliver novel bio-enabling formulations and new biopharmaceutic tools to predict in vivo performance to improve efficiency and cost-competitiveness in drug development, thus facilitating earlier access of patients to “breakthrough therapies”.(43)

- The on-going project UNGAP (Understanding Gastrointestinal Absorption-related Processes) funded by the European Commission – Horizon 2020 under the COST (European Cooperation in Science and Technology) program research (i) differences between specific patient populations, (ii) regional differences along the gastrointestinal tract, (iii) the intraluminal behavior of advanced formulations, and (iv) the food-drug interface(44) and count on academia specialists.

As the results of all these efforts and research in biopharmaceutics will take time until being massive used, some possibilities for prioritize could be: BCS classes II and IV, pharmacovigilance inefficacy signals, bioinequivalence results in studies identifying the molecules with higher risk, and products that have never submitted a major change after the MA approval..

Using BCS class II and IV and the possibility of using the RMP instead of previous conditions, the following decision tree is proposed for this class of medicinal products.

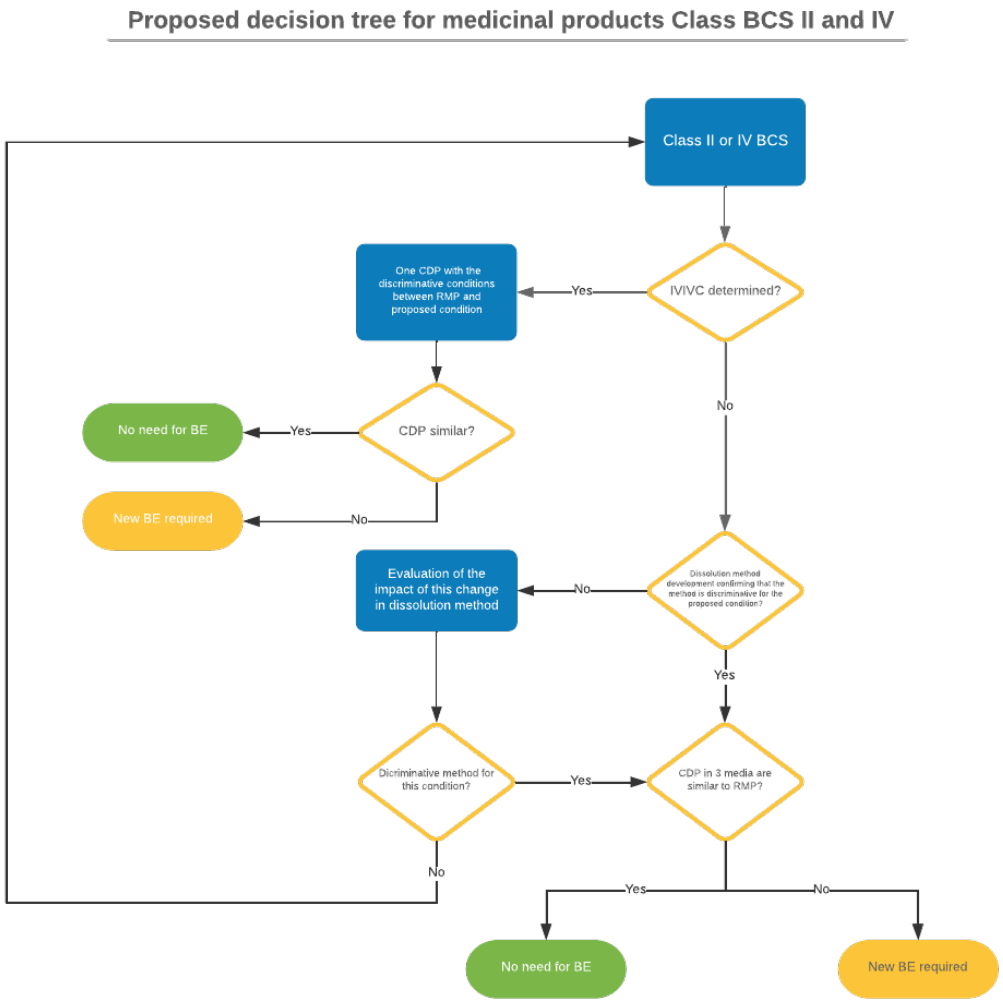

Figure 6 – Proposed decision tree for class BCS II and IV of medicinal products.

7 Conclusion

The IVIVC topic is a challenge that gets attention and effort from both industries and regulators. The regulators are right on being conservative while the knowledge of these technologies is still getting more robust and more data is collected.

The upgrade in actual development models and requirements brings less worries regarding the products that were included on the market in a more recently regulatory and scientific scenario.

While we already have new generic products being developed considering de-formulation and quality by design tools, most products are not updated for this scenario which could bring worries regarding more complex products developed in empirical approaches.

To make it possible to provide more updated information regarding the maintenance of BE between reference and generics, investigation with in vitro tests can be required to be conducted by the holders to estimate the amount and impact of work to be done.

