Critical Assessment - Implementation of ICH Guidelines in Brazil

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List of Abbreviations

Abbreviation	Term
ANVISA	Agência Nacional de Vigilância Sanitária (The National Agency for Health Surveillance)
API	Active Pharmaceutical Ingredient
BRIC	Brazil, Russia, India and China
CEP	Certificate of Suitability
CMC	Chemistry, Manufacturing and Controls
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Documents
DMF	Drug Master File
eCTD	Electronic Common Technical Documents
GMP	Good manufacturing practice certificates
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MoH	Ministry of Health
NDA	New Drug Application
NeeS	Non-eCTD Electronic Submission
NRArr	National Regulatory Authority of Regional Reference
PAHO	Pan American Health Organization
SNVS	Sistema Nacional de Vigilancia Sanitaria (Brazilian Health Regulatory System)
SOPs	Standard Operation Procedures
SUS	Sistema Unico de Saúde (Brazilian National Health System)
WHO	World Health Organization

Summary

In November 2016, The Brazilian National Agency for Health Surveillance (Agência Nacional de Vigilância Sanitária - ANVISA) became a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Brazil was the first country in Latin America to join the ICH as a member, and together with South Korea, were the first two countries to be accepted into ICH as regulatory members. Joining the ICH, the agency has to fulfil with some obligations such as implementation of guidelines. As a commitment, within five years, ANVISA should adopt a set of five ICH guidelines that mainly concerns the Quality, Pharmacovigilance, Clinical Research, implementation of the Common Technical Document (CTD) and Medical Dictionary for Regulatory Activities (MedDRA).

The thesis provides a critical assessment to implement the ICH guidelines in Brazil, with focus on the ICH guidelines for stability testing ICH Q1 and for the Common Technical Documents ICH M4, for registration of new medicinal products. Both guidelines have been selected due to major differences between the current Brazilian regulations and ICH guidelines, leading to a huge challenge for the Brazilian Health Authority and the locally established Pharmaceutical Companies to implement these guidelines. Although many differences still in existing and efforts will be needed to implement the ICH guidelines in Brazil, ANVISA is putting a lot of efforts to implement the guidelines within the next years, in an open communication with the Industries, in order to reduce as much as possible, the impact.

The implementation of the ICH guidelines will bring many benefits for the Industry and Regulator. By implementing the ICH guidelines in Brazil, the country will contribute to the global regulatory harmonisation, which will bring a great benefit to the public health and important medicines will be faster available to the patients.

1. Introduction and Objective

Brazil is the largest country in the Latin America region and is considered important for the global pharmaceutical market [1]**.** The National Agency for Health Surveillance (Agência Nacional de Vigilância Sanitária - ANVISA) in Brazil was inaugurated in 1999. It is responsible for regulating the production and marketing of pharmaceuticals, foods, cosmetics, disinfectants, tobacco derivatives, medical devices, diagnostic reagents, pesticides, human blood / or organ derived productsand tissues for transplantation [2]. ANVISA has a strong international position having several bilateral, regional and international agreements and is part of regulatory convergence initiatives.

ANVISA was initially recognised by the Pan American Health Organization (PAHO) in 2010 as a National Regulatory Authority of Regional Reference (NRArr). Subsequently, it became part of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); first, in 2015, it was accepted as an observer [2], and at the end of 2016, ANVISA became a member of the ICH**.**

Brazil was the first country in Latin America to join the ICH as a member, and – together with South Korea – was one the first two countries to be accepted as regulatory members outside of the initial ICH region. This was possible, as the ICH implemented reforms in 2015, which opened the organisation to regions outside of the original ICH zone comprising EU, USA and Japan [3]. As a member of the ICH, the experts from ANVISA joined the ICH working groups, which contributed significantly to the development of products and fast approvals of medicines in Brazil. In addition, the participation of ANVISA in the ICH will help to align the Brazilian legislation on medicines with international best practices leading to a regulatory convergence [4]. Joining ICH as a member, ANVISA must fulfil extensive obligations such as the implementation of several guidelines, classified in 3 different levels: immediate implementation, implementation within 5 years and long-term implementation. Currently, ANVISA has its own regulations, which are not aligned with the ICH standards [2, 5].

The objective of this thesis the critical assessment of the implementation of ICH guidelines in Brazil, focusing on the ICH guidelines for stability testing ICH Q1 [6] and the guidelines covering the Common Technical Document (CTD) ICH M4 [7] with

regard to the registration of new medicinal products. Both guidelines have been selected due to major differences between the current Brazilian regulations and ICH guidelines, leading to a major challenge for the Brazilian Health Authority and the locally established Pharmaceutical Companies with regard to implementing the ICH guidelines.

This thesis reflects the status as per 01.12.2018.

2. ICH Overview (Objective, Organisation, Structure)

Efforts to globally harmonise regulatory activities had been initiated by various organisations in the past decades. ICH was founded in 1990 by representatives of the regulatory agencies and industry associations of EU, Japan and the USA, paying tribute to the increasing global drug development activities and to achieve regulatory harmonisation around the world with focus on the efficacy, safety and quality of medicinal products The need for harmonisation was brought up by globally operating pharmaceutical companies, since the different country-specific requirements led to additional costs, as well as time and resource-consuming, which resulted in a delay of introducing new medicines into the market [4].

In order to meet the needs of the patients and to improve the efficiency of new drug development and registration processes, the ICH seeks regulatory harmonisation across the regions. Initially, they focused on the harmonisation among the leading regions EU, USA and Japan [8]. However, on 23 October 2015 the ICH launched a new ICH Association, which was established during an inaugural assembly meeting in Geneva. The extended association is known as the “International Council for Harmonisation of technical requirements for pharmaceuticals for human use (ICH)”. The main goals of the new structure are to globally harmonise the regulatory framework and requirements for pharmaceuticals and to create a venue that allows the leading pharmaceutical regulatory authorities and industry stakeholders to be more involved in the harmonisation processes. The understanding that some non-ICH countries are major contributors to the global pharmaceutical market represented a novelty within ICH [3, 8].

At this moment, ICH consists many regulatory members from different regions, as follows [9]:

- **Founding Regulatory Members -** European Commission (Europe), Food & Drug Administration (US) and Pharmaceuticals and Medical Devices Agency (Japan)
- **Founding Industry Members -** European Federation of Pharmaceutical Industries and Associations (Europe), Japan Pharmaceutical Manufacturers

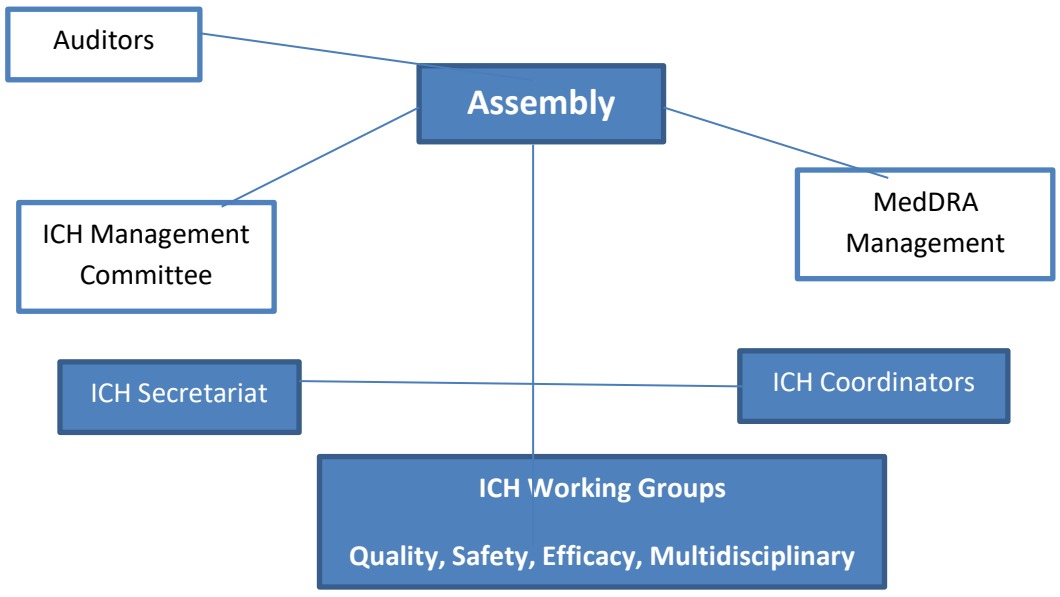
Association (Japan) and The Pharmaceutical Research and Manufacturers of America (US)

- **Standing Regulatory Members -** Health Canada (Canada) and Swissmedic (Switzerland)
- **Regulatory Members -** ANVISA (Brazil), CFDA (China), HSA (Singapore), MFDS (Republic of Korea), TFDA (Chinese Taipei)
- **Industry Members -** BIO, IGBA, WSMI

The ICH mainly consists of four major parts [9]:

1. The ICH Assembly comprises all members and observers, who are responsible to govern the ICH and make decisions especially with regard to ICH guidelines adoptions.
2. The ICH Coordinators are responsible for the distribution of ICH documents to the appropriate persons from their organisation and to follow up on actions within their respective a predefined timeframes and represent the main point of contact for the ICH Secretariat.
3. The ICH Secretariat is mainly responsible for the preparation of documents and the organisation of meetings.
4. The ICH Working Groups are established for each technical topic selected for harmonisation.

Figure 1: Organisation ICH [9]



2.1 ICH Guidelines

The ICH brings together regulatory authorities and pharmaceutical industry associations to discuss scientific and technical aspects of drug registration. To date, the ICH has developed more than 60 guidelines related to aspects of quality, safety, efficacy and multidisciplinary categories. The generation of a harmonised ICH guideline consists of a five step approach. As a first step, the Expert Working Group (EWG) prepares a consensus draft of the Document based on the goal from the Concept Paper. Step 2 is reached when the Assembly has confirmed consensus to proceed with the regulatory consultation; during this phase the ICH Regulatory Members endorse or reject the draft guideline. Further, in step 3, the draft guideline is made public available within the regulatory community for consultation and discussion. After that, the final document is adopted by the ICH Regulatory Members, representing step 4. And finally, instantly following the previous step, the implementation of the guidelines in the ICH regions are conducted in the scope of step 5 [10].

2.2. Stability – ICH Guidelines

The goal of a stability study is to control the quality of drug product or drug substance, which may vary with time. A stability study takes into consideration several environmental factors such as temperature, humidity and light. By means of a stability study the re-test period as well as appropriate storage conditions for the drug substance or the shelf-life for the drug product are established. The ICH has published several guidelines in order to give guidance to the applicant on stability testing [6, 11, 12, 13, 14].

