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VICERRECTORIA ACADÉMICA

SCHOOL OF EDUCATION AND FOREIGN LANGUAGES

TRANSLATION AND ANALYSIS OF SOME DOCUMENTS FROM ENGLISH INTO SPANISH AND FROM SPANISH INTO ENGLISH FOR CALOX FOR COSTA RICA, S.A.

Thesis Submitted to Obtain the Licentiate Degree in English with Concentration in Translation

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SEDE ARANJUEZ

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Dedication

I want to dedicate this research work, first of all, to God, who is the one who has guided my steps in all the plans I have made. Second, to my parents for their unconditional support for being a great example of dedication, struggle, and sacrifice, for encouraging me and being part of all my achievements, and also for getting involved in every possible way in the successful completion of this project. In addition, to my family and friends for their encouragement, as they always willingly and enthusiastically assisted me in any way they could.

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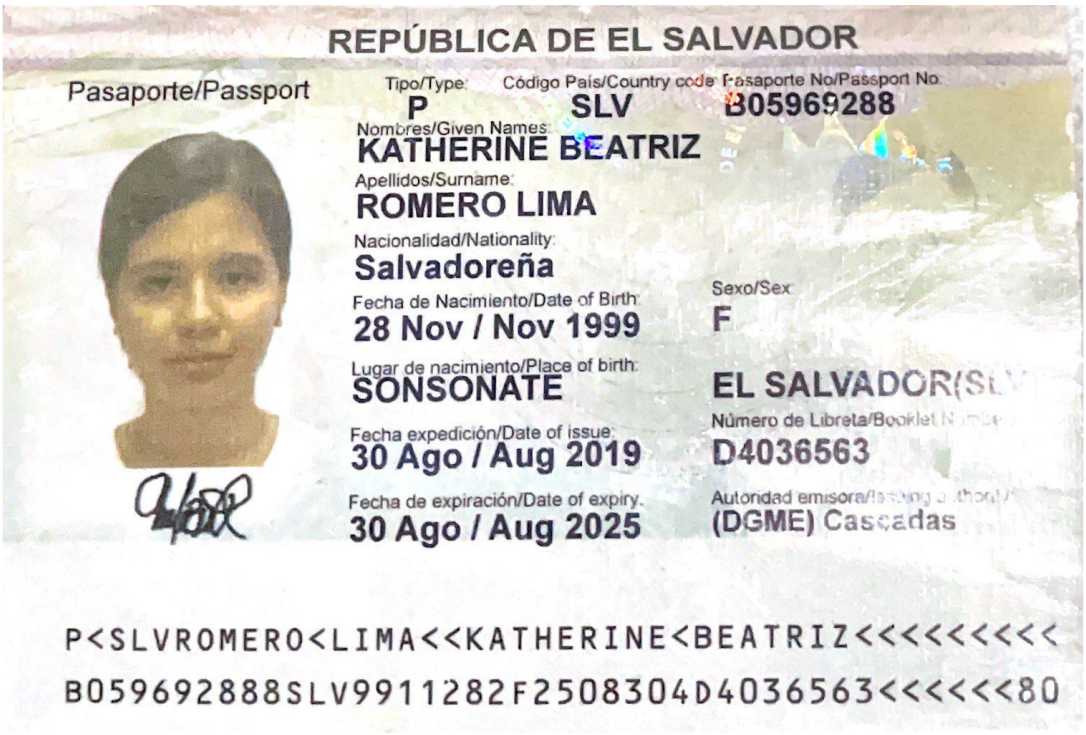

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Abstract

The upsurge and development of globalization in the modern world has demanded the adoption of new forms of communication. Based on these needs, translation has been taking on a preponderant role in society and has become a vital tool. For this reason, the objective of this research was to analyze the effects of the procedures and methods used to translate documents from English to Spanish and from Spanish to English for the company CALOX, of Costa Rica, S.A. Therefore, the qualitative method was utilized to compile the information by employing a descriptive design. Likewise, data collection was carried out using a text analysis table, a color-coding method, and the creation of glossaries. As a result of an in-depth analysis, it was determined that the application of the different translation methods and procedures allowed for accurate translations in both languages.

Resumen

El surgimiento y el desarrollo de la globalización en el mundo actual, ha exigido la adopción de nuevas formas de comunicación. Con base a estas necesidades, la traducción ha ido tomando un papel preponderante en la sociedad y se ha convertido en una herramienta de vital importancia. Por tal motivo, el objetivo de esta investigación es analizar los efectos de los procedimientos y métodos utilizados para traducir los documentos de inglés a español y de español a inglés para la empresa CALOX de Costa Rica, S.A. Por tanto, para recopilar la información, se utilizó el método cualitativo empleando un diseño descriptivo. Asimismo, la recopilación de datos se llevó a cabo mediante el empleo de una tabla de análisis de textos, un método de codificación por colores y la creación de glosarios. Como resultado de un análisis profundo se determinó que la aplicación de los diferentes métodos y procedimientos de traducción permite lograr traducciones precisas en ambos idiomas.

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Chapter I

Introductory Framework

This chapter aims to delve into the problem statement, the existing biases in the subject of study, the objectives to be achieved in this research, the feasibility of the study and the evaluation of the shortcoming, as well as the justification and the purpose of the study, the history, and the desired scope of the research process.

1.1 Problem Statement

Many companies have entered the international market, taking many of their products and services to different parts of the world. For this reason, if these companies wish to maintain a stable position in the international market, they must establish good relationships with companies and clients from different parts of the world. The Costa Rican business market is focused on attracting clients from other countries and regions. Therefore, the biggest challenge these companies or entrepreneurs must overcome to export their products to other parts of the world is the language. Therefore, they are forced to provide their customers with information about their products and services for their use or consumption.

However, certain obstacles can complicate these partnerships. These differences are often structural, as these interactions are mainly between countries and people who do not speak the same language, which makes contact difficult. A multiplicity of languages obstructs cultural exchange. Text translation allows companies to provide clear and precise specifications and instructions for what they wish to market, helping to overcome the language barrier in any part of the world. Therefore, it allows people from different linguistic backgrounds to safely consume or

use the products exported from their country of origin to other parts of the world where the language differs.

CALOX is currently a company that exports medical products to other countries, translating in its entirety documents such as prescriptions, medical instructions, general guidelines, and treaties, among others. Due to the broad business market that CALOX of Costa Rica S.A. has, it is crucial to have an adequate translation of the products they offer. For this reason, it is pertinent to have good material adapted to each region to manage these alliances; in this way, linguistic or cultural interference will not impede establishing itself in other countries. The company's biggest challenge is providing consumers with a clear and accurate translation at its different manufacturing points in Latin America. In this way, it enables its customers to consume its highly reliable products. Consequently, the research question is: What is the effect of the use of procedures and methods in the translation and analysis of some documents from English into Spanish and from Spanish into English for CALOX of Costa Rica, S.A.?

1.2 Objectives of the Investigation

1.2.1 General Objective

To analyze the effect of the procedures and methods used to translate some documents from Spanish into English and for English into Spanish for CALOX of Costa Rica, S.A.

1.2.2 Specific Objectives

1. To translate some documents from Spanish into English and for English into Spanish for CALOX of Costa Rica, S.A.

2. To apply various translation techniques to the documents in order to achieve accurate target texts.
3. To evaluate the effect of the translation techniques applied to the documents.
4. To create a glossary with the most relevant terminology found in both texts.

1.3 Justification of the Study

Every day, new multinational companies emerge that offer a diversity of products and services to society. Due to these companies' great impact worldwide, a need for effective communication between the company and the consumer arises. For this reason, translation is essential for multinational companies. With a professional translation, doing business with people and entities abroad is possible.

In the case of Costa Rica, the growing activity of transnational companies and entities makes translation even more important in the country. According to Beirute (2022), General Manager of PROCOMER Costa Rica, the Costa Rican market is facing an export sector that continues to renew itself progressively and to seek opportunities in international markets, which has demanded the reorientation of technical and training requirements in some specific areas such as the development of knowledge and skills in translation. Many Costa Rican companies are dedicated to exporting goods and services to other parts of the world, with exports of Precision and Medical Equipment being the ones that are constantly increasing. For 2022, exports of these types of goods were 34%, achieving a growth of 12% ($85 million more than in February 2021. Due to the export and globalization of Costa Rican companies, the exhaustive use of translation is required to allow companies to have the appropriate material and guides adapted to their particular conditions.