All the mentioned points would challenge both regulated and regulators to reduce human beings' exposure to BE and enhance the competitiveness of the generic market that is the responsible for a much larger access to treatments.

The main point observed in all regions researched concerned the absence of requirements or instructions to control the dissolution profile against the reference listed drug, when no major change that requires a new BE is demanded.

Similar results of CDP with f_2 above 50 were simulated and fragilities regarding the use of the previous condition instead of the RMPs demonstrated that attention should be directed to this issue, as no requirement for periodic comparative dissolution profile against RMP is part of the regulations of ANVISA, EMA and FDA and no monitoring program has been identified.

It was possible to conclude that there are possibilities to have generics on the market that are no longer bioequivalent, considering the similarity factor in CDP requested by the 3 HAs that was part of this research.

The immediate release products were considered more vulnerable than modified release

products, given fewer constraints on the classification of change as minor and moderate, being also more complex to have IVIVC determined.

Further research including other HAs, like PDMA (Pharmaceuticals and Medical Devices Agency) in Japan, that has already implemented monitoring programs, would bring other possibilities for solving or mitigating the risks until we have more applicable tools for BE prediction.

As the objective of this research was to assess regulatory requirements for the raised hypothesis, it was considered confirmed that there is a regulatory gap for proofs required for minor and moderate changes, when the comparator to be used in the CDP is the previous condition, instead of the RMP.

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9. Annexes

Annex 1 – *ANVISA´s* changes classification

Changes	Performance tests	Relevant Conditionals	Type of application	Classification
a. minor change in the manufacture process	CDP between the proposed condition and the previous condition. CoA of 1 batch of the DP with the proposed condition.	Related to minor changes/inclusions of noncritical manufacturing parameters or steps. Critical or noncritical parameters and steps are those defined at the manufacturing process validation.	Immediate implementation. It does not require individual protocol. Annual report.	**Risk 1**
b. major change in the manufacture process	CDP between the proposed condition and the RMP. BE study between the proposed condition and the RMP. In the case of manufacturing changes or inclusions that do not impact the drug release system or that do not change the type of production process, this proof may be replaced by a technical justification of absence. CoA of 1 batch of the DP with the proposed condition.	Related to major changes/inclusions of critical manufacturing parameters or steps as changes from/to wet granulation to high sheer or dry manufacturing with direct compression. Critical or noncritical parameters and steps are those defined at the manufacturing process validation.	Requires individual filing. Should await a favourable manifestation from Anvisa for implementation.	**Risk 1**
d. minor change of equipment	CDP between the proposed condition and the previous condition. CoA of 1 batch of the DP with the proposed condition.	Refers to the substitution, inclusion, or exclusion of equipment with the same or different design and operating principle for noncritical steps or with the same design and operating principle for critical steps of the manufacturing process. This does not apply to the change or inclusion of equipment that have a potential impact on the modified release system. A	Immediate implementation. It does not require individual protocol. Annual report.	**Risk 1**

		concomitant change in capacity, equipment automation, or minor change in the production process because of the equipment change are allowed. Steps and equipment considered to be critical are those defined on manufacturing process validation.		
e. major change of equipment	CDP between the proposed condition and the previous condition. CoA of 1 batch of the DP with the proposed condition.	Refers to the substitution, inclusion, or exclusion of equipment with different design and operating principle for critical steps and equipment considered to be critical are those defined on manufacturing process validation.	Requires individual filing. Should await a favourable manifestation from Anvisa for implementation	**Risk 5**
f. minor inclusion of batch size	CDP between the proposed condition and the previous condition.	Refers to the increase in batch size for immediate release dosage forms, decrease in batch size for all dosage forms, and increase in batch size of up to ten (10) times the reference batch size for modified release drug products and specialized dosage forms. Reference batch is the last batch used for proving the safety and efficacy by PE, BE, and clinical trials. This is not applicable to drug products with a concentration of active ingredient lower than two percent (2%) per dosage unit in relation to the formulation, except for solutions. This is not applicable to oral solid drug products whose reference batch size is smaller than one hundred thousand (100.000) pharmaceutical units or ten percent (10%) of the batch size produced in industrial scale, whichever is greater. A concomitant minor change in the production process and change in equipment capacity and/or automation is allowed, provided that such change is a result of the batch size inclusion.	Immediate implementation. It does not require individual protocol. Annual report.	**Risk 5**
g. major inclusion of batch size	CDP between the proposed condition and the RMP. BE study between the proposed condition and the RMP.	For those changes that do not fit in change 5.f	Requires individual filing. Should await a favourable manifestation from Anvisa for implementation.	**Risk 1**