Table 1: ICH Guidelines – Stability

Module	Topic	Last update	Information contained
Q1A	Stability Testing of New Drug Substances and Products	2003	This document provides guidance on stability testing for new drug substances and drug products considering relevant temperatures and humidity values of different climatic zones.
Q1B	Stability Testing: Photostability Testing of New Drug Substances and Products	1996	As annex to the main stability guideline (ICH Q1A), this document gives guidance on how to evaluate the light sensitivity of new drug substances and products.
Q1C	Stability Testing for New Dosage Forms	1996	This document provides stability guidance for new formulations of already approved medicines and definition of circumstances under which reduced stability data can be accepted.
Q1D	Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products	2002	General principles for reduced stability testing (e.g.: bracketing and matrixing designs)
Q1E	Evaluation of Stability Data	2003	This guidance provides possible situations where extrapolation of retest periods/shelf-lives beyond the real-time data may be appropriate (e.g.: statistical approaches to stability data analysis)
Q1F	Stability Data Package for Registration Applications in Climatic Zones III and IV	2006 (withdrawn)	The ICH Steering Committee endorsed the withdrawal of the Q1F Guideline decided to leave definition of storage conditions in Climatic Zones III and IV to the respective regions and WHO.

2.3 The Common Technical Document (CTD) – ICH Guidelines

Many countries have established regulatory requirements related to quality, safety and efficacy. These have to be fulfilled by the applicant to obtain a new marketing authorisation (MAA) in the respective country. In November 2000, the ICH published the guideline M4 related to the common registration format of the dossier (Common

Technical Document - CTD) leading to a format harmonisation across the ICH country members. For the pharmaceutical industry, this was a significant benefit, which spared the need to reorganise/reformat the information for submission to the various regulatory authorities.

In addition, regulatory reviews and communication between individual health authorities and the applicants were improved by a standard document of common elements [7, 15, 16, 17].

Table 2: ICH guidelines – M4

Module	Topic	Last update	Information contained
M4	Organisation	2016	Guidance on dossier organisation including the granularity document that provides guidance on document location and pagination
M4Q	Quality	2002	Guidance on quality documents and the quality overall summary (QOS) for chemical and pharmaceutical data including data for biological/ biotechnological products
M4S	Safety	2002	Guidance on the structure and format of the nonclinical overview, nonclinical study reports as well as summaries
M4E	Efficacy	2016	Guidance on the structure and format of the clinical overview, clinical study reports as well as summaries

In order to structure all dossier-relevant information uniformly across the countries, the ICH guideline for a Common Technical Document (CTD) has been created.

The CTD is comprised of five modules [7]:

- **Module 1** includes purely administrative information as well as country-specific documents such as application forms, or the prescribing information.
- **Module 2** contains the quality overall summary, as well as summaries of the non-clinical and clinical parts of the dossier.
- **Module 3** comprises the CMC (Chemistry, Manufacturing and Controls) information with regard to drug substance and drug product. It also includes

regional (CMC) information following the requirements of the individual countries.

- **Module 4** contains the non-clinical study reports.
- **Module 5** includes the clinical study reports that prove the positive benefit-risk ratio of the drug product.

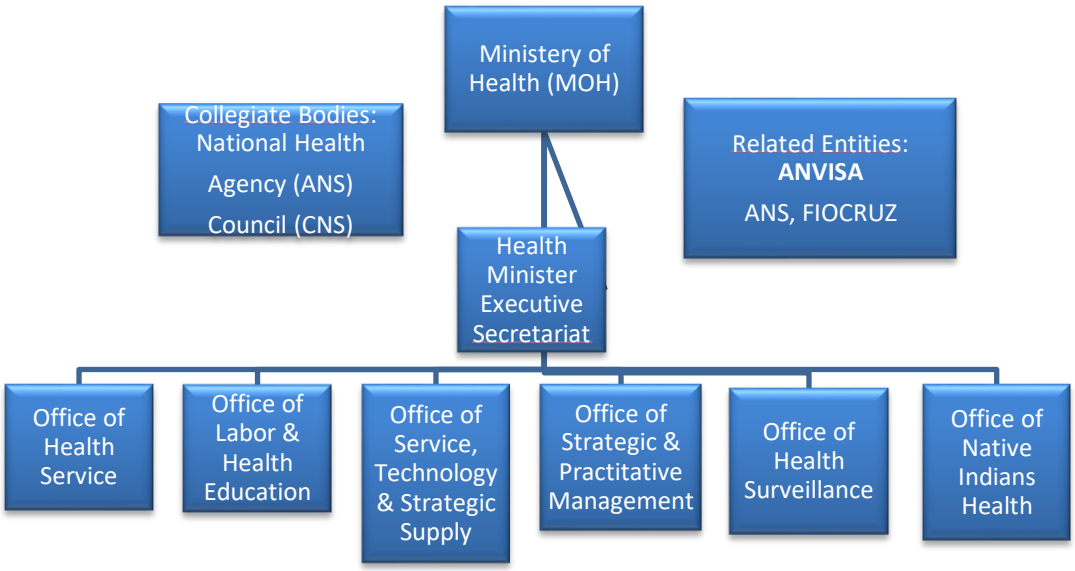
In addition to the determination of a harmonised dossier structure, the ICH published guideline M8 [18] to implement the submission of the CTD electronically. The electronic CTD (eCTD) represents a specification for the dossier, stored in the eCTD directory structure, which can be accessed through the XML backbone (XML is a specification or standard that is used in eCTD submissions). It enables electronic transfer, review, and maintenance of regulatory information and is a standard messaging format between industry and agency. Both, the CTD and the eCTD implementation resulted in higher quality dossiers, as well as better efficiency in the review processes. In the case of eCTD, the additional benefit is the security on the information content, since the transfer of information is done electronically. The type of submission used in the transition period between the CTD and eCTD is called Non-eCTD Electronic Submission (NeeS) [7, 18]. Table 5 in Chapter 5 of this thesis outlines the different types of submissions (CTD in a paper, NeeS, and eCTD); refer there for further information.

3. Brazilian Regulatory Environment

Brazil is the largest country in South America and the fifth largest nation in the world. It is located on the eastern side of the continent and more than 210 million live there [1]**.** The pharmaceutical market in Brazil is expected to rise from $25.5 billion in 2016 to $29.9 billion in 2021 [1]. Main reasons for this are the improving living conditions as well as a growing elderly population (there is an increase of life expectancy in Brazil due to a lower mortality rate), which goes along with an increasing number of patients with chronic diseases. Based on that, the patients will need more medicines expanding the market for pharmaceuticals in the country [1]**.**

In addition, Brazil is part of BRIC, which represents a specific group of four developing countries (Brazil, Russia, India and China). Due to their promising, emerging markets, which are based on the demographic and economic potential of each individual country, the BRIC countries are expected to rank among the world's largest and most influential economies in the 21st century [19]. The regulatory body for drug registration, ANVISA, was created by Law 9.782, of January 26, 1999 [2]. ANVISA´s role is to promote the protection of the population's health by executing sanitary control of the production, marketing and use of products and services subject to health regulation, including related environments, processes, ingredients and technologies, as well as the border control (import and export) in harbous and at airports[2]. All products must be registered by ANVISA before being allowed to be marketed in Brazil [20]. The agency is managed by a Collegiate Board of Directors and is an independent organisation linked to the Ministry of Health (MoH); it is part of the Brazilian National Health System (Sistema Unico de Saúde - SUS) and acts as coordinator of the Brazilian Health Regulatory System (Sistema Nacional de Vigilancia Sanitaria- SNVS). The Ministry of Health in Brazil basically consists of six secretaries, who are responsible for any activities and strategies related to the Brazilian health policy. It is linked to independent organisations such as ANVISA; its structure is presented in Figure 2 [21].

Figure 2: Ministry of Health – Brazil



ANVISA has created several product categories to better differentiate between the medicinal products registration procedures and requirements. The categories are (1) New Product, (2) Innovative Medicinal Product, (3) Similar Product, (4) Generic Medicinal Product, (5) Herbal Medicinal Product, (6) Biological Medicinal Product, etc. The complete list of product categories along with the corresponding category definition can be found in Annex 1 of the present document [22]. A Marketing Authorisation Holder (MAH) of a Brazilian MA is required to be legally established in Brazil; in addition, it needs to be authorised as manufacturer or importer by the Federal Health Authority. In other words, an international company not established in Brazil is not allowed to apply for a marketing authorisation in Brazil [22, 23].

4. ANVISA as ICH Member

ANVISA was the first country in Latin America to become part of the ICH. The corresponding positive decision was made in a meeting held on 9 November 2016 in Osaka, Japan, after positive recommendation of the steering committee. The committee recognised that ANVISA satisfactorily met the requirements for membership [5]**.** Prior to this decision starting 2015, ANVISA took on the role of an ICH observer . As a member, the Agency was allowed to appoint experts, who joined the individual ICH working groups.

In the scope of the ICH membership ANVISA is required to adopt a set of five ICH guidelines within five years time. These guidelines mainly concern pharmacovigilance and clinical research activities, the implementation of the Common Technical Document (CTD) as well as the implementation of the Medical Dictionary for Regulatory Activities (MedDRA) [2].

The detailed implementation plan for the five ICH guidelines is presented below [24]:

- **Level 1 – Immediate Implementation**
  - Q1: Guidelines for Stability Testing [6]
  - Q7: Good Manufacturing Practices Guide for Active Pharmaceutical Ingredients [25]
  - E6: Guidelines for Good Clinical Practice [26]
- **Level 2 – Implementation Within 5 Years (until November 2021)**
  - E2A: Clinical Safety Data Management [27]
  - E2B: Data elements for transmission of Individual Security Reports [28]
  - E2D: Post-Approval Security Data Management: Definitions and Standards for Expedited Reports [29]
  - M4: Common Technical Documents for the Registration of Medicinal Products for Human Use [7]
  - M1 MedDRA [30] (a term directly related to pharmacovigilance, with descriptions of adverse events)
- **Level 3 – Long-term Implementation**
  - Adoption of the remaining the ICH guidelines

5. Current Regulations in Brazil

5.1 Stability Studies

5.1.1 Stability Studies – Active Pharmaceutical Ingredient

The stability study requirements for the Active Pharmaceutical Ingredient (API) differ depending on the country of API manufacture. In accordance with ANVISA guidance no. 02 from 2013 [31], if the API is manufactured in Brazil or manufactured in other climate zones and used for the manufacture of drug products within Brazil for dedicated for the Brazilian market, the stability studies need to follow the requirements of climatic zone IVb. If the drug product is manufactured overseas (any climatic zone outside zone IVb), the corresponding API does not need to be tested according to ANVISA requirements [31].