CALOX is a Costa Rican pioneer in the manufacture and marketing of high-quality-generic-human and veterinary medicines. The company was founded in 1935, starting its operations under the name of Biogen Laboratories. Later, in 1965, CALOX became associated with McKesson, a well-known North American corporation with a long tradition in the field of medicine since 1833. Through this alliance, CALOX considerably strengthened its technological capacity and marketing activity. By 1990, CALOX became a 100% Venezuelan company, establishing 1996 a strategic alliance with Sukia Farmacéutica, a Costa Rican company with 50 years of experience in its market. Today, CALOX has two manufacturing plants: one in Venezuela and the other in Costa Rica, supplying directly to Venezuela, Costa Rica, Panama, Nicaragua, Honduras, Guatemala, El Salvador, and the Dominican Republic, and indirectly through maquilas to commercial partners in Venezuela and the rest of Central America and the Caribbean.

For CALOX of Costa Rica S.A., translation has become an indispensable tool since the kind of services they offer require using a common terminology system to refer to their products. Translating documents such as research, instructions, manuals, general product guidelines, and medical prescriptions, among others, is vital to keep communication afloat in their different markets. By translating these documents, the aim is to make it possible for multilingual communication to flow and for sensitive information to remain safe, since for the company, how the message of its products and services is delivered determines whether customers will buy its products.

Based on the previously mentioned, this research aims to analyze the effect of the procedures used to translate some documents from Spanish into English and from English into Spanish for CALOX de Costa Rica, S.A. It is also intended to determine the effect of the translation

procedures on the documents provided by CALOX de Costa Rica S.A. This will be done using an in-depth analysis of the texts and a color code to indicate the procedures most commonly used in translation and the creation of glossaries that allow the identification of important terms.

The beneficiaries of the research are CALOX company, since through the translation of the documents, they intend to reach those clients who need to learn the source language and the members they have abroad. In addition, another beneficiary will be the CALOX Word Department since the translation of these documents are indispensable in this area of the company, as they are required to develop subsequent works. On the other hand, this research will help those who intend to conduct future research. Moreover, through this research, it is planned to achieve the elaboration of a faithful and accurate translation in the target language, which will allow for obtaining authentic and natural texts, trying to adjust the message to the needs of the readers of the target language, but always being faithful to the meaning of the original text. In this way, to obtain coherent translations of the documents of CALOX de Costa Rica S.A. and to generate a greater reach in the products and services offered by the company in different parts of Latin America and its different headquarters.

1.4 Antecedents

The translation took place during 2000 B.C. in the Mesopotamian era when Gilgamesh's "Sumerian poem" was translated into the Asian language. Other early translation works discovered involved Buddhist monks translating Indian scriptures into Chinese. On the other hand, one of the first written pieces of evidence of this process was the Rosetta Stone, discovered in 1799 during the Napoleonic expedition to Egypt. The stone contained parallel inscriptions in

two languages (Egyptian and Greek) and three scripts (Greek, Egyptian demotic, and Egyptian hieroglyphics).

The first known significant translation was the Hebrew Bible, which dates back to the third century. Later, the need for more translation increased with the expansion of spiritual theories and religious texts. As a result, religion brought the drive to spread religion and strengthen faith, which meant there was a necessity to translate religious content into different languages. On the other hand, among the first known religious translations is the translation of the Old Testament Bible into Greek in the third century B.C., best known as the *Septuagint*, which was the translation of the Bible from Hebrew into Greek.

It is important to highlight that translating the Bible into Greek became fundamental for future Bible translations that followed in many languages. Protestantism was established in the fourth century A.D., which also generated the necessity to continue translating the Bible and other religious content into other languages. In ancient Roman times, the ruling class took full advantage of Christianity to rescue the crumbling empire. Thus, religious translation was taken as a communication tool, and in this way, great translators like St. Jerome emerged. He emphasized using "sense-for-sense" translation in literary translation while supporting "word-for-word" translation in religious translation since Jerome affirmed that "literary translation" and "religious translation" should be treated differently.

Nonetheless, different views have been raised over time, and through comparative analysis of many examples in the Bible translated by Jerome, Brown (1992) established that for the Old Testament "sense-for-sense" approach was adopted. While Kraus (1996) pointed out that Jerome's Bible translation binds to a "sense-for-sense" approach by perusing Jerome's translation preparation and the influence of religious politics and cultural context on his translation.

However, Cicero and Jerome held almost identical views on retaining the original style in literary translation. Cicero considered that "There was no need to render word for word in the process of translation, but to preserve the general style and force of the language" (Cicero, 1949, p. 365). Jerome stated, "The translator's responsibility lied in correctly understanding the original and fully conveying the substance of the original" (Jerome, 2014, p. 29); this is based upon the theory that translation quality depends on the translator's language knowledge and precise comprehension.

Jerome inherited and developed Cicero's translation theory to a certain extent. Despite conducting several studies, scholars still need to reach a consensus concerning Jerome's translation approaches. For literary translation, he alleged that a translator should march the original text, a captive, into his native language. As for religious translation, Jerome handled the case of holy scriptures as an exception that "even the syntax contains a mystery" (Jerome, 2014). On the other hand, a more in-depth investigation into Jerome's translation views has discovered that he contradicted himself when discussing translation strategy, considering the Bible translation as an example.

On the flip side, Jerome did much organizational work before the retranslation of the Bible, involving special studies on Hebrew names and places, translation of proper nouns, and different cultures. These studies made Jerome visualize that it was extremely difficult to translate the words and phrases of the original Bible literally into Latin. It was challenging to convey every word of a person in consistence with the length of the original text. Determining that the translator, to some extent, was a "rewriter." In the end, Saint Jerome translated the Bible to Latin, and the Latin Bible became the principal book in the Roman Catholic church.

Later on, in the late 4th century, the spread of Buddhism led to large-scale ongoing translation endeavors extending across thousand years right through Asia. Kumarajiva's translations greatly influenced Chinese Buddhism; he was a scholar and translator famous for his prolific translation into Chinese of Buddhist texts written in Sanskrit, with a clear and straightforward text centered more on conveying the meaning than on accurate literal rendering. Years later, after the Arabs conquered the Greek Empire, they made translation efforts to make all Greek philosophical and scientific works available in Arabic. In the 12th and 13th centuries, the Toledo School of Translators became a meeting point for European scholars who, attracted by the high salaries offered to them, came, and settled in Toledo, Spain, to translate important philosophical works. They also translated religious, scientific, and medical works from Arabic, Greek, and Hebrew into Latin and Spanish. Toledo was a city of libraries that offered a wealth of manuscripts and one of the few places in medieval Europe where a Christian could be exposed to the Arabic language and culture.

The Toledo School of Translators went through two distinct periods. The first period (in the 12th century) was headed by Archbishop Raymond of Toledo, who advocated translating philosophical and religious works, mainly from classical Arabic, into Latin. These Latin translations helped advance European scholasticism and, thus, European science and culture. King Alfonso X of Castile led the second period (in the 13th century). In addition to philosophical and religious works, scholars also translated scientific and medical works. Castilian, rather than Latin, became the final language, establishing the foundations of the modern Spanish language. Afterward, Geoffrey Chaucer made the first fine translations into English in the 14th century. Chaucer translated the *Roman de la Rose* from French and the works of Boethius from Latin. He also adapted some works by the Italian humanist Giovanni Boccaccio

to produce his own *Knight's Tale* and *Troilus and Criseyde* in English. Chaucer was regarded as the founder of an English poetic tradition based on translations and adaptations of literary works in languages that were more "established" than English, beginning with Latin and Italian.

The Elizabethan translation period saw considerable progress beyond mere paraphrasing toward an ideal of stylistic equivalence but no progress in verbal accuracy. Cervantes, a Spanish novelist famous for his *Don Quixote*, expressed his opinion of the translation process by offering a rather desperate metaphor for the result of translations. According to Cervantes, the translations of his time, except those from Greek into Latin, were like looking at a Flemish tapestry from the reverse side. While the main figures of a Flemish tapestry can be distinguished, they are obscured by loose threads and lack the clarity of the obverse.

In the second half of the 17th century, the English poet and translator John Dryden tried to make Virgil speak "in words such as he would probably have written had he lived and been English." Nevertheless, Dryden did not perceive the need to emulate the Roman poet's subtlety and conciseness. At the outset of the nineteenth century, Romanticism discussed the issue of translatability and untranslatability, but it was until 1813 that these topics were discussed in depth. The German translator Friedrich Schleiermacher wrote a seminal paper on *The Different Methods of Translating* in the same year. Where is translation expressed further word-for-word, literal, sense-for-sense, or free translation? "A real translation is transparent; it does not cover the original, does not block its light, but allows the pure language, as though reinforced by its own medium, to shine upon the original all the more fully" (Reza, 2012).