Annex 2 – FDA´s changes classification

Changes in batch size (scale-up/scale-down) **Post approval changes in the size of a batch from the pivotal/pilot scale biobatch material to larger or smaller production batches call for submission of additional information in the application. Scale-down below 100,000 dosage units is not covered by this guidance. All scale-up changes should be properly validated and, where needed, inspected by appropriate agency personnel.**				
Changes	**Performance tests**	**Relevant Conditionals**	**Type of application**	**Classification**
Level 1	Dissolution documentation None beyond application/compendial requirements. In Vivo BE Documentation None	Change in batch size, up to and including a factor of 10 times the size of the pilot/ biobatch, where: 1) the equipment used to produce the test batch(es) is of the same design and operating principles. 2) the batch(es) is (are) manufactured in full compliance with CGMP's; and 3) the same standard operating procedures (SOP's) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).	Annual report	**Risk 2**
Level 2	Dissolution documentation Case B testing In Vivo BE Documentation None	Changes in batch size beyond a factor of ten times the size of the pilot/biobatch, where: 1) the equipment used to produce the test batch(es) is of the same design and operating principles; 2) the batch(es) is (are) manufactured in full compliance with CGMP'S; and 3) the same SOP's and controls as well as the same formulation and manufacturing procedures are used on the test batch(es) and on the full-scale production batch(es).	Changes being effected supplement	**Risk 2**
Manufacturing **Manufacturing changes may affect both equipment used in the manufacturing process and the process itself.**				
Equipment				
Level 1	Dissolution documentation None beyond application/compendial requirements. In Vivo BE Documentation None	This category consists of of 1) change from non-automated or non-mechanical equipment to automated or mechanical equipment to move ingredients; and 2) change to alternative equipment of the same design and operating principles of the same or of a different capacity.	Annual report	**Risk 6**
Level 2	Dissolution documentation Case C dissolution profile	Change in equipment to a different design and different operating principles.	Prior approval supplement	**Risk 3**

	In Vivo BE Documentation: None			
Process				
Level 1	Dissolution documentation None beyond application/compendial requirements. In Vivo BE Documentation: None	This category includes process changes including changes such as mixing times and operating speeds within application/validation ranges.	Annual report	**Risk 3**
Level 2	Dissolution documentation Case B dissolution profile In Vivo BE Documentation None	This category includes process changes including changes such as mixing times and operating speeds outside of application/validation ranges.	Changes being effected supplement	**Risk 5**
Level 3	Dissolution documentation Case B dissolution profile In Vivo BE Documentation In vivo BE study. The BE study may be waived if a suitable in vivo/in vitro correlation has been verified.	This category includes change in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder.	Prior approval supplement with justification;	**Risk 1**

Annex 3 – EMA´s changes classification

B. QUALITY CHANGES B.II FINISHED PRODUCT B.II.b) Manufacture B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product				
Changes	**Performance tests**	**Relevant Conditionals**	**Type of application**	**Classification**
a) Minor change in the manufacturing process	3. For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action). For herbal medicinal products, comparative disintegration data may be acceptable. 4. Justification for not submitting a new BE study according to the relevant (Human or Veterinary) guidance on BA. 5. For changes to process parameter(s) that have been considered to have no impact on the quality of the finished product, declaration to this effect reached in the context of the previously approved risk assessment.	1. No change in qualitative and quantitative impurity profile or in physic-chemical properties. 2. Either the change relates to an immediate release solid oral dosage form/oral solution and the medicinal product concerned is not a biological/immunological or herbal medicinal product; or the change relates to process parameter(s) that, in the context of a previous assessment, have been considered to have no impact on the quality of the finished product (regardless of the type of product and/or dosage form). 3. The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process. 4 The currently registered process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls. 5. The specifications of the finished product or intermediates are unchanged. 6. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy. 7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch and at least 3 months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised, and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the	IA	**Risk 4**

		approved shelf life (with proposed action).		
B. QUALITY CHANGES **B.II FINISHED PRODUCT** **B.II.b) Manufacture** **B.II.b.4 Change in the batch size (including batch size ranges) of the finished product**				
Changes	**Performance tests**	**Relevant Conditionals**	**Type of application**	**Discussion**
a) Up to 10-fold compared to the originally approved batch size	2. Comparative dissolution data on at least one pilot batch of the current and proposed dimensions (no significant differences regarding comparability see the relevant (Human or Veterinary) guidance on BA). For herbal medicinal product comparative disintegration data may be acceptable. 3. Justification for not submitting a new BE study according to the relevant (Human or Veterinary) guidance on BA. 4. Samples of the finished product where applicable (see NTA, Requirements for samples in the Member States). 5. Results of the appropriate Ph. Eur tests demonstrating equivalence in characteristics/correct dosing.	1. No change in qualitative and quantitative impurity profile or in physico-chemical properties. 2. Either the change relates to an immediate release solid oral dosage form/oral solution and the medicinal product concerned is not a biological/immunological or herbal medicinal product; or the change relates to process parameter(s) that, in the context of a previous assessment, have been considered to have no impact on the quality of the finished product (regardless of the type of product and/or dosage form). 3. The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process. 4 The currently registered process must be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls. 5. The specifications of the finished product or intermediates are unchanged.	IA	**Risk 4**