5.1.2 Stability Studies – Drug Product

Brazil established different regulations with regard to the conduction of drug product related stability studies. These cover different study aspects:

- RE 01/2005 on medicinal products [32]
- RDC 45/2012 on active pharmaceutical ingredients [33]
- RDC 08/2001 on some specific medicines [34]
- Legislative Ruling IN 04/2007 on homeopathic medicines [35]

Being a member of the ICH, ANVISA was obligated to immediately implement the ICH Q1 [24].

The aim of ANVISA is to replace all current regulations (refer above) by a new regulation, which is in line with the ICH Q1 guidelines [6]. The draft of this regulation is currently under public consultation [36]. For the time being, the stability study requirements in Brazil mainly follow the international rules, in particular the ICH, but unfortunately there still many specific requirements in place for Brazil. For example, there are more mandatory tests then required by the ICH guidelines. The necessity of these tests is justified by ANVISA due to Brazil's location in climatic zone IVb [32,24]. In addition, the current valid Brazilian regulations require follow-up stability tests of drug product every 12 months; those studies must be performed in Brazilian territory, even for imported products (in bulk or primary packaging) [32].

Differences in stability study requirements may hinder industry's ability to implement scientific advances and limit the availability of medicinal products for patients due to delays associated with implementing these divergent requirements [37].

It is important to mention that Brazil initially adopted the ICH guideline Q1F with regard to the climatic zone classification. However, due to the lack of support from Zone IV countries claiming higher humidity than the recommended 65%, Brazil implemented the WHO (World Health Organization) climatic zone IVb category (hot/very humid; 30ºC/75% RH) (refer to Annex 2 for an overview of the climatic zones) [38, 39].

Based on the current Brazilian stability study regulations, these are the general requirements for long-term and accelerated stability studies in Brazil [32]:

- **Climatic Zone IVb (WHO)**
  hot and humid (30°C ± 2°C/75% RH or 40°C ± 2°C/75% RH)

- **Minimum data for submission**
  3 batches covering a minimum storage period of 12 months for long-term stability studies or 6 months for accelerated and ongoing / long-term stability studies

- **Shelf-life**
  For a New Drug Application (NDA), the maximum provisional shelf-life is 24 months (in case the minimum stability data covering a storage period of 12 months is presented). The granted shelf-life has to be confirmed with completed long-term stability studies covering the full shelf-life by the time of the Renewal submission (5 years after of granting the MA). Accelerated stability data or 12-months long-term stability data, which confirm the stability-indicating quality parameters of a drug product to change equal to or less than 5.0% in comparison to the batch release analysis results, are accepted for granting the initial, provisory shelf-life.

- **Frequency of the tests**
  0, 3, 6, 9, 12, 18, 24 months in case of long-term stability studies and 0, 3, 6 months for accelerated stability studies

- **Mandatory tests, unless a technical justification is presented**
    - appearance
    - quantification of active ingredient
    - microbiological limits
    - quantification of degradation products
    - In addition for solids
        - dissolution (solids)
        - hardness (solids)
    - In addition for semi-solids or liquids
        - pH
        - sedimentation rate after agitation (for suspensions)
        - clarity of solutions
        - phase separation (for emulsions and creams)
        - loss of weight (for water-based products)

  All tests must be performed at each testing time point; exceptions are the test for hardness as well as the tests for microbiological purity, which are just obligatory at the start and at the end of the stability study establishing drug product's shelf-life.

- **Storage conditions for accelerated and long-term stability studies**

  The following table 3 and table 4 provide an overview of the storage conditions applicable for accelerated and long-term stability studies [32].

Table 3: Accelerated Stability – Drug Product

Conditions	**Package**	**Temperature and Humidity**	**Storage Condition**
Room	Semi-permeable	40ºC ± 2ºC / 75% UR ± 5% UR	15ºC –30ºC
Room	Impermeable	40ºC ± 2ºC	15ºC –30ºC
Frozen	All	-20ºC± 5ºC	-20ºC

Table 4: Long-Term Stability – Drug Product

Conditions	Package	Temperature and Humidity	Storage Condition
Room	Semi-permeable	30ºC ± 2ºC / 75% UR ± 5% UR	15ºC –30ºC
Room	Impermeable	30ºC ± 2ºC	15ºC –30ºC
Frozen	All	-20ºC± 5ºC	-20ºC
Refrigerated	All	5ºC ± 3ºC	2ºC –8ºC

5.1.3 Follow up Stability Studies

A follow-up stability study is mandatory for the drug product and requested every 12 months, including all tests of a long-term stability study. The number of selected batches depends on how many batches are produced per year (e.g.: one batch of follow-up stability for production above 15 batches/year) [32]**.**

5.1.4 Photostability Studies

In 2005, ANVISA published a guideline for photostability studies together with the resolution RE 01/2005, which is in line with ICH Q1B. In this document, ANVISA describes how to perform a photostability test, defining light sources and providing information on the test chamber as well as the test procedure. The guidance also includes considerations for conducting the test, analysis of the samples as well as the evaluation of the test results [32]. A photostability study intended for the initial marketing authorisation application of a drug product in Brazil is mandatory to be performed with three batches for the drug product.[11]**.** In addition to the guideline on photostability studies, the Brazilian resolution RDC 53/2015 established requirements for the control of degradation products and the performance of specific studies with regard to degradation products, which are not in line with the ICH guidelines [40].

5.2 Dossier Format

The current Brazilian dossier requirements differ from those of the Common Technical Document (CTD) in terms of dossier structure and content requirements [7, 41]. Brazil has a specific dossier format for the marketing authorisation. The currently valid resolutions for each medicinal product category (refer to Annex 1) specify dossier

content and structure required to be presented by the applicant [23]. In addition, a checklist of dossier requirements is available on ANVISA`s website, which precisely describes the documents that need to be submitted as well as their sequence. This checklist is updated on a regular basis; in case the applicant does not submit an application in accordance with this checklist, the application will not be positively validated [41].

But although ANVISA is increasingly strict with the dossier requirements, it is still possible to deviate from the checklist if the deviation is very well justified.

Nonetheless, for conducting an application submission to ANVISA, the ICH CTD dossier needs to be re-formatted according to the Brazilian dossier structure requirements, including several additional documents specific for Brazil [42].

In addition, resolution RDC 25 (published in 2011) sets provisions on the procedure of documentation submission to ANVISA [43]. For some types of procedures such as an NDA, the documents can be submitted to ANVISA electronically directly over ANVISA's website. The application form is called "Formulario de Peticao (FP)"; it is a common word document applicable for the submission of an NDA (all types of products) to ANVISA [2]. For regulatory procedures that do not allow electronic document submission, the relevant documents need to be submitted in paper and in person, directly to ANVISA`s premises. The documentation submitted to ANVISA shall be in Portuguese according to the regulation, but in practice some parts of the dossier can be presented in English. Also, the dossiers shall be presented in A4 format, broken up into volumes by dividers. Official documents issued by other health authorities in foreign languages, which are used for registration purposes in Brazil, must be accompanied by a certified translation in accordance with legal requirements [43].

Translation of documents not only takes additional time but also leads to additional costs. The need to have bilingual dossiers, Portuguese and English, increases the number of documents (double), and a bigger space is needed to archive the number of documents. In addition, pharmaceutical companies must have a well-organised change management in place in order to manage the changes in each language.

The Brazilian dossier mainly consists of two parts: the administrative and the technical reports (including quality, clinical and non-clinical information).

Besides the documentation requested in the ICH countries, ANVISA has some additional requirements, which are mainly related to the quality and administrative parts. For example, the master batch records for the drug product and chromatograms

of the analytical analysis are required. For a new registration, many administrative documents such as the application form, the Certificate of Pharmaceutical Product (CPP), Good Manufacturing Practice (GMP) certificates, etc. are required to be submitted in Portuguese, the official language in Brazil. Outside of the EU, a CPP is required when a regulatory agency relies on the assessment of another agency; in case a CPP is available, there is no need to perform a full regulatory assessment for that product. In Brazil, although ANVISA performs a full assessment of the dossier, the agency requests the CPP in order to find out if the drug product has already been approved by another regulatory agency before giving the approval in Brazil. Therefore, the CPP is mandatory in Brazil.

The Brazilian dossier structure is as follows [41, 22]:

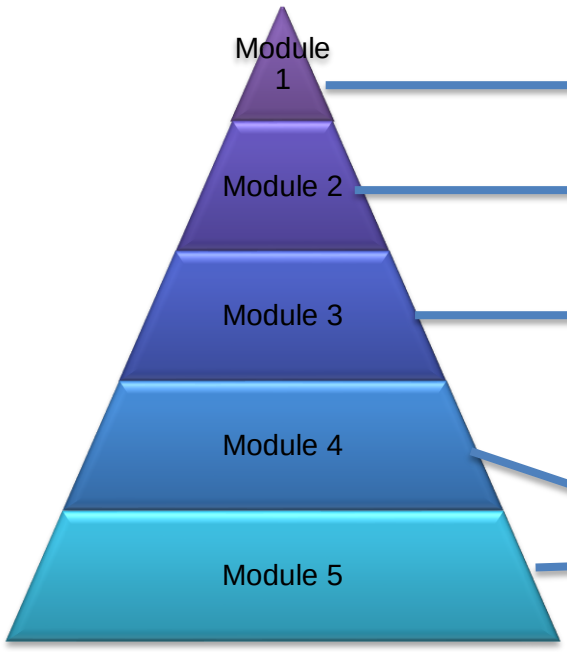
- Cover letter and application form
- Proof of payment
- Certificates: GMP (issued by ANVISA)
- Proof of registration in the country of origin for imported medicines
- Documentation on the active pharmaceutical ingredient
- API quality control by the manufacturer of the finished product
- Quality control of the excipients by the manufacturer of the finished product
- Quality control of primary and secondary packaging as well as the wrapping material
- Technical report on the formulation development
- Manufacture and packaging instruction
- Summary report of process validation
- Quality control of the finished product carried out by the manufacturer in the country of origin
- Product quality control performed by the importer in Brazil
- Stability studies of the finished product
- Safety and efficacy summary and reports

6. Assessment of the Current Status Regarding the Implementation of ICH Guidelines in Brazil

6.1 ICH CTD Versus Brazilian Dossier

The table 4 below provides an overview on the Brazilian and the ICH CTD dossier structure based on the outlines of the Brazilian dossier format, which is applicable for all categories of medicines. The first part of the Brazilian dossier mainly includes administrative documents such as the application form, the proof of payment, as well as further legal documents and certificates (e.g. the CPP, GMP certificates, etc.). A document similar to the Quality Overall Summary of the ICH CTD (Module 2.3) is not required for Brazil. However, the clinical and non-clinical summaries and overviews, which are similar to Modules 2.4 through 2.7 in the ICH CTD, are mandatory. The core part of the dossier is the quality part, where the information from CTD Module 3 can be used although it has to be restructured. In addition, specific Brazilian requirements have to be fulfilled, for example GMP certificate issued by ANVISA. Together with the clinical and non-clinical summaries and overviews, the information included in ICH CTD Modules 4 and 5 are required to prepare the safety and efficacy reports [7, 22, 41], which are mandatory for the Brazilian dossier.