Schleiermacher argues that the real question is how to bring the source text writer and the target text reader together. On the other hand, Friedrich concludes that the best strategy is to achieve that the translator has to render in such a way as to procure the same message as the

original reader would have. In his studies, he explained that this could not be done by having recourse to an alienating rather than naturalizing" method of translation, ensuring that the source text's language and content are translated. In the early XX century, these ideas are redefined from the viewpoint of the modernist movement. According to Walter Benjamin, in his essay, *The Task of the Translator*, the hallmark of an excellent translation is to express a reciprocal idea between both languages. His book describes that the translator's task is to reach out to and release that potentiality in the target language. Reza (2012) states, "The co-existence and complementation of the translation with the original releases this pure language." Expressing that there must be fidelity to the original text.

In the period of the French and American revolutions, most of the translators focused on rendering the translated work simpler and untroublesome. Then, accuracy was yet to be of vital importance for translators; in case of finding any problem or difficulty in translation, the portion used to be omitted completely. Due to this, many errors were led. For this reason, during the Industrial Revolution, translation accuracy began to be required as the top priority by linguists worldwide. Consequently, in the 17th century, the first ideas about mechanical dictionaries began to be put forward due to the demand for accurate translation.

Nevertheless, in the 20th century, the first concrete proposals were performed, issued independently in 1933 by the French-Armenian George Artsrouni and by the Russian Peter Smirnov Troyanskii. Afterward, in 1937, a prototype was demonstrated since Artsrouni designed a storage device on paper tape which could be used to find the equivalent in other languages. In the research *Machine Translation: A Brief History* by Hutchins (1995), Artsrouni suggested three stages of mechanical translation:

> First, an editor knowing only the source language was to undertake the 'logical' analysis of words into their base forms and syntactic functions; secondly, the machine was to transform sequences of base forms and functions into equivalent sequences in the target language; finally, another editor knowing only the target language was to convert this output into the normal forms of his language. (p. 3)

A few years after Troyanskii's invention, Warren Weaver of the Rockefeller Foundation and Andrew D. Booth proposed the idea of using computers for translation. Afterward, Booth investigated the mechanization of a bilingual dictionary and made a collaboration with Richard H. Richens, who had independently been working on the utilization of punched cards to produce word-for-word translations of scientific abstracts. Even so, in 1949, Warren Weaver compiled a set of proposals to turn the idea of machine translation into reality. He mixed up information theory, code-breaking lessons learned during the Second World War, and the principles of a coherent language to assist the progress of machines in translating one language to another. He put forth the prospects and suggested some methods such as war-time cryptography techniques, Shannon's information theory, statistical methods, and the exploration of the language's underlying logic and universal features.

The Georgetown-IBM experiment was one of the earliest machine translation successes was t. In 1954, IBM showcased a machine that could translate Russian sentences into English at its New York office. A handpicked sample of 49 Russian sentences was translated into English, employing a restricted vocabulary of 250 words and just six grammar rules. The machine could only translate a few sentences, but the idea captivated the world. In the 1950s and 1960s, research focused on empirical trial-and-error approaches, generally adopting statistical methods with immediate working systems as the core and theoretical approaches. At that time, much effort was

devoted to improving basic hardware (paper tapes, magnetic media, and access speeds) and devising programming tools for language processing. Some groups were forced to set one's minds to theoretical issues, especially in Europe and the Soviet Union.

For political and military reasons, most U.S. research was on Russian-English translation, and most Soviet research was on English-Russian systems. The research under Erwin Reifler at the University of Washington (Seattle) epitomized the word-for-word new approach. It implicated the construction of large bilingual dictionaries where lexicographic information was adopted for selecting lexical equivalents and solving grammatical problems without using syntactic analysis. As a result, it paved the way for English translations with rules for local output reordering. It applied a huge lexicon that widely used English cover terms for Russian polysemes, incorporated phrases and clauses, and the classification of vocabulary into sublanguages.

In the 1950s, they have seen an enhancement and quality in computing and formal linguistics, particularly in syntax. There were many imminent breakthroughs and fully automatic systems operating within the time. During the 1970s, Canada created the METEO System for translating weather reports from English to French. The system translated some 80,000 words per day and was in good enough condition that it was employed from 1977 to 2001 before being updated with a new system. Globalization was pushing the necessity for machine translation like never before. The Soviet Union, France, Germany, and the U.K. worked hard to crack machine translation. Such needs spurred the governments and private firms to continue their efforts. However, the perfect machine translation system eluded them.

As time progressed, translation was centered in other areas, and the literary translation world was taking off. One of the most important texts of New World indigenous literature was the *Popol Vuh*. The word Popol Vuh means *Libro de la estera*. Written in the western highlands of

Guatemala around 1550, the *Popol Vuh* is a collection of myths and historical accounts of great importance for studying the indigenous peoples of Guatemala. The names of its authors are unknown, but there are indications that it was written by prominent members of the nobility of the Quiché kingdom, which dominated a vast region of the Guatemalan highlands at the time of the Spanish conquest. Written in a careful poetic style, it is also a masterpiece in literary terms. The accounts of the Popol Vuh are closely related to other mythological texts compiled in early colonial times, as well as to many oral traditions preserved to this day in the indigenous communities of Guatemala and other parts of Mesoamerica.

The Popol Vuh addresses themes that attempt to elucidate the meaning of the text based on the speech and customs of the current Maya who inhabits the highlands. It also points to current studies on linguistics, archaeology, ethnography, and the history of Maya iconographic art, which refers to the researcher himself in the introductory text. Then, among Mesoamerican peoples, mats or mats were symbols of the authority and power of kings; they were used as seats for rulers, high-ranking courtiers, and heads of lineages. For this reason, the book's title has been translated as *Libro del Consejo*. The oldest surviving text of the Popol Vuh is a transcription of the Quiché text made in the early 18th century by the Dominican friar Francisco Ximénez, who also made the first known translation into Spanish. Ximénez presented the Quiché text in a double column next to the Spanish version and entitled it “Empiezan las Historias del Origen de los Indios de esta Provincia de Guatemala”.

This manuscript is in the Ayer collection of the Newberry Library in Chicago. It was taken from the National University of Guatemala library by the French Abbé Charles Etienne Brasseur de Bourbourg, who published it for the first time in complete form in 1861. Since then, there have been numerous editions and translations. In recent decades it has been shown that they also

find close parallels in classical Maya art. In particular, the scenes painted on polychrome pottery from the Classic period in the Maya lowlands feature figures of gods and mythological scenes related to the myths of the Popol Vuh. During the last 300 years, the Popol Vuh has been translated approximately 30 times into seven languages. According to Allen J. Christenson's research, it was discovered that various dictionaries and grammar books compiled in antiquity were needed to translate it. He collaborated with various experts to translate this work for about three decades. Currently, the importance of this text continues and can be verified by reviewing its numerous published versions.

On the other hand, Allison Calderon, a student of Universidad Internacional de las Amércicas in Costa Rica, conducted research entitled: "Translation of several documents from English into Spanish for the Latin American network of open access repositories and several articles from Spanish into English for Appy." The research aimed to analyze the effect of the procedures and methods used to translate a series of documents and articles. The investigation used different instruments: a text analysis chart, a color-coded technique, and two glossaries. During the research, thirteen translation procedures were selected for the translation of the documents in order to achieve a faithful translation of the target text. The translation process is defined as "The most used translation techniques were transposition and modulation and amplification.” After carrying out the translations and investigating the different methods, it was concluded that the most appropriate translation method was the semantic one since it allowed naturalness in translating the documents.

1.5 Scope

1. To apply several translation procedures and techniques to the documents.
2. To create accurate, natural, and cohesive texts in the target language.

3. To analyze the effect of the different translation procedures and techniques.

Chapter II

Theoretical Framework

This chapter set forth the definition of the most important terms. In addition, it deals with the different kinds of text styles, stylistic scales, text functions, and all that concerns the translation process. It is explicated how the method and translation procedures work, their importance, their features, and how they are applied in the translation process. Furthermore, the process of creating a glossary is detailed, as well as its importance in the translation process and its relevance for translators.

2.1 Text Analysis

In this part, the translator analyzes the text comprehensively to ensure that the original text has been wholly and correctly understood. One of the essential steps in translation is text analysis, which has to be carried out before starting the translation. Therefore, translation-oriented text analysis should ensure a full grasp and correct interpretation of the text and explicate its linguistic and textual structures and their relationship with the system and norms of the source language. Likewise, this section defines the different kinds of text styles.

2.1.1 Text Styles

To translate, text styles must be taken into account, which means paying attention to what is unique to the text and its choices, being aware of patterns in the text, and paying close attention to the nature and function of the text. According to Nida (as cited by Newmark, 1988), there are four types of text styles:

1) *Narrative*: a dynamic sequence of events where the emphasis is on the verbs or for

English, 'dummy' or 'empty' verbs plus verb-nouns or phrasal verbs ('He made a sudden appearance,' He burst in).

(2) *Description* emphasizes linking verbs, adjectives, and adjectival nouns.

(3) *Discussion,* a treatment of ideas, with emphasis on abstract nouns (concepts), verbs of thought, mental activity ('consider, 'argue,' etc.), logical argument and connectives,

(4) *Dialogue,* with emphasis on colloquialisms and phaticisms. (p.13)

Text styles play an important role in translation. Each style can be viewed and examined from different perspectives. Therefore, the translator has to adjust the translation to the target language addressee depending on its style; identifying it allows the translator to communicate effectively using the appropriate vocabulary and tone required for each style.

2.1.2 Stylistic Scales

Stylistic scales refer to the degree of formality of a text. In this section, the different scales of formality are discussed. How they are used, and their major features are determined to create a better understanding of them.

2.1.2.1 Scale of Formality

Maintaining the appropriate formality in the different texts is important since each has a particular purpose in front of the reader. To ensure that a text has the appropriate formality, it is necessary to avoid using certain forms of written communication and try to use a particular language depending on the type of audience. According to Newmark (1988), there are eight types of scale of formality:

Officialese The consumption of any nutriments whatsoever is categorically prohibited in this establishment.

Official The consumption of nutriments is prohibited.

Formal You are requested not to consume food in this establishment.

Neutral Eating is not allowed here.

Informal Please don't eat here.

Colloquial You can't feed your face here.

Slang Lay off the nosh.

Taboo, Lay off the fucking nosh. (p.14)

The scales of formality can vary from legal documents with their particular language to commercial letters and even colloquial texts whose lexical are those used by any person in a conversation in daily life.

2.1.2.2 Scale of Generality or Difficulty

Each text or translation must consider its audience and to whom it is addressed and, based on this, use the most appropriate and suitable vocabulary so that the readers can understand it without generating any interference or difficulty while reading or translating it. Suppose the translator wants the receiver of the target text to be able to receive the message of the source text. In that case, the different guidelines of a pre-established organization of formality must be considered, and the ideas to be communicated must be structured according to the intentionality pursued. According to Newmark (1988), there are six types of scales of generality and difficulty.

Simple

The floor of the sea is covered with rows of big mountains and deep pits.

Popular

The floor of the oceans is covered with great mountain chains and deep trenches.

Neutral (using basic vocabulary only)

A graveyard of animal and plant remains lies buried in the earth's crust.

Educated

The latest step in vertebrate evolution was the tool-making man.

Technical

Critical path analysis is an operational research technique used in management.

Opaquely technical (comprehensible only to an expert)

Neuraminic acid in the form of its alkali-stable methoxy derivative was first isolated by Klenk from gangliosides/ (Letter to Nature, November 1955, quoted in Quirk, 1984) (p.14)

The scales of formality range from the simplest to the most technical and complicated, and taking this into account helps the success of the communication and the relationship between the author and the readers. They have to be considered in the translation process to ensure the message is understood by the entire audience of the target language without any barrier.

2.1.2.3 Scale of Emotional Tone

It is essential to have a consistent and appropriate tone of communication since it generates an effective interaction with readers. It involves various aspects: the language you use, the types of paragraphs, the type of sentences you use, and whether or not you use catchy headings. According to Newmark (1988), there are four scales of emotional tone:

Intense: (profuse use of intensifiers) ('hot') Absolutely wonderful. . . ideally dark bass . . . enormously successful. . . superbly controlled.

Warm: Gentle, soft, heart-warming melodies

Factual: ('cool')

Significant, exceptionally well-judged, personable, presentable, considerable

Understatement ('cokT)

Not. . . undignified. (p.14)

Finding the right tone of communication is important in translation; it can help highlight the strengths or flaws of a translation. Tone can also reflect the author's understanding of a subject, as it enhances the reader's comprehension of the hidden meanings behind the strongly figurative language.

2.1.3 Text Function

Characterizing a text's principal function and identifying how it is organized (its structure) contributes to its correct interpretation. In other words, function and structure help orient the translator to the communicative strategy. In this part, the distinct text functions are delved into how they work, and a brief explanation of each one and their relevance in the translation are defined.

2.1.3.1 Informative

Informative texts are concerned with any topic of knowledge. The informative function is employed to describe the world or reason about it. This kind of text is important for logic; they affirm or deny propositions as the statement of a fact. Regarding the format, this kind of text is usually standard; it includes textbooks, technical reports, articles, newspapers, periodicals, scientific papers, theses, minutes, agendas, and meetings.

On the one hand, informative function generally utilizes a modern non-regional, non-class, non-idiolectal style. Moreover, it concerns four points on a scale of language varieties. The first point is distinguished by a non-emotive, technical style for academic papers, featured in

English by passives, present and perfect tenses, latinized vocabulary, literal language, jargon, multi-noun compounds with empty verbs, and no metaphors. The second point includes a neutral or informal style with defined technical terms for textbooks known by first person, present tenses, plurals, basic conceptual metaphors, and dynamic, active verbs. The third point is an informal, warm style for popular art books or science, characterized by simple grammatical structures, a wide range of vocabulary to accommodate definitions and many illustrations, simple vocabulary, and stock metaphors.

The fourth point comprehends a familiar, racy, non-technical style for popular journalism, defined by surprising metaphors, short sentences, unconventional punctuation, adjectives before proper names, and colloquialisms. Most informative texts could be better written and often inexact, and the translator must correct their facts and style. English has a greater variety of styles because it is lexically the product of several language groups, such as Norse, Saxon, Classical, and French. In addition, it has been in intimate contact with a wide diversity of other languages being practiced worldwide.

2.1.3.2 Expressive

The expressive function emphasizes the sender's value statements or expression of emotions regarding the object of reference. “The core of the expressive function is the mind of the speaker, the writer, the originator of the utterance. He uses the utterance to express his feelings irrespective of any response” (Newmark, 1988, p.39). In other words, it reports the feelings or attitudes of the writer to evoke emotions in the reader. Some examples of expressive function are poetry and literature, where much of ordinary language discourse expresses emotions or attitudes.

The expressive function can be either explicit or implicit. Respecting explicit expressivity uses verbs and nouns to express connotations. Contrary to implicit expressivity, which is referential at the surface, the expressive function can be identified within the framework of a certain culture-specific value system. Therefore, implicit expressivity relies on shared value systems. According to Newmark (1988, p.39), the major features that expressive text types have are:

> (1) *Serious imaginative literature.* Of the four principal types -lyrical poetry, short stories, novels, plays - lyrical poetry is the most intimate expression, while plays are more evidently addressed to a large audience, which, in the translation, is entitled to some assistance with cultural expressions.
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> (2) *Authoritative statements.* These texts of any nature derive their authority from the high status or the reliability and linguistic competence of their authors. Such texts have their authors' personal 'stamp,' although they are denotative, not connotative. Typical authoritative statements are political speeches, documents, etc., by ministers or party leaders; statutes and legal documents; scientific, philosophical, and 'academic' works written by acknowledged authorities.
>
> (3) *Autobiography, essays, personal correspondence.* These are expressive when they are personal effusions when the readers are from a remote background. (p. 39)

For translators, it is fundamental should be able to distinguish the individual components of the texts, such as unusual collocations, original metaphors, untranslatable words, unconventional syntax, neologisms, archaisms, dialects, odd technical terms, physicists, and colloquial expressions due to the individual components constituting the expressive element of the definitive texts.

2.1.3.3 Vocative

Vocative texts are usually addressed to a readership than a reader. "The core of the vocative function of language is the readership, the addressee" Newmark (1988, p. 41). In other words, Vocative texts are used to call upon the readership to act, think, or feel. Some authors also know them as conative, operative, pragmatic, and instrumental functions. Some examples of vocative texts include propaganda, persuasive writing, request, cases, theses, instructions, and popular fiction, which aim to entertain the reader.