Table 4: Comparison of ICH CTD and Brazilian Dossier Organisation

ICH CTD Triangle	Brazilian Dossier Organisation
	Administrative documents, including application form and certificates Summaries and overviews for non-clinical and clinical are required. Quality data for the finished product, API and excipients, packaging material information, description of formulation development, manufacturing report, and stability studies Safety and efficacy report

Focusing on the requirements for registration of a new drug product in Brazil, the Table 5 below describes on a high level the similarities of requirements between the ICH CTD and the Brazilian Dossier [7, 41, 44] . The differences between the requirements from ANVISA and the ICH CTD are discussed in the next chapters (6.2 Assessment Implementation ICH M4, 6.3 Assessment implementation Q1- Stability Studies).

Table 5: Brazilian Dossier Requirements and corresponding ICH CTD Modules

Brazilian Dossier	**Corresponding CTD Module**
1-Administrative documents	
Application forms (form 1 and form 2) duly completed, stamped and signed	Module 1 – regional specific requirements
Proof of payment	
Mock-ups	
For National products: Copy of the valid Good Manufacturing Practices Certificate (GMPC) issued by ANVISA for the production line in which the drug, subject to registration, will be manufactured, including packaging if applicable, or a copy of the inspection request protocol for the purpose of issuing the GMP certificate.	
For imported products: Specify the phase of the drug product to be imported as a finished product, bulk product or in primary packaging. Copy of the valid Good Manufacturing Practices Certificate (GMPC) issued by ANVISA, for the production line in which the drug, subject for registration, will be manufactured. The respective sworn translation or a copy of the protocol for requesting for the issuance of the GMP certificate is required. If the product is imported on bulk or primary packaging: copy of Certificate of Good Manufacturing and Control (GMPC), issued by ANVISA, for the production line of the company responsible for the packaging stage.	
Proof of registration in the country of origin for imported medicines: - Statement with the global regulatory situation. - Certificate of Pharmaceutical Product (CPP) in accordance with the standard adopted by WHO or a copy of the approval in the country of origin, pursuant to article 18 of Law 6360/76 [45]. - translation of the Pharmaceutical Product Certificate (CPP) or the letter of approval of the registration in the country of accordance with article 18 of Law 6360/76	

<table>
<tr><td colspan="2">2- Technical report – Quality</td></tr>
<tr><td colspan="2">2.1 – Active Pharmaceutical Ingredient (API)</td></tr>
<tr><td>Documentation of the manufacturer of active pharmaceutical ingredients not subject to registration with ANVISA, including:

-Technical Documentation of the Manufacturer of the Drug (Master File of the Drug - DMF) in its latest version, including the close part.

-Document of the official sanitary organ of the country of origin proving authorisation for the activity of manufacturing API.</td><td>3.2.S.1 General Information:
3.2.S.1.1 Nomenclature
3.2.S.1.2 Structure
3.2.S.1.3 General properties

3.2.S.2 Manufacture:
3.2.S.2.1 Manufacturer(s)
3.2.S.2.2 Description of manufacturing process
3.2.S.2.3 Control of materials
3.2.S.2.4 Control of critical steps and intermediates
3.2.S.2.5 Process validation and/or evaluation 3.2.S.2.6 Manufacturing process development

3.2.S.3 Characterisation
3.2.S.3.1 Elucidation of structure and other characteristics
3.2.S.3.2 Impurities

3.2.S.7 Stability
3.2.S.7.1 Stability summary and conclusions 3.2.S.7.2 Post-approval stability protocol and stability commitment
3.2.S.7.3 Stability data</td></tr>
<tr><td colspan="2">API Quality Control by the Manufacturer of the finished product</td></tr>
<tr><td>Comparative table of the specifications adopted by the API manufacturer with the specifications adopted by the finished product manufacturer for the API with the justifications for any differences.</td><td rowspan="6">3.2.S.4 Control of Drug Substance
3.2.S.4.1 Specification
3.2.S.4.2 Analytical Procedures
3.2.S.4.3 Validation of Analytical Procedures
3.2.S.4.4 Batch Analyses
3.2.S.4.5 Justification of Specification

3.2.S.5 Reference Standards or Materials

3.2.S.6 Container Closure System</td></tr>
<tr><td>Document containing API specifications adopted by the manufacturer of the finished product.</td></tr>
<tr><td>Justifications and technical references used to construct the specifications adopted by the manufacturer of the product completed for the API.</td></tr>
<tr><td>Document containing updated API analytical methods adopted by the manufacturer of the finished product.</td></tr>
<tr><td>Protocols and Validation Reports / Adequacy of analytical methods.</td></tr>
<tr><td>Certificates of analysis of the lots of API used in the manufacture of batches of medicament submitted for registration, issued by the input manufacturer and by the manufacturer of the finished product.</td></tr>
</table>

2.2- Excipients - information and quality control	
Document containing the specifications adopted.	**3.2.P.4 Control of excipients** 3.2.P.4.1 Specifications 3.2.P.4 .2 Analytical procedures 3.2.P.4.4 Justification of Specifications 3.2.P.4.5 Excipients of Human or Animal origin 3.2.P.4.6 Novel Excipients
Document containing updated analytical methods.	
Copy of the reference pharmacopoeia used, if applicable.	
Declaration of the accomplishment of all the tests listed in the official monograph.	
Certificates of analysis of the excipients.	
Excipients of animal origin on control of Encephalopathy Transmissible Spongiform	
2.3- Packaging material information	
Quality Control of Primary, Secondary, Packaging and Wrapping Material:	**3.2.P.7 Container Closure system**
Description of the materials used in the primary, secondary functional packaging, wrap and accessories, except diluents.	
Document containing the specifications and methodologies adopted and adequacy to the general chapters of the pharmacopoeias recognised by the agency.	
Declaration regarding the performance of all the tests listed in the specifications.	
Certificates of analysis issued by the manufacturers of the materials and the finished product.	
2.4- Formulation development	
History of batches produced during development with detailing of the qualitative and quantitative composition and its equivalence, bioequivalence, stability and other applicable tests.	**3.2.3.P.1 Description and Composition of the Drug Product** **3.2.P.2 Pharmaceutical development** 3.2.P.2.1 Components of the Drug Product 3.2.P.2.1.1 Drug Substance 3.2.P.2.1.2 Excipients 3.2.P.2.2 Drug Product 3.2.P.2.2.1 Formulation Development 3.2.P.2.2.2 Overages 3.2.P.2.2.3 Physicochemical and Biological Properties 3.2.P.2.3 Manufacturing Process Development 3.2.P.2.4 Container Closure System 3.2.P.2.5 Microbiological Attributes 3.2.P.2.6 Compatibility
Critical evaluation of the formulation of the product subject to submission with the necessary justification of the components used in the Qualitative, quantitative and functional aspects.	
Characterisation of the API in terms of particle size and solubility or technical justifications for non-necessity characterisation.	
Characterisation of the API for the polymorphism with the evaluation of possible conversions between the polymorphic forms during manufacturing and throughout the stability study of the finished product. Justify the impact of polymorphs on efficacy, safety and performance of the product.	
Characterisation of the API as to its enantiomeric forms and their respective impact on the efficacy, safety of the product and controls the desired shape.	
Safety data of the innovative use of excipients in the formulation, including use in a new route of administration.	
Technical justification for choosing the specification (physico-chemical characteristics) of the excipients that may have an impact on the final product performance or manufacturing process.	
Demonstration of the effectiveness of the preservative system.	

Technical justification for the use of additional quantities of the API in order to compensate for losses in the process production	
Dissolution method development report.	
Assessment of the compatibility of the API (s) with the excipients.	
Assessment of the compatibility of the primary packaging with the product, including extractables and leachables for parenteral and inhalation formulations.	
Documentation proving the functionality (effectiveness) of grooves in the case of grooved tablets and rationale for the presence of sulcus.	
Study of the degradation profile for all concentrations, according to RDC 53/15 [40].	
Identification data of degradation products that exceed the limits described in Art. 9, § 4 of RDC 53/15 [40].	
2.5- Manufacturing report	
Flowchart of the manufacturing and packaging process, containing all unit operations, inputs and outputs of materials, controls in process, identification and operational parameters of the equipment used and description of the intermediates that are stored.	**3.2.P: Drug product** 3.2.P.3.1 Manufacturers 3.2.P.3.2 Batch Formula 3.2.P.3.3 Description of manufacturing process and process controls 3.2.P.3.4 Control of critical steps and intermediates 3.2.P.3.5 Process validation and/or evaluation **3.2.A Appendices** 3.2.A.1 Facilities and equipment's
Copy of the Instruction of Manufacture and Packaging of a batch of each concentration, with due record of execution of all steps related to production and packaging.	
Annex I of RDC 200/2017 [41] filled in with data from the other lots, including a copy of the analysis reports of the quality of the medicinal product, the weighing sheets, the performance calculation sheets of the handling steps, packaging and final.	
Certificates of analysis for the three lots of each concentration.	
Summary report of process validation	
2.8 Finished product - Quality Control	
Document containing the specifications adopted by the manufacturer of the finished product.	**3.2.P.5 Control of Drug Product** 3.2.P.5.1 Specification(s) 3.2.P.5.2 Analytical Procedures 3.2.P.5.3 Validation of Analytical Procedures 3.2.P.5.4 Batch analyses 3.2.P.5.5 Characterisation of impurities 3.2.P.5.6 Justification of Specification 3.2.P.6 Reference Standards or Materials **Pharmacopoeias:** In Europe, the monographs
Justifications and technical references used to construct the specifications adopted by the manufacturer of the finished product.	
Description of the General Chapters applicable to the product in accordance with the pharmacopoeias recognised by the technical justification if any tests are not covered. In Brazil, if the monographs are available in the Brazilian Pharmacopeia, is strongly recommended to be used, However, other Pharmacopoeia such as European Pharmacopoeia and US Pharmacopoeia are also accepted.	
Rationale for non-performance of the residual solvent test in cases where it is not specified in the specification.	
Document containing updated analytical methods.	
Declaration if the methods and specifications cited in the previous item are also used for stability purposes and, if technical justifications for the difference.	

Protocols and Validation Reports / Adequacy of analytical methods for all companies involved in the flow of development or transfer of the analytical method.	of the European Pharmacopoeia are mandatory. If an excipient is not covered by a monograph of the Ph. Eur., then reference should be made to another national Pharmacopoeia (e.g. BP) or USP, JP
Graphical representation of the dissolution profile of 1 batch submitted for registration.	
Product Quality Control performed by the Importer:	
Comparative table of specifications adopted by the importer of the finished product with the specifications adopted with justification of the differences.	
Document containing the specifications adopted by the importer of the finished product.	
Document containing updated analytical methods.	
Protocols and Validation Reports / Adequacy of analytical methods performed by the importer.	
Certificate of analysis issued by the importer for each concentration.	
2.9- Stability Studies	
Protocols for accelerated and long-term stability studies conducted with 3 (three) lots for each concentration.	**3.2.P.8 Stability** 3.2.P.8.1 Stability Summary and Conclusion 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment 3.2.P.8.3 Stability Data
Reports on the results of accelerated and long-term stability studies. The reports must include the assessment and discussion of results obtained and also the analyses of statistical trend, when applicable, and conclusions regarding conservation of validity according to the RE 01/20015 [32]	
Protocols of stability studies conducted with 3 batches for each concentration of the drug product where after in-use stability studies a change in their original shelf-life or in the original preservation care is observed.	
Reports on stability studies after reconstitution / dilution and in use stability including discussion of results obtained and conclusions regarding conservation and shelf-life.	
Protocols of photostability studies conducted with 1 (one) batch for each concentration in the industrial condition.	
Reports of photostability studies, including discussion of the results obtained and conclusions regarding the use of preservatives and shelf-life.	
3. Safety and Efficacy Report	
Safety and efficacy report according to specific guidance, containing: -Report of non-clinical trials; and - Report of phase I, II and III clinical trials.	**Module 2 Common Technical Document Summaries** 2.4 Nonclinical Overview 2.5 Clinical Overview 2.6 Nonclinical Written and Tabulated Summaries 2.7 Clinical Summary **4 Nonclinical Study Reports** 4.1 Table of Contents of Module 4 4.2 Study Reports 4.3 Literature References

	5 Clinical Study Reports 5.1 Table of Contents of Module 5 5.2 Tabular Listing of All Clinical Studies 5.3 Clinical Study Reports 5.4 Literature References

6.2 Assessment implementation ICH M4- CTD

6.2.1 Administrative requirements

Good Manufacturing Practice (GMP) – ANVISA is responsible for the regulatory review and as well as for GMP inspections. The GMP certificate issued by ANVISA is mandatory for the registration of a new drug product in Brazil (for all manufacturing sites). Initially, a new drug application can be submitted without this certificate, but it should include an official request for a GMP inspection of the respective manufacturing site. The new drug application can only be approved after successful GMP inspection and the availability of the corresponding GMP certificate. In contrast to other countries, Brazil does not accept GMP certificates issued by other Authorities (e.g.: EU HA) are not accepted for the registration of a new drug in Brazil; a GMP inspection performed by ANVISA is mandatory. For example, between EMA and US FDA there is a mutual recognition agreement in place: in case an EU authority already inspected the site and issued a GMP certificate, US FDA accepts this certificate and vice versa [41].

A study was performed to evaluate the outcomes of the ANVISA inspections compared with other inspecting authorities, considering the timeframe of two years (2015-2016). The conclusion was that ANVISA found more deviations than other authorities, which may be caused by different requirements. The harmonisation of GMP requirements and mutual recognition of GMP inspections, is necessary to avoid duplication of work (less inspections) and also decrease of costs - for the manufacturer as well as for the authority. Also, it would speed up the process of bringing new medicines to the Brazilian market [46]. As Brazil is an ICH member adhering to ICH principles, ANVISA could rely on ICH inspections and Agencies from US/EU/JP could rely on Brazilian inspections in future. This would be a benefit for the evolving ICH community and would save time and money.

Certificate of Pharmaceutical Product (CPP)- With the submission of a new drug application to ANVISA, it is common practice for an applying pharmaceutical company to proof that the product has already been authorised in another country (preference: high surveillance country like EU, US, Canada). This normally done by the provision of a CPP as part of the application documentation.

The CPP is not mandatory for the submission of a new drug application, but it is mandatory to be provided to ANVISA before the start of the application evaluation and the ultimate approval. This requirement was established in 1976 and the intention was to rely on the assessment of the drug product by another country. However, nowadays with the evaluation of each dossier by ANVISA itself, this requirement does not make sense any longer. This is particularly true, because ANVISA is recognised by the high quality of its dossier evaluations [41].

The need for an official approval of a drug product in other country prior to the drug product's authorisation in Brazil leads to a delay in availability of the products for the patients in Brazil. As a member of the ICH and with focus on global harmonisation, the CPP might no longer be required by ANVISA in the future.

Translation- Officially, the entire Brazilian dossier must be in Portuguese. However, in practice the clinical and non-clinical study reports may be accepted in English and only the summaries need to be translated to Portuguese. However, it should be taken into account that there is a risk to receive a deficiency letter or a complete rejection from ANVISA due to the submission of English study reports. Furthermore, mock-ups in Portuguese are also required for submission.

Overall, the translation of dossier into Portuguese must be high quality, which means additional, high costs for the applying pharmaceutical company. Global dossiers are usually in English and are accepted by all ICH countries; the translation to Portuguese is only needed for Brazil. Official documents in foreign languages (non-Portuguese) used for registration purposes in Brazil, issued by the foreign health authorities, must be accompanied by a sworn translation in accordance with the Brazilian law.

6.2.2 Technical Report – Quality Requirements

The core part of the Brazilian dossier is the quality part, which is called technical report. The ICH CTD has a higher granularity for the Quality Overall Summary (QOS) and Module 3 when compared to ANVISA's Technical Report (single pdf). The ICH granularity allows to re-use documents: e.g. documents regarding packaging materials or, excipients, which are used in several products can be simply re-used. Therefore they need to be assessed one time only, saving time and money and increasing quality and transparency [7,41]. As described below, there are many additional requirements in Brazil when compared to the ICH requirements.

Local quality control- In order to bring ANVISA-authorised, imported products to the Brazilian market, a local repetition of the product release tests must be performed in Brazil for all imported drug product batches. In addition, for a laboratory in Brazil to perform the release tests, a successful transfer of each analytical method must be carried out. This requirement is not aligned with ICH requirements. A pharmaceutical company from a foreign country must have a local laboratory in Brazil to perform local analysis. In June 2018, ANVISA published a new regulation (RDC 234/2018) that allows companies to outsource the local analysis (product release), but the external laboratory must be in Brazil and certified by ANVISA [41, 47]. The outsourcing of the drug product analysis in Brazil is only allowed if the following criteria are met [47]:

- The contracted company to carry out the activity of quality control must be qualified by the contracting company, which is responsible for evaluating the competence of the contractor.
- In the qualification process, the contracting company must ensure that the requirements of good laboratory practice are met by the contracted company; meeting these requirements can be demonstrated by:
    - I - qualification with the Brazilian Network of Analytical Laboratories in Health (REBLAS) for the contracted tests;
    - II - compliance with the provisions of Resolution RDC No. 11 of February 16, 2012 and its subsequent updates;
    - III - Certification of Good Manufacturing Practice, in case the contracted company it is an officially approved manufacturer of medicinal drug or biological products;
    - IV - accreditation according to ISO 17025 for the tests contracted; or

- V - proof of compliance with Good Laboratory Practices, according to internationally recognised guidelines.

Drug Substance

For the drug substance part of the Brazilian dossier, the complete Drug Master File (DMF), including open and closed part, must be submitted to ANVISA. In Brazil, the Certificate of Suitability (CEP) is not accepted. The CEP is issued by the EDQM (European Directorate for Quality of Medicines and Health Care) after the drug substance has been evaluated to comply with the requirements of the European Pharmacopoeia.

In case the monograph of the API is available in the Brazilian Pharmacopoeia, the applicant should give preference to this one and test the active substance accordingly, but compliance of the API with the European Pharmacopoeia is also accepted. Even though the European Pharmacopoeia can be used as monograph reference, The CEP is recognised by many countries (ICH and non-ICH) such as all member states of the European Union, Australia, Canada, New Zealand, Tunisia and Morocco [41, 48].

In addition, stability studies for the API are also required by ANVISA. In case the drug substance is manufactured overseas, any climatic zone is accepted. However, if the API is manufactured in Brazil or manufactured in other climate zones and exported to Brazil for manufacturing drug products for the Brazilian market, the API stability studies need to follow the requirements of Zone IVb, according to the Brazilian regulation RDC 45/2012 [31] [33].

Raw data

Specific raw data are requested by ANVISA, which are mainly related to the quality part of the dossier: Master batch records of three drug product batches and chromatograms related to the analytical tests, if applicable, must be included in the dossier. ANVISA can request to look at the raw data during GMP inspections; nonetheless, this data is also required to be included in each Brazilian dossier. Raw data is not required for ICH CTDs, but can be included as a regional information (Module 3.2.R); for example, executed batch records are also required for applications in the USA [15, 41].

List of equipment

A complete list of all equipment used during the manufacturing process of the drug product should be provided, including the working principle (class) and by drawing (subclass) in the Brazilian Dossier. In addition, the minimum and maximum capacity of each piece of equipment needs to be included. Such details about each piece of equipment is only requested by ANVISA. According to the ICH Module 3.2.A.1. Facilities and Equipment are only requested for Biotech products while in Brazil, they are requested for all product types [7, 41].

6.2.3 Safety and Efficacy Report

For the clinical and non-clinical part of the Brazilian dossier, a report following a specific format needs to be prepared. The summaries and overviews from ICH CTD Modules 2.4 through 2.7 can be used together with the study reports from ICH CTD Module 4 and 5, to prepare and compile the reports on safety and efficacy, as required by ANVISA. Thus, the content requirements from Brazil for clinical and non-clinical documents are aligned with ICH requirements.

It is important to point out that there are specific requirements for efficacy studies regarding products for life threatening or highly debilitating diseases. In these cases, ANVISA accepts that the applicant submits phase II clinical trial reports together with initiated phase III trials, or finalised phase II clinical trial reports, considering that the available data is enough to support safety and efficacy of the drug product [16, 17, 41].