The first factor in all vocative texts is the relationship between the writer and the readership, which is carried out by different types of socially or personally determined grammatical relations or forms of address such as request, persuasion, command, relations of power or equality, infinitives, imperatives, indicatives, subjunctives, impersonal, passives, titles, hypocoristically names, and tags. On the one hand, the second factor is that vocative texts must be written in strictly comprehensible language to the readership. On the other hand, the third factor is that the vocative function is restricted to a separate section of recommendation, opinion, or value judgment. Vocatives texts are crucial to information structure because they entail indexical reference to the addressee; their contribution to the sentence's meaning does not seem to be truth-conditional; they are very similar to syntactic and pragmatic topics. Generally, vocatives have three interpretations according to their syntactic position in the sentence: non-argument such as parenthetical elements, which do not participate in syntactic relation; subjects, when they are used in imperative, exclamative, or optative sentences, agree with the verb and fulfilling the additional requirement not to be duplicated by a pronoun; appositions, when they occur together with a pronoun.

2.1.4 Translation Methods

Translation methods are applied to the whole text. A good translator must have sufficient knowledge to know how to use the different translation methods appropriate for each content to ensure the successful transmission of the message. For this reason, they are defined and detailed in depth in this section.

2.1.4.1 Semantic translation

Semantic translation is used for definitive texts. It focuses on the aesthetic value, which means the beautiful and natural sounds of the source language text, compromising on meaning where appropriate so that no assonance, wordplay, or repetition jars in the target language text. According to Newmark (1981), "Semantic translation attempts render, as closely as the semantic and syntactic structures of the second language allow the exact contextual meaning of the original." It accepts the creative exception to 100% fidelity and allows for the author's intuitive empathy with the original.

This kind of translation is readable; however, it remains with the original culture and assists the reader only in its connotations if they constitute the essential message of the text. It tends to be fiddlier and stiffer. "Semantic translation is always inferior to its original since it involves loss of meaning." It tends to be more specific and over-translate; it is more detailed than the original in transferring nuances of meaning. On the other hand, it allows the translation of less important cultural words by effective terms or culturally neutral third parties, but not by cultural equivalents (Newmark, 1981, p.42). Semantic translation is literal and loyal to the source text author; besides, it has source language bias.

2.1.4.2 Communicative translation

Communicative translation is employed for informative and vocative texts. It focuses on the second reader. “Communicative translation attempts to produce on its readers an effect as close as possible to that obtained on the readers of the original” (Newmark, 1981, p.39). In communicative translation is possible to correct or improve the logic; to switch and replace poor with elegant, or at least functional, syntactic structures; to remove obscurities; to eliminate repetition and tautology; to exclude the less likely interpretations of an ambiguity; to modify and clarify jargon and regularize bizarreries or idiolect. Likewise, it permits correcting mistakes of the fact, and slips, frequently stating what one has done in the footnote.

On the one hand, communicative translation bears on the word or the word group. On the other hand, it has a target language bias; it is free and considered idiomatic. "It attempts to make the reading process easier for the TL reader 'who does not anticipate difficulties or obscurities and would expect a generous transfer of foreign elements into his own culture as well as his language where necessary' (Newmark, 1981, p. 39). It must spotlight the force rather than the content of the message. It is likely to be smoother, simpler, clearer, more direct, more conventional, tending to under-translate, and it utilizes more generic terms in difficult passages. In this kind of translation, the translator is endeavoring in his language to improve the writing of the original unless he is reproducing an orthodox formula of correspondence. Moreover, it must deepen the force rather than the content of the message. Typically, communicative translation is simpler, clearer, smoother, more conventional, and more direct.

2.2 Translation Procedures

Translation procedures are necessary for effective and empathetic communication between different cultures. To improve translation efficiency; besides, they are essential to ensure the quality of the translation. In this segment, there is an endeavor to define the main concepts of the

translation process. Each translation procedure resembles a higher degree of complexity; therefore, it is crucial to spotlight each of them in deepen.

2.2.1 Transposition.

A shift called Catford or transposition, as called Vinay and Darbelnet, is a translation procedure embodying a change in the grammar from the source language to the target language. Transposition comprises replacing one-word class with another without changing the message's meaning. Besides being a special translation procedure, it can also be applied within a language. For instance: *I a annoncé qu'il reviendrair*, can be re-expressed by transposing a subordinate verb with a noun, thus: *Il a annonce son reroup?* In this case, the first expression is called the base expression, while the second is called transposed expression. From a stylistic point of view, the base and the transposed expression do not have the same value. Therefore, translators must choose to carry out a transposition if the translation thus obtained fits better into the utterance or allows a particular nuance of style to be retained. The transposed form is typically more literary.

There are distinct types of transposition: obligatory transposition and optional transposition. On the one hand, obligatory transposition originates when the target language has no other choices because of the language system. On the other hand, an optional transposition occurs when the translator can choose the sake of style if it fits better into the utterance. A common type of transposition is the switch from singular to plural; for instance, the singular word *furniture* for the plural word *muebles.* Another type is naturalness transposition; for example, *He will soon be back*, the exact translation would be: *Estará de vuelta pronto*; however, in the target language sounds more natural to say *No tardará en ven.* The last type is grammatical category transposition, when a grammatical change is generated from the source to the target language.

2.2.2 Modulation

Modulation is an inversion of logical categories. This is a method in which translators seek to maintain naturalness by applying many forms of the message by changing the point of view. This procedure is usually chosen when translators find that literal translation would result in deficient or unnatural translation. According to Vinay and Darbelnet (1958), “Modulation is a variation of the form of the message, obtained by a change in the point of view." The change can be accepted when a literal or transposed translation results in a grammatically correct utterance. The modifications that occur due to modulation may seem very risky, but in most cases, it is obligatory. According to Vinay and Darbelnet (1958), a translator who does not modulate is not a translator. Hence, effective modulation is crucial since it is considered a test of the translator's sensitivity, imagination, and experience, which requires great ingenuity and expressive power.

To apply this procedure, unusual or unfamiliar forms that overload or hinder communication with the receiver and the assimilation of the message should be avoided. The misuse of modulation produces a distortion in the message. This procedure tends to involve the translator's subjectivity; therefore, the translator must have a broad perception to convert the meaning into a more functional one since not having it may affect the central semantic features of the meaning or the literal and etymological sense. Modulation is considered one of the most difficult phases in the oblique system. The more advanced the method, the more careful the translator must be when applying the modulation, so the translator must have a broad knowledge of the language and stylistics.

There are two kinds of modulation: fixed and free. With fixed or obligatory translation, the translator searches for a new point of view on the phrase, first by comprehending the meaning of the original sentence and then by searching in the target language to find a similar and identical

phrase, always considering the right factors. For example, *in Al license de las manos* with the fixed modulation, we keep the same connotation in the same idea; however, this time, the phrase and all its factors work in the target language. Free or optional modulation is only performed due to the translator's preferences. In this case, the original translation is complete and works just fine. However, the translator finds another way to present the phrase or sentence. For instance: *Te lo dejo* translated means *I leave it to you*. It is a clear example of a phrase that fits just fine. However, the translator can change it to *You can have it*, a phrase that fits better in the context.

2.2.3 Omission

This translation procedure enables the translator to delete or not include certain words or parts of the speech. They are removed from the translated version as they do not add importance to the target language. Moreover, it focuses on the reader to make the reading more enjoyable and smoother. Omission seeks to provide the reader with smooth and easy reading. It does not seek to change or modify the sentences. For example, *I can hear music* translated to *Oigo música en la otra oficina in the next room.*

To apply this procedure, the translator has to account for every portion and aspect of cognitive and pragmatic sense in the source language. Nevertheless, it is justified in pruning or eliminating redundancy and unnecessary words or phrases in translation. Omission prevents the translation from overloading with unnecessary elements such as pleonasms and tautologies. The purpose of omission is not to distort the message in the target language simply by attempting to include all original segments.

2.2.4 Amplification

The amplification procedure uses more words in the target text to cover syntactic or lexical gaps. In this procedure, the translator adds extra information that may be lacking from the translated version. According to Vasquez Ayora (1977), amplification is a complementary method combined with other processes to produce a dynamic transfer to the target text. This procedure also covers the function of completion or lengthening, where a target-text word grammatically needs the support of another word or more context. Amplification aims to achieve clarity of the text and not to overload the style. It is useful when there is a lack of equivalence in the target language; hence, the need for extra information. This procedure is also quite useful when the source's text needs more structure and sense, as the translator can take liberty and add what it is missing. However, amplification should never change or modify the original text's meaning.

2.2.5 Explicitation

An explicitation procedure is utilized to introduce precise details into a target text. In this process, the translator aims to provide a more detailed explanation of the source text. According to Vazquez-Ayora (1977), explicitation entails expressing what is implicit from the SL into the TL" (p. 349). In other words, explicitation is an explanation. This is achieved using different vocabulary without changing too much from the original text. Such a procedure tries to replicate what is implied in the original text. This procedure is helpful even when the translated version of the original text needs to convey the whole meaning of the original. However, with explicitation, it is possible to achieve the same meaning and context as the original. For instance, *Ten Grand attached* translated through explicitation to *Diez billets de los grandes como recompensa.*

2.2.6 Literal translation

Word for Word or literal translation refers to the direct transfer of source language text into a grammatically or idiomatically suitable target language text, in which the translator's task is limited to observing the compliance to linguistic servitudes of the target language. “This is a coincidental procedure, used when the SL term is transparent or semantically motivated and is in standardized language” (Newmark, 1981, p.75). It ranges from one word to one word, group to group, collocation to collocation, clause to clause, and sentence to sentence.

On the other hand, literal translation is the basic translation procedure, both communicative and semantic, due to translation starting from there. Nevertheless, when there is any translation, the literal translation is generally out of the question. This type of translation above the word level is the only correct procedure if the source language and target language meaning correspond more closely than any other; in other words, the referent and practical effect are equivalent, "In which the SL grammatical constructions are converted to their nearest TL equivalents, but the lexical words are again translated singly, out of the context" (Zakhir et al., 2009, p.122). This means that the words not only allude to the same thing but have similar associations and appear equally frequently in this kind of text. Likewise, the meaning of the source language unit is not affected by its context in such a way that the meaning of the target language unit does not correspond to it; generally, the more specific or technical a word, the less it is likely to be affected by context.

2.2.7 Punctuation changes

Although punctuation looks quite similar in each language at first glance, many changes must be made from one language to another since each language has its own punctuation rules and different uses; besides, they have unique characteristics in each language; thus, these must be respected when translating. Therefore, the translator needs to know the rules of the two languages

to be translated and thus respect the punctuation belonging to each language without damaging the meaning. According to Kirkman (2006)," Punctuation marks are integral parts of writing." They do two jobs. One is grammatical, and the other is rhetorical. There must be a rigorous platform for punctuation marks to have a cohesive, natural, and accurate translation. Punctuation marks are not only grammatical rules of each language, but they are also important to express emotions and suspense; they indicate pauses to create an atmosphere of a text. These marks are a vital part of each language; they carry the syntactic of the text and the translation. Even if punctuation marks are used diversely in each language, they have the same connotation.

2.2.8 Compensation

Compensation occurs when the translator recreates certain factors found in the original text that are lost in the translation process. "It is the replacement of untranslatable elements of the source text with similar elements, that is to compensate for the loss of information and can produce the similar effect on the reader of the target text" (Hordiienko, 2011). This method helps the translator compensate for semantic losses; furthermore, it modifies the sentence's grammatical structure and adds the original text's linguistics and semantic context. In the example, *how are you, sir*? Translated through compensation to *¿cómo se encuentra hoy señor?* It can be identified how even though a word has an equivalent and part of the meaning is lost; therefore, a need for compensation emerges to restore that meaning. Not only there was a need to compensate for the formality of the sentences, but there were lost punctuation marks, and not using compensation meant that some of the meaning and tone in the target language would be lost.

2.2.9 Equivalence

Equivalence leads to an endeavor to convert the content while maintaining the context and meaning of the original. Many view languages as having equivalent words and translating from

one to another involves finding a matching word, but remaining faithful to the original text is the golden rule. A literal translation is practically useless when the meaning behind the words is not upheld. According to Nida (as cited by Newmark, 1981), it "Is not the same as literal translation, and the two terms must therefore be kept distinct." Equivalence only works when the translator completely understands what the source text is trying to convey. It covers more than just the meaning of the content but also the tone and style of the delivery.

Equivalence is intimately related to the human experience that gives each language its characteristic point of view and its symbol. The expected reaction must obey the author's intention, the nature of the message, and even the type of audience. When looking for the most universal and classical forms, it must be considered that the equivalences selected must belong to the same functional level of the language and participate in more or less the same frequency as the original expression. Formal Equivalence also knew as structural correspondence. According to Newmark (1981). "This attitude to translatability and comprehensibility has given rise to dynamic equivalence, a translation method that may helpfully be seen in terms of its counterpart formal equivalence." It is a relationship that leads to merely formally replacing one word or phrase in the source language with another in the target language.

There are some types of equivalence. Among them is the equivalence of large signs; here, the translation is carried out from a maximum perspective and not based on the minimum semantic units. The main idea is considered without trying to translate every little detail. The equivalence of metaphors and idioms. The translation of a metaphor can give rise to three operations: the modulation of a metaphor by transforming it into a non-metaphorical expression, the modulation of a metaphor into a simile, and the equivalence of one metaphor with another.

Whereas idioms are poured: from an idiom to a plain expression, from a plain expression to an idiom, and from one idiom to another (equivalence).

Another type is the cultural equivalent. According to Newmark (1988), the cultural equivalent is the approximate translation of a cultural term of the source language by another cultural term of the target language. Approximate cultural equivalents have limited use in translation. However, they can be used in general texts, in advertising and propagandistic texts, and when you want to give a small explanation to readers who do not know the culture of the source language. There is also the functional equivalent, valid for cultural words, consisting of using a culturally neutral word and sometimes adding a new specific term. Thus, it neutralizes or generalizes the source language word and sometimes adds a detail. Finally, there is synonymy, which consists of turning to a close target language equivalent for a source language word within a context, whether or not there is an exact equivalent. This procedure is used when a source language word has no clear equivalent in the target language and is not important in the text. It is used, above all, with adjectives and adverbs of quality, which, in principle, are "outside" the grammar, and their importance is less than that of other sentence components.

2.2.10 Adaptation

Adaptation is the freest form of translation. This procedure is mainly used for plays, comedies, and poetry; the theme, characters, and plot are often preserved, the source language culture is converted to the target culture, and the text is rewritten. “Adaptation: use of a recognized equivalent between two situations. This is a matter of cultural equivalence, such as *Dear Sir* translated as *Monsieur;* Yours ever as *Amities*. Both the above illuminate what sometimes happens in the process of translating, but they are not usable procedures" (Newmark, 1988, p.91). They are adapted to convey the message better.

When presented with a cultural phrase or an idiom in the source language, the translator must adapt it by using something that evokes the same sense as the original. Adaptation takes the initial translation and makes it culturally accurate by modifying the content. It takes the initial translation and makes it culturally accurate by modifying the content; in addition, not only do phrases and idioms need to be adapted, but also cultural references that require equivalences to relate to the audiences. In the following example, the word *Football* may mean the same across Europe and Latin America; however, for audiences living in the United States, there must be an adaptation to *Soccer*.

2.2.11 Borrowing

Borrowing occurs when a word or an expression is taken from the source language and used in the target language but in a naturalized form; this means it is made to conform to the rules of grammar or pronunciation of the target language. It is normally used when there is no target language equivalent that can help preserve the source text's cultural context. Borrowed words may often have different semantic significations from those of the original language. For example, “the Moroccan word 'Tammara,' which is borrowed from Spanish, means in Moroccan Arabic 'a difficult situation,' whereas in Spanish it conveys the meaning of a 'type of a palm tree'” (Zakhir et al., 2009, p.115). It is important to point out that borrowing in translation is not usually justified by the lexical gap in the target language; however, it can mainly be utilized as a way to preserve the local color of the word, as well as can be used out of fear of losing some of the semiotic aspects and cultural aspects of the word if it is translated.

2.2.12 Calque

Calque, or 'Through-Translation' as Newmark (1988) calls it, is produced when the translator imitates the source language's structure or manner of expression. This is the literal

translation of a borrowed word in layperson's terms. The major difference between calque and borrowing is that the latter transfers the whole word. There are four types of calques: structural or syntactic calque, typographic calque, orthographic calque, and paronymous calque or loan word.

Structural or syntactic calque results from the erroneous connection between the elements of a sentence or expression; for instance, *to* as *en orden a*n instead of *para,* to *find guilty* as *encontrar culpable* instead of *declarar culpable*. In other words, the product is the creation of a third language, in this case, Spanglish. Contrary to typographic calque, this ensues when typographical conventions that exist only in the source language are transferred to the new language. Further, it occurs when typographical conventions that only exist in the source language are transferred to the new language. For instance, English's employment of capital letters has started to creep into Spanish, as well as using italics for emphasis and certain uses of quotation marks.