Overall, the Brazilian dossier differs in many aspects from the ICH CTD with regard to content requirements and dossier format. There are many additional administrative documents required for the Brazilian dossier, which are – if at all – only part of Module 3.2.R in the ICH CTD.

The ICH guidelines on safety and efficacy of drug products are accepted in Brazil. The major differences are located in the quality part, as ANVISA has many requirements, which are specific for Brazil. All these differences challenge global submissions and globally acting pharmaceutical companies [41, 44].

6.2.4 Type of Submissions

When applying for the authorisation of a drug product in Brazil, the documentation must be presented according to the order given in the corresponding checklist, which is available at the ANVISA website. This document is frequently updated. In addition, the

application must be accompanied by a numbered index of the application documentation.

The applicant is requested to add an electronic copy of the dossier on CD-ROM / DVD, containing all documents (compiled in one file in a pdf format) that are presented in paper. This way, text search and copy of texts as well as documents are possible. This means that the paper version of the dossier must be printed and submitted to ANVISA (in person). ANVISA is located in Brasilia, the capital of Brazil. Since many applicants do not have an office / subsidiary there, the service to submit the dossier to ANVISA is often performed by an external / contracted company [43].

As a member of the ICH, ANVISA must implement the ICH M4 guideline regarding the Common Technical Dossier (CTD) in Brazil until 2021. There are significant benefits and challenges in the adoption of ICH CTD in paper, CTD (NeeS) and eCTD considering the work processes, workflows and maintenance / updating of the Agency database [24]. Table 6 (below) outlines the individual ICH-conform submission types [49, 50].

The table 6 below outlines the different types of submissions [51, 52].

	CTD in paper	**NeeS** Non-eCTD Electronic Submission	**eCTD**
Compilation/Division of the dossier	Compiled electronically with volumes, tabs and slip-sheets, then printed to paper	Folders and files	Compiled electronically with electronic documents in folders
Navigation	CTD navigation by TOCs and volume	Navigation by TOCs in the PDF	eCTD navigation by XML bone
Specific Navigation	Cross-references includes target CTD section number. Navigation on manual document , by TOCs, page numbers and caption cross references	Cross-references are hyperlinked to targets. Navigation by TOCs, bookmarks and hyperlinks	Hyperlinks andbBookmarks
Life Cycle Management	Single submissions	Single submissions	Related submissions
Validation	Manually	Possible, but limited to	Full life cycle maintenance, full

		submission package	validation, always up-to-date dossier
Assessment/ ANVISA review	Manually	Electronically and collaborational	Electronically and collaborational; Basis for cross product review

The electronic Common Technical Document (eCTD) format and the Non eCTD electronical Submissions (NeeS) have been set as standard format in Europe. The European Medicine Agency (EMA) accepts only eCTD, whereas other European countries NeeS still being accepted [53]. The implementation of the CTD in a paper form in Brazil will lead to less impact to the industry and to the agency as it is in line with the actual submission practices. Since no technology is needed, ANVISA could implement the CTD immediately.

The implementation of the CTD in a paper form in Brazil will lead to streamlining regulatory processes for the pharmaceutical industry as well as for ANVISA, as the CTD is in line with actual submission practices. Since no technology is needed, ANVISA could implement the CTD immediately. The initial implementation of the CTD format in paper would allow the industry and the Agency to get used to the new format, the organisation of the modules and the granularity. As a second step, the electronic version could be implemented during the life cycle of the product. However, the paper submission has very high costs and needs time. In addition, it is more difficult to evaluate the paper dossier by the agency, to search information, to navigate it and it requires storage space for the dossiers. In addition, there is little to no possibility for the implementation of life cycle management in a paper dossier. On the other hand, the electronic non-eCTD electronic submission (NeeS) would reduce costs and time for preparation and would facilitate the search of information and navigation through the submission for ANVISA, reducing time requirements for the evaluation. In case of NeeS, there is no need for a specific software to prepare and compile the dossier; however, a software validator is required.

ANVISA must define a specification for the Brazilian Module 1 (administrative structure) before the implementation in order to enable the IT Vendors and companies to implement tis to the CTD and eCTD submission creation. Furthermore, especially for ANVISA in Brazil, a tender process need to be initiated for implementation of submissions in electronic format. This can take an extended period of time [24].

Besides selecting and acquiring a corresponding software, ANVISA also needs an implementation plan including the training of users. The latter is applicable for pharmaceutical companies as well.

The disadvantage with NeeS is that there is no possibility for life cycle management. Finally, the eCTD is the one with more benefits overcoming the challenges of the other two submissions types by reducing the costs and time for preparation, facilitating the navigation in the dossier and allowing life cycle management of the product.

The main point is that it is necessary to implement a specific technological infrastructure at ANVISA and in the pharmaceutical industry [7, 18]. The following items need to be considered by ANVISA, in order to be able to accept / implement electronic submissions:

- CTD reviewing tool
- Portal or gateway for the submission
- Hardware including backup and recovery
- System validation
- SOPs and trainings

As part of the initial implementation plan, ANVISA visited other Regulatory Agencies such as TGA (Australia), Health Canada (Canada) and SwissMedic (Switzerland) in order to obtain information about the experiences and challenges with regard to the implementation of CTD and eCTD. In addition, the intention was getting to know the technological tools used. The outcome of these meetings was the conclusion that it is very important for both, the pharmaceutical industry as well as for ANVISA, to acquire the necessary knowledge of the ICH guideline M4. In addition, ANVISA should frequently post Q&A documents and conduct educational trainings.

The adoption of the CTD format has benefits for both parties (pharmaceutical industry and ANVISA), and a clear communication between both is essential. For both, eCTD and NeeS, investments (time and money) are required. ANVISA clearly stated that there would be a transition period for the CTD submission types with an open communication between ANVISA and applicant.

Overall, even though the eCTD would be the most beneficial option, due the long tender process in Brazil to acquire the software, ANVISA decided to implement first

the CTD in paper together with the electronic media (CD-ROM/DVD) in order to be able to fulfil the ICH timelines (until 2021). The current eCTD Protocol Pilot Project, including the acquisition of a technological solution, all steps of the tool installation, definition of validation criteria, internal flows and submission guides, is foreseen for 2022. The CTD guideline will be applicable for all product categoriess (Annex I), for new drug applications and post-approval submissions. The guideline will cover all ICH M4 guidelines [7].

Once the final CTD guidance is published, there will be a transition period where the use of the CTD format will not be mandatory. For the products already registered, the CTD format will be applicable in the next post-approval submission, within the life cycle of the medicinal product. During this period, between non-mandatory adoption of the new format and the mandatory implantation of the CTD, the CTD format and dossier baselines will not be mandatory [2, 24]. Nonetheless, a baseline submission is usually recommended at the time of changing to CTD/eCTD to give the affected Health Authority access to all or at least part of the previously submitted dossier. When the eCTD lifecycle is initiated and accepted by a regulatory Authority, all subsequent submissions related to the dossier normally have to be submitted in eCTD format as well [54]. ANVISA needs to define a solution for this point as well (e.g. no review o**n** baselines, but commitment from the applicants to only provide already assessed documentation in the scope of a baseline submission).

6.3 Assessment of implementation regarding ICH Q1 – Stability Studies

Stability studies are essential to establish the retest period for an active substance and the shelf life of a drug product along with the corresponding storage conditions.

The ICH Q1 guideline provides guidance on the core stability data, which are required for new drug substances and products. It also includes a clear statement that different situations can happen, and alternative approaches may be acceptable if justified [6]. On the other hand, the currently valid Brazilian requirements for stability studies contain rigid requirements, which are not in accordance with the ICH guidelines.

It is important to know that the Brazilian regulatory system is based on Resolutions, which are mandatory to be followed. Even though there are additional guidelines in place, they are only in place for explanatory / recommendatory purposes, but they have

to be aligned with the relevant Resolutions in force. For example, ANVISA must have a Resolution with mandatory requirements for stability and photostability testing, and can in addition issue guidelines to make recommendations on how the companies can better fulfil these mandatory requirements [20, 22]. Therefore, in order to implement the ICH guidelines and to achieve ICH harmonised requirements, ANVISA will need to revise the existing Resolutions and consequently amend the related guidelines. With different and additional requirements, the harmonisation cannot be achieved [37].

According to the current Brazilian resolution for stability studies of new medicinal products, all stability protocols and reports, regardless of the pharmaceutical form, must contain the following information [32]:

- Description of the drug product and specification of the primary package
- Batch number of each batch involved in the study
- Manufacturer's description of the drug product, active ingredients
- Appearance
- Study plan: material, methods (design) and schedule.
- Start date of the study
- Amount of active ingredient and corresponding analytical method
- Quantification of degradation products and corresponding analytical method
- Microbiological limits
- Dissolution (solid form)
- Hardness (solid form)
- pH (liquid and semisolid forms)
- Sedimentation rate after agitation in suspensions (liquid and semisolid forms)
- Clarity of solutions (liquid and semisolid forms)
- Phase separation in emulsions and creams (liquid and semisolid forms)
- Loss of weight in water-based products (liquid and semisolid forms)

There is a major impact if the definitions of the requirements are not clearly specified; this may cause different interpretations of the applicants and ANVISA. This lack of standardisation/clarification of requirements, might lead to the pharmaceutical company not being able to refer to the same stability data as used for other international submissions. This could generate delays and additional costs for the pharmaceutical industry and might impact the availability of medicinal products on the

Brazilian market [32]. For example, for bracketing and matrixing, the ICH Q1A(R2) has clear definitions [6]. However, the reduced plan for stability studies in medicinal products presented by the Annex 1 of the Resolution RE 01/2005 currently in force in Brazil, does not follow the same definitions as ICH Q1A(R2). This document presents the definition for “bracketing” and matrixing. Unfortunately there is no literal translation to Portuguese for the word “bracketing”, thus ANVISA chose the word “agrupamento” (translation to English: grouping). According to their understanding, it has the same meaning. Some terms without translation, should be used in English in order to avoid any misunderstanding. The concepts of agrupamento (bracketing) and matrizacao (matrixing) are similar to those of ICH Q1D [6, 13, 32].

6.3.1 Stress Testing (DS) / Photostability testing (DP)

ICH Requirements

Stress testing for drug substance and photostability studies for drug product are required to identify degradation products that are formed under accelerated and long-term conditions. In addition, the identification of degradation products under the stress conditions supports the development and validation of analytical procedures. The aim of these studies is to ensure that the external factors (e.g.: light exposure) does not result in unacceptable change in the product [6, 11]. .