On the other hand, orthographic calque usually arises in the transliteration of proper names, places, and ethnicities. Spelling and writing conventions of the source language that make little or no sense in the target language are imitated. Regarding proper names in different languages (anthroponyms), the main difference is when two languages use different alphabets. When the alphabets are the same, the names are written the same; however, there are some exceptions, such as historical figures and classic authors whose name has a traditional translation, the names of royal families and nobility, and the names of popes and saints. When the alphabets are distinct, English transliterations rely on the source language to provide a jumping-off point; the best known is the Hanyu Pinyin system for Mandarin Chinese. Despite this, there still exist multiple disputed spellings in other languages. By contrast, the paronymous calque or loan word refers to the product of an erroneous correspondence between two words that have similar forms

or etymologies but have evolved differently in their respective languages to the point that they now have different meanings (semantic transfer). It usually happens when two words are etymologically related in English but with a slight difference in meaning; nevertheless, it is also possible that the error comes from the calque of the grammatical category.

2.2.13 Sentence inversion

Sentence inversion ensues when two components in a sentence switch place when translating into the target language. The aim of utilizing this technique is to improve the naturalness of the sentence. Similarly, this kind of inversion refers to the order of words, which is why it is usually used when translating long sentences. For instance, the main objective is previously explained, as you observed. Translated as, como pudo observar, el objetivo ha sido previamente explicado.

An inverted sentence is a complete thought established in reverse order or the verb before the subject. This technique is implemented to alter sentence structure or to place emphasis. Besides, they add variety to translation. The writing would be boring and repetitive if all sentences had the same pattern. Rearranging sentence structure so that the verb comes before the subject enhances the translator's originality. In many languages, often the structure of questions requires inverting sentences; for instance, in English, a question mark at the end of the sentence is one signal that a question is being asked. Another signal is placing the verb first before the subject. In like manner, Spanish questions begin with an upside-down question mark, then the inverted sentence structure is followed by another question mark at the end.

The use of inverted sentences is only applied with certain grammatical structures and is also used to accentuate or emphasize sentences. The most common cases of sentence inversion

occur when a sentence begins with an adverb phrase, when the sentence begins with and is modified by a negative adverb or adverb phrase, with conditionals that omit the word *if* and use *had, were,* and *should*; after the preposition *so* plus an *adjective* plus *that*, in questions, in sentences that give a command. Commands are a type of inverted sentence where the subject is often missing or is implied. Likewise, sentence inversion differentiates questions from statements. When used with statements, it adds multiplicity to writing but can sound rather formal.

2.3 Glossaries

Glossaries are important to any translation. Creating a glossary aims to make content-specific words easily accessible to the reader. Encountering many unfamiliar industry-specific words may be overwhelming for readers. This is why authors define words related to the topic within a glossary. This section will be explained why it is essential to create a glossary, the relevance for translators, and the translation process.

2.3.1 Relevance for the translator

A translation glossary is a useful tool that aids translators in using the correct terms since they contain a list containing specific terms from each industry. Translators need to have a perfect command of the language and use accurate, appropriate terms. Glossies are essential because a translation glossary permits translators to use a term consistently throughout the translation. Therefore, creating a glossary aids the translator in keeping track of the different terminologies used within the translated text to guarantee good employment of certain terms. A good translation requires the translator to work meticulously with each term.

2.3.2 Relevance for the translation process

Creating a glossary is vital in the translation process because they guarantee consistency if you use more than one translation resource. It aids the translator in making sure that each time a defined key term appears in any language, it is used consistently and correctly. Glossaries become more essential, especially true in the case of tight deadlines when the translator is working on various elements of a project simultaneously. By helping to eliminate uncertainty in the translation process, the glossary will enforce consistency and clarity, shorten the time it takes to translate a document and reduce the overall cost of translation over time.

2.3.3 How to Create a Glossary

Before undertaking a specialized glossary for the specific demands of a particular company or group, a set of both printed and electronic glossaries in different fields and formats should be thoroughly examined. Thus, the works analyzed will serve as a basis for concrete examples of what will be presented in this chapter on formatting, ordering, literacy, and components. After collecting and storing the information, the next step is elaborating the glossary. To do this, the content and format of the glossary must be defined. Then, the general organization of the glossary should be determined, and whether it is appropriate to include a preface, indications for the user, a table of abbreviations used, or appendices. In addition, consider whether it is appropriate to divide the glossary into several sections, such as Spanish-English or English-Spanish, or sections by topic. The steps to follow for the elaboration of a glossary are the following. First, the nature of the glossary must be determined, then the content of the glossary must be defined, and finally, the format must be defined. In this part, the order of the terms is determined, the order of the aspects in each article is defined, and the type of letter, the size, and everything related to the format that will be used are specified.

Chapter III

Methodological Framework

This chapter outlines the research approach and defines the different data collection methods, analysis, and interpretation. Withal, the research design is established; the information sources are stetted out, and the analysis of the variables is determined. In addition, it is justified why the instruments were selected to collect the information and its vitality in the investment process. Finally, it explains how the data collected was analyzed.

3.1 Research Approach

A qualitative method is a research method whose focal point is to obtain data through open-ended and conversational communication. It is based on social science and disciplines such as psychology, sociology, and anthropology. On the other hand, qualitative research methods can be in-depth interviews, focus groups, ethnographic research, content analysis, and study research, beings its aim to design research in a way that aids in understanding the behavior and perception of a target audience regarding a particular topic. According to Creswell (2008):

> Qualitative inquiry employs different philosophical assumptions, strategies of inquiry, and methods of data collection, analysis, and interpretation. Although the processes are similar qualitative procedures rely on text and image data, have unique steps in data analysis, and draw on diverse inquiry strategies. (p.173)

Thus, this research methods allow for in-depth and further probing of interviewees based on their responses, where the interviewer and the researcher intend to understand their motivation.

Qualitative research methods are mostly descriptive and communicative so that inferences can be easily obtained from the data drawn. According to Creswell (2008), "The process of research involves emerging questions and procedures, data typically collected in the participant's setting, data analysis inductively building from particulars to general themes, and the researcher making interpretations of the meaning of the data." In other words, it is a means for comprehending the meaning groups or individuals ascribe to a social problem. Consequently, in this research, the quantitative method was used since it facilitates the analysis of the documents.

By contrast, quantitative methods are based on applying statistical and mathematical measurements or numerical analysis of data collected through polls, questionnaires, and surveys. Quantitative research focuses on gathering numerical data and generalizing them across groups of people or describing a particular phenomenon under study. This represents a set of sequential processes. Each stage precedes the next, and we must include steps. Moreover, one of its main features is that data are often represented using structured research instruments in numbers and statistics, habitually arranged in tables, charts, figures, or other non-textual forms. Besides, the results are normally based on larger sample sizes that are representative of the population. This method reflects the need to measure and estimate the magnitudes of the phenomena or research problems. Likewise, the researcher poses the study problem delimited and concretely relates to the phenomenon.

On the other hand, the mixed method approach combines and uses quantitative and qualitative data in the same study. Gunnell (2016) states, "Mixed methods research is a research design with philosophical assumptions as well as methods of inquiry." As a methodology, it involves philosophical expectations that lead to data analysis. It allows combining the qualitative and quantitative approaches in many phases in the research process. "As a method, it focuses on

collecting, analyzing, and mixing both quantitative and qualitative data in a single study or series of studies" (Gunnell, 2016). Its main goal is to combine quantitative and qualitative methods to provide a better understanding of the research problems than can be achieved by either approach alone.

3.2 Research Design

The descriptive design is a research method that describes the features of the phenomenon at hand. This methodology mainly describes the nature of a demographic segment. Its purpose is to explain the research subject without explaining why a particular phenomenon occurs. This means that the research method focuses more on the object of the research subject than on its reason. As a researcher, you can only observe and gather valid and reliable responses and examine them. This research method, like market research, is best used to understand concepts. Some distinctive features of descriptive research are that it allows us to collect and describe the demographic segment’s nature. Moreover, the descriptive research method collects quantifiable information to analyze samples statistically. On the one side, none of the variables are influenced in any way, and on the other hand, the variables' constitution or behavior is not in the hands of the researcher. Descriptive research is carried out using different types of methods, such as observations, surveys, and case studies. The descriptive method uses observational methods to conduct a description of the research and explain it.

3.3 Information Sources

There are different kinds of information sources, and they can be classified into primary, secondary, and tertiary sources. Primary sources contribute with the most direct evidence of a topic being developed in a research project and should usually be given high significance for

inclusion in the research process. Secondary sources develop an analysis and argument by researchers who have explored primary sources and searched to explore their meaning. Finally, tertiary sources show overviews and synopses of issues raised by secondary sources or help a researcher to identify primary and secondary sources. Each one addresses a role, which is to help the researcher to develop a project. The differences between primary, secondary, and tertiary sources are ambiguous. Time is a defining element in determining the way we classify sources. An individual document may be a primary source in one context and a secondary source in another. Encyclopedias are regularly considered tertiary sources, but a study of how encyclopedias have changed on the internet would use them as primary sources.