Assessment of Brazilian Requirements

ANVISA issued a guideline on how to perform photostability studies as attachment to the current Brazilian resolution for stability studies (RE 01/2005). The guidance is aligned with the ICH Q1B [11]. However, while the ICH guidelines require the photostability study to be performed with at least one drug product batch, three drug product batches are required to be photostability tested by ANVISA. This means, that the companies need to perform the study with two additional batches for the submission in Brazil [32].

Besides of the requirements regarding photostability studies, the Brazilian Resolution RDC 53/2015 establishes requirements for the control of degradation products. The requirements for stress testing are basically aligned with the ICH guideline. However, the scope of this regulation was expanded beyond the ICH guideline, including specific requirements and recommendations for the degradation product studies. The company must perform the degradation studies for all strengths of the medicinal product.

ANVISA accepts technical rationale when any of these conditions do not apply. For the implementation of the degradation studies, ANVISA published prioritisation list (Resolution RDC 53 Annex I and II) based on the therapeutic classes of the products. The medicinal products already approved for marketing where the therapeutic class has been included in Resolution RDC 53 Annex I, have to comply with this regulation by 31-Dec-2017 and where included in Resolution RDC 53 Annex II, by 21-Dec-2019. For all other medicinal products already approved, compliance must occur by 31-Dec-2020 [43].

6.3.2 Specification and required tests

ICH Requirements

Tests related to physical, chemical and microbiological stability aspects of drug substance as well as drug product must be performed in the scope of ICH-conform stability studies. The test results have to conform to the specified parameters' acceptance criteria. These tests are needed to monitor and confirm that the drug substance / drug product does not experience any change in quality during storage under the defined conditions, which can potentially impact safety and/or efficacy of the drug product.

Sometimes the shelf-life and the release specification for drug product differ slightly. This is acceptable but needs to be justified. According to the guideline ICH Q6A on specifications for test procedures and acceptance criteria for new drug substances and new drug products (chemical substances), the following tests are mandatory: description, identification, assay and impurities including organic impurities, inorganic impurities (degradation products) and residual solvents.

Tests other than those listed above may be needed in special situations [6, 10].

Assessment of Brazilian Requirements

The Brazilian regulation has more mandatory tests than established by the ICH guidelines. All mandatory tests must be performed unless a technical justification is presented. For all drug products the following test are mandatory: appearance, quantification of active ingredient, microbiological limits. In addition, for solids: dissolution and hardness tests and for semi-solids or liquids: pH, sedimentation rate after agitation in suspensions, clarity of solutions solutions, phase separation in

emulsions and creams and loss of weight in water-based products. All tests must be performed at each stability test point, except for the tests for hardness and microbiological purity, which are solely obligatory at the beginning and at the end point (= shelf-life) of the stability study [32].

6.3.3 Testing Frequency

ICH Requirements

The testing frequency for the long term stability studies should be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period/shelf-life. For the stability test under accelerated storage conditions, a 6 months study is recommended employing a testing frequency of three months (0, 3 and 6) (ICH, Q1A(R2) guideline- Stability Testing of New Drug Substances and Products, 2003).

Assessment of Brazilian Requirements

The testing frequency for stability studies in Brazil is the same as defined in the ICH guidelines. The reduced designs (matrixing and/or bracketing), where the testing frequency is reduced or certain factor combinations are not tested at all, can be also applied (ANVISA, Brazilian Resolution – RE Nº 1 – Stability Studies on medicinal products, 2005).

6.3.4 Storage Conditions

ICH Requirements

In general, the stability studies for drug products applying long-term and accelerated storage conditions are sufficient. However, if there is any significant change in the quality of the drug product (e.g.: failure to meet the acceptance criteria), studies employing intermediate storage conditions must be conducted [6].

Storage	Study	Storage condition	Minimum Time Period Covered by Data at Submission
Room	Long-term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months

Refrigerator	Long-term	5°C ± 3°C	12 months
Freezer	Long-term	- 20°C ± 5°C	12 months
Room	Intermediate*	30°C ± 2°C/65% RH ± 5% RH	6 months
Room	Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months
Refrigerator	Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

*If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

Assessment of Brazilian Requirements

In 2005, Brazil implemented the stability study requirements for WHO climatic Zone IVb category (hot/very humid; 30ºC/75% RH); this condition is not considered in the ICH guidelines. For the registration of the product, according to the specific resolution for stability studies (RE 01/2015), long-term stability study of 12 months or the report of the 6 months accelerated stability study are mandatory. However, RDC 200/2017 which regulates general requirements for the registration of new products, requests long-term and accelerated stability studies. Both regulations are in force with contradictory information. The main issue is that, after the official approval of a drug product, the Brazilian regulation requires follow-up stability studies every year. In addition, stability studies for imported products (as bulk or in primary packaging), have to be carried out on Brazilian territory [6, 32, 41].

6.3.5 Stability Commitment

ICH Requirements

For the submission of a new drug application, long-term stability studies on three production batches covering the proposed re-test period for drug substance and shelf-life for drug product are required. The commitment for stability studies is acceptable in the following situations [6]:

- *"If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed re-test period for drug substance or to proposed shelflife for the drug product.*

- *If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed re-test period/shelf life and to place additional production batches, to a total of at least three, on long term stability studies through the proposed re-test period/shelflife.*
- *If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long term stability studies through the proposed re-test period/shelflife."*

Assessment of Brazilian Requirements

A commitment is only acceptable for the first situation in Brazil (submission includes data from stability studies on at least three production batches). For example, if the submitted stability studies contain data for 12 months (minimum for submission) and the shelf-life is intended to be 24 months, the applicant can commit to submit the remaining data once they are available. In case of the other two situations, commitments are not accepted by ANVISA. The limited possibilities for stability study commitments in Brazil lead to delays regarding drug product approval in Brazil compared to other countries [32].

6.3.6 Stability Evaluation

ICH Requirements

The results of the stability studies need to be evaluated in order to guarantee that the physical, chemical, biological and microbiological aspects do not show relevant changes over the storage period, which might impact the quality of the drug substance / drug product. Certain variability can be accepted; however, the results must be within the pre-specified parameter ranges. Extrapolation of the real time data applying long term storage conditions is accepted and the applicant can request to extend the re-test period/shelf-life for the drug substance / drug product based on this data. However, in order to be accepted, this request needs to be technically justified (allowing extrapolation to 36 months based on 24 months stability data) [14].

Assessment of Brazilian Requirements

The Brazilian regulations offer limited options for alternative risk-based approaches and scientific justifications with regard to extrapolating stability data. The only stability data extrapolation, which is acceptable for ANVISA, occurs once an accelerated

stability report or 12-months long-term report, which presents a variation equal to or lower than 5.0% of the corresponding parameter's batch release analysis result, can be approved for purposes of the provisory 24 months shelf life [32].

7. Impact on the Pharmaceutical Industries and Health Authority in Brazil

The implementation of the ICH guidelines in Brazil triggers major impact on the pharmaceutical industry as well as for ANVISA and requires substantial efforts from both sides. For the pharmaceutical industry (local companies and/or subsidiaries), particularly in the beginning, there will be a need for time and money consuming trainings, the creation and implementation of new internal guidelines / standard operation procedures (SOPs); in case of the implementation of electronic submissions (e.g.: eCTD), adequate technological infrastructure will be required [24]. For subsidiaries of global companies, the knowledge on ICH guidelines should already be available within the company; also, most of the dossiers are probably already available in CTD format in accordance with the ICH requirements. However, the local pharmaceutical companies with products registered in Brazil only will need more time and effort to implement the ICH guidelines, e.g.: re-format the dossiers and perform new stability studies according to the ICH requirements. As the scientific level of each ICH guideline is high and reflects current technology, the local and small pharmaceutical companies will be more affected as they will need more resources to achieve the necessary ICH standards [55].

At first, the implementation of the ICH requirements might cause a certain delay for application submissions in order to introduce the corresponding changes. However, once the changes are implemented, it will reduce the amount of time and effort (for both, the pharmaceutical industry and ANVISA) involved in the conversion of the dossier of one regulatory submission to another reducing the delay of patient access to new innovative medicines. Furthermore, the harmonisation of the documents will reduce duplication of studies such as different clinical studies, and stability studies currently performed in order to comply with different regulations in different countries [37]. The time saved can be re-invested into the digital structure.

The local health authority, ANVISA, faces similar consequences as the pharmaceutical industry does. ANVISA will also need to invest in ICH guideline trainings in order to learn and be able to evaluate the provided documents. In case of the implementation

of electronic submissions (e.g.: eCTD), technological infrastructure will be required at ANVISA. Even though the ICH guidelines contain a common standard for requirements, there is no guidance on the review of documents. By establishing harmonised requirements, the authorities can have better interactions, increasing the transparency of the review process and, hopefully a common standard of review will be achieved.

Besides all efforts required in the beginning, the implementation of the ICH guidelines will facilitate the exchange of information among regulatory authorities, streamline the regulatory assessment process, resulting in a more rapid access to new medicines.

Regulatory harmonisation offers many benefits to both regulatory authorities and the pharmaceutical industry, and has a positive impact on the protection of public health [2,24,55].

8. Conclusion and Outlook

ANVISA was the first regulatory authority in Latin America to become a member of the ICH [5]. Joining the ICH, the agency has to fulfil some obligations such as the implementation of ICH guidelines [2]. The aim of this work was the critical assessment of the implementation of the ICH guidelines in Brazil with specific focus on the requirements for stability testing (ICH Q1) and in the Common Technical Document (ICH M4). Both guidelines have been selected due to the major differences between the current Brazilian resolutions and ICH guidelines. The stability studies are very important in order to check the quality of the drug substance / drug product considering several environmental factors such as temperature and humidity.

In Brazil, there are many regulations in place covering different aspects of the stability studies [2]. The current stability studies in Brazil follow the international rules, in particular the ICH requirements, but there are still many differences [32].

The aim of ANVISA is to replace all regulations by a single one, which is in line with the ICH guidelines Q1 [36]. With regard to the dossier format, ANVISA currently still requires a specific Brazilian dossier. An existing CTD can be used if re-formatted for the submission to ANVISA. However, many additional dossier

requirements need to be considered for the submission of a new drug application in Brazil [7, 41].

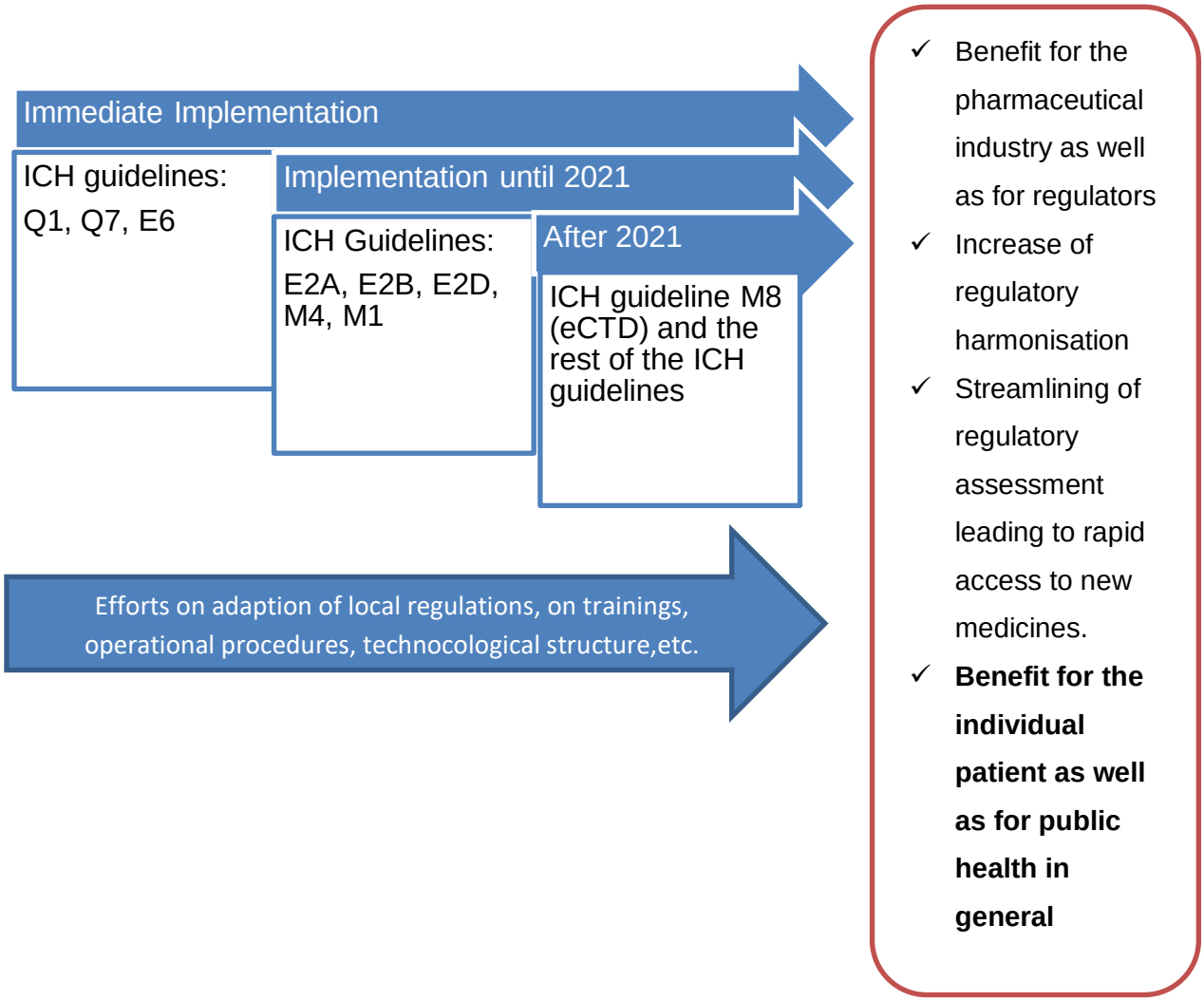
Based on the present assessment, many differences still exist between the current Brazilian resolutions and the ICH guidelines. Substantial efforts from both sides, ANVISA as well as the pharmaceutical industry, will be required in the beginning in order to implement the ICH guidelines in Brazil. But although many efforts and investments will be needed, it is clear that the adaption of the Brazilian dossier to the CTD format and the implementation of further ICH requirements will result in a tremendous benefit for both, the pharmaceutical industry, avoiding the need to reformat the dossier for each new drug application in Brazil, as well as for ANVISA, facilitating the regulatory reviews and communication with other health authorities.

ANVISA is putting a lot of effort in implementing the ICH guidelines. This includes open conversation with the pharmaceutical industry, in order to reduce the impact for both sides as much as possible and ultimately achieve the goal. ANVISA is gaining experiences on the ICH principles and soon they will feel more confident to completely fulfil all ICH requirements, and reduce the number of additional requirements for Brazil.

The harmonisation of the documents will reduce duplication of studies such as different clinical studies, and stability studies, which are currently performed in order to comply with different regulations of individual countries. This will speed up the access to medicinal products for the patients in Brazil.

The implementation of the ICH guidelines will ultimately result in tremendous benefits for the pharmaceutical industry as well as for ANVISA. And the regulatory harmonisation on the international level will lead to substantial benefits for public health; innovative, new medicinal products will be available faster for the patients in Brazil (see Figure 3).

Figure 3: Outlook - Implementation of ICH Guidelines in Brazil


Immediate Implementation
ICH guidelines:
Q1, Q7, E6
Implementation until 2021
ICH Guidelines:
E2A, E2B, E2D, M4, M1
After 2021
ICH guideline M8 (eCTD) and the rest of the ICH guidelines
Efforts on adaption of local regulations, on trainings, operational procedures, technocological structure,etc.
✓ Benefit for the pharmaceutical industry as well as for regulators
✓ Increase of regulatory harmonisation
✓ Streamlining of regulatory assessment leading to rapid access to new medicines.
✓ Benefit for the individual patient as well as for public health in general

9. Annexes

Annex 1 – Categories of medicinal products in Brazil

Terminology	Definition	Legal Framework
New Product	A product formulated with synthetic or semisynthetic active ingredients, isolated or in association. For product registration purposes: New pharmaceutical forms; new strengths; new routes of administration and new therapeutic indications (in Brazil) of a product formulated with synthetic or semisynthetic active ingredients by a pharmaceutical company which is not the registration holder of products formulated with that specific active ingredient. A product that results from: - A modification of the pharmacokinetic properties; - Withdrawal of an active ingredient of a product already registered at the ANVISA; - New salts, isomers, although the corresponding molecular entity has been already approved for registration.	Resolution RDC 200/2017
Innovative Medicinal Product	A medicinal product approved for marketing in Brazil, formulated with at least one active ingredient that has been patented (expired or not) by the laboratory in charge of the research and marketing in the country of origin. Generally, it is considered as the Reference Medicinal Product by ANVISA	Resolution RDC 16/2007
Similar Product	A product formulated with the same active ingredient(s) of an innovator medicinal product. It has to be marketed in the same strength, the same pharmaceutical form, the same dosage scheme and for the same therapeutic, diagnosis and prevention indications and for the same route of administration as that of the reference medicinal product already approved for marketing by the ANVISA. The similar medicinal product may differ from the reference medicinal product in what concerns to the size and format, expiry period, packaging excipients; it has proven efficacy, safety and quality. Similar medicinal products have to have a commercial (brand) name.	Resolution RDC 200/2017
Generic Medicinal Product	A product formulated with the same active ingredient(s) of a reference medicinal product. Generic medicinal products are marketed in the same strength, the same pharmaceutical form, the same dosage scheme, the same therapeutic, diagnosis and prevention indications and for the same route of administration. It is interchangeable with the reference medicinal product. Marketing usually occurs after the innovator's patent has expired. Generic medicinal products have no brand name. They are	Resolution RDC 200/2017

	marketed under the Brazilian Common Denomination (DCB) or the INN, in case the DCB is not available.	
Herbal Medicinal Product	Is formulated exclusively with herbal pharmaceutical active ingredients. Safety and efficacy have been scientifically4 proved to the relevant health authority and quality has proven to have a reproducible profile.	Resolution RDC 26/2014
Biological Medicinal Product	Is formulated with an active ingredient of known biological activity that has undergone all manufacturing stages and that has already been approved for marketing in Brazil. It is considered a new product when it has not yet been approved for marketing in Brazil. The definition of similar medicinal products does not apply to biological medicinal products. Biological medicinal products include, as defined by ANVISA: vaccines-immune biologicals that contain antigenic substances able to induce specific immunity, hyper immune serums, blood by products, biomedicines, biological products formulated with live, etc.	Resolution RDC 55/2010
Specific Medicinal Product	Is a category of medicinal products that for the registration purposes, include: Rehydration solutions, solutions for dialysis or enema, or plasma substitutes; Polyelectrolyte concentrates for haemodialysis; Parenteral nutrition; Large and small volume solutions, such as water for injection, glucose or sodium chloride solutions, other electrolytic or alcoholic solutions for enteral or parenteral use; Opotherapeutic5 products and products including an herbal active ingredient used alone or in association with herbal derivates and/or minerals and/or aminoacids and/or proteins and/or herbal active ingredients. Medicinal products made with quercetin, hesperidin, diosmin, troxerutin, coumarin, ornithine, silymarin, acetylmethionine, methionine, betaine, acetylcysteine and bile acids, used alone or in association. Products for the prevention of dehydration and for hydration maintenance. Antiacid products, used alone or in association, and/or other products except those listed in the RDC 199. Medicinal products with vitamins and/or minerals for topical or parenteral use. Medicinal products with vitamins and/or minerals and/or aminoacids and/or proteins for oral use, with at least one component above the recommended limits established in the RDI. Medicinal products using herbal derivates in association with vitamins and/or minerals and/or aminoacids and/or proteins and/or herbal active ingredients. Pharmaceutical products for topical use using camphor, except those listed in RDC 199.	Resolution RDC 24/2011

Homeopathic Medicinal Product/ Dynamised Homeopathic Product	Formulated with substances that undergo successive consecutive dilutions followed by succussions (shaking) or any other form of rhythmic agitation; they have preventive or curative potential and are administered based on homeopathic, anthroposophist, or homotoxicological therapy principals. Anthroposophic products are dynamised medicinal products that follow the anthroposophic principles Anti-homotoxic products are dynamised medicinal products prepared based on the homeopathic and homotoxicological principles	Resolution RDC 26/2007

Source: Legal Definitions and Marketing Requirements in Brazil [22]

Annex 2 Climatic Zones

Zone	Type of Climate
Zone I	Temperate zone
Zone II	Mediterranean/Subtropical zone
Zone III	Hot dry zone
Zone IVa	Hot humid/Tropical zone
Zone IVb	Hot/higher humidity

Source: ICH climatic zones [4]

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

Ort, Datum Unterschrift