Primary sources are original material. They refer to information that is shown for the first time. According to the University of Minnesota Crookston (n.d.), some examples of primary sources are "Theses, dissertations, scholarly journal articles (research-based), some government reports, symposia and conference proceedings, original artwork, poems, photographs, speeches, letters, memos, personal narratives, diaries, interviews, autobiographies, and correspondence." All of them are considered primary sources. These sources provide evidence as they are first described without commentaries or interpretation. They show original thinking and discoveries and present fresh information. These sources permit researchers to get as close to original ideas, events, and empirical studies as possible.

Moreover, primary sources were created in the period under study. In addition, primary sources are featured by the information they impart and their relationship to the research question since they have yet to be extracted through interpretation or evaluation. Rather, the interpretation and evaluation of primary sources cater as the basis for other research, recurrently presented through secondary and, in a more general sense, tertiary sources. Primary sources habitually are

created at the beginning of the information cycle. Commonly attempt to describe and explain primary sources.

The secondary source aims to summarize, interpret, reorganize, or provide added value to a primary source. According to the University of Minnesota Crookston (n.d.), "Some secondary sources are textbooks, edited works, books, and articles that interpret, or review research works, histories, biographies, literary criticism and interpretation, reviews of law and legislation, political analyses and commentaries." Secondary sources are not evidence but a discussion of evidence, comments, notes, and reports. They are accounts reported after the fact giving the benefit of hindsight. In other words, secondary sources are no evidence but a commentary on and discussion of evidence. The main features of secondary sources are interpretations of the information written after the event and offer a review critique.

Even sources presenting facts or interpretations about situations are secondary only if they are based on direct participation or observation. Secondary sources usually rely on other secondary sources and methods to reach results. Since primary sources are often direct reporting, secondary sources are the fundamental sources of analysis about the primary sources. Secondary sources written by experts may be far more informative and convenient than primary sources when trying to interpret research data or understand a complex topic. Tertiary sources aim to list, summarize, and restate ideas or other information. In other words, they try to index, abstract, organize, compile, or digest other sources. They are characterized because they tend to come last in the publication cycle. In addition, they tend to be factual. According to the University of Minnesota Crookston (n.d.), "Dictionaries, encyclopedias, almanacs, fact books, Wikipedia, bibliographies, directories, guidebooks, manuals, handbooks, and textbooks, indexing and abstracting sources are examples of tertiary sources."

In other words, they are derived from information and compilation of primary and secondary sources. Moreover, tertiary resources give critical overviews of topics by providing a more concise version of information gathered from other (usually secondary) resources. The primary and secondary sources referenced by a tertiary source are only sometimes fully credited. In addition, tertiary resources often provide data in a more convenient form and can provide context useful in explaining information from primary and secondary sources.

3.4 Analysis Categories

3.4.1 Translation

It consists of transmitting the same message from one language to another, considering the source and target language's culture, space, and time. Moreover, it is a bridge of communication between two different languages. (Thomson, 2001)

3.4.2 Translation procedures

They are the tools to transfer the meaning from the source to the target language. Translation procedures are applied to formulate an equivalence to transfer elements of meaning (Pinchuck, 1977)

3.4.3 Translation Methods

Translation methods are techniques used to translate whole units of text. Newmark defined eight methods of translation: word-for-word translation, literal translation, faithful translation, semantic translation, communicative translation, adaptation, free translation, and idiomatic translation. (Newmark, 1988)

3.4.4 Glossary

A glossary is a section at the end of a written work that defines confusing, technical, or advanced words. Furthermore, it facilitates readers' and translators' search for technical and unknown terminology. (Ellis, 2020)

3.5 Data Collection Instruments

To attain the present research objectives, two instruments and one technique were selected. The first instrument is a text analysis chart, where each text element will be analyzed by employing several aspects. In addition, color coding will be employed to identify the texts' translation procedures. As the final instrument, a glossary of terminology will be created in both languages (English and Spanish) to ensure the strength and comprehension of unknown terms.

3.5.1 Text analysis chart

The first instrument is a text analysis chart, allowing further analysis and comparison of the texts (English and Spanish) through several aspects. In the first column, the text style, the text function, the scale of formality, the scale of generality or difficulty, the scale of emotional tone, and the translation methods are analyzed. The category to which the English text belongs will be determined in the second column, considering the previously mentioned aspects. The last column will establish the analysis and categorization of Spanish text. Such an analysis aids to identify and classify the different elements of the texts and consider them to create a more accurate translation.

Table 1

Text analysis	**Documents from English into Spanish**	**Documentos del español al inglés**

Text Style		
Text Function		
Scale of Formality		
Scale of Generality or Difficulty		
Scale of Emotional Tone		
Translation Method		

Table 1 showcases the analysis of the elements of the texts.
Source: Researcher's creation

3.5.2 Color coding

As a second point, a color-coded chart will be implemented. This is a technique that intends to pinpoint all the translation procedures in the texts by making use of different colors. First, 30 paragraphs will be handpicked (15 paragraphs from the English texts and 15 paragraphs from the Spanish texts). Furthermore, the selected paragraphs must include their corresponding translation; in total, there must be 60 paragraphs, and each paragraph must contain approximately 100-150 words. To carry out this technique, eleven translation procedures will be applied; each assigned a different color.

Table 2

Translation procedure	**Color Assigned**
Punctuation changes	
Adaptation	
Literal Translation	

Transposition	
Explicitation	
Amplification	
Compensation	
Omission	
Modulation	
Equivalence	
Sentence inversion	

Table 2 illustrates the translation procedures.
Source: Researcher's creation

3.5.3 Glossary

The last instrument is a glossary. It is intended to provide a guide to the various tasks of terminology management, both to facilitate the translation process and to ensure that the translation is done in the best possible way. First, a glossary will be created in each language (English and Spanish). Likewise, a minimum of 25 words will be used to elaborate on this instrument. Such instrument comprises four columns; in the first column is placed the source language term; in the second column, the target language term is indicated; in the third column, the grammatical category is specified; ultimately, the fourth column contains a definition of the term.

Table 3

Documents from English into Spanish

Source Language Term	Target Language Term	Grammatical Category	Definition

Table 3 sets forth the most important terms.
Source: Researcher's creation

Table 4

Documentos del español al inglés			
Término en el idioma de partida	**Término en el idioma de llegada**	**Categoría gramatical**	**Definición**

Table 4 puts forth the most important terms.
Source: Researcher's creation

3.6 Collection data process and data analysis

To carry out the data collection process, a general reading of the documents will be made to comprehend what the text is about and to determine the intention of the text and the way it is written, to select a fitting translation method. Then comes a second reading to encounter any grammatical problem that may pose difficulties in transferring the message and to identify any anomalies or possible errors in the target language; in this step, All the terminology and

phraseology requiring specific treatment will be listed. Likewise, research will be effectuated on the topics of each document in order to have a big picture of the subject and acquire a suitable vocabulary.

After that, the first instrument will be employed, fulfilling the text analysis; the different elements of the texts will be categorized to determine the text's style and function, the stylistic scale and formality, and the scale of formality and tone. Once these elements are categorized, the translation of the documents will begin, and translation procedures will be carefully selected to produce the message as accurately as possible in the target language. When the translation is completed, a final reading will be done to find grammar, punctuation, and naturalness inconsistencies. Consequently, the color-coded technique will be implemented; 30 paragraphs will be carefully selected with their corresponding translation. The original paragraph will be placed in the source language and below its equivalent in the target language. Once this step is done, the translation procedures will be identified in the translated version. In the last step, the glossaries will be created.

Chapter IV

Translations

Estudios de biodisponibilidad presentados en NDA o IND - Consideraciones generales

Guía para la industria

Departamento de Salud y Servicios Humanos de los Estados Unidos
Administración de Alimentos y Medicamentos
Centro de Evaluación e Investigación de Fármacos (por sus siglas en inglés CDER)
Abril de 2022
Farmacología clínica

Estudios de biodisponibilidad presentados en NDA o IND - Consideraciones generales

Guía para la industria

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Estudios de biodisponibilidad presentados en NDA o IND

Consideraciones generales

Guía para la industria[1]

Esta guía representa el criterio actual de la Administración de Alimentos y Medicamentos (por sus siglas en inglés FDA o Agencia) sobre este tema. No concede ningún derecho para ninguna persona y no es vinculante para la FDA ni para el público. Si cumple con los requisitos de los estatutos y los reglamentos pertinentes, puede utilizar un enfoque alternativo. Para analizar un enfoque alternativo, comuníquese con la oficina de la FDA responsable de esta guía, como se indica en la portada.

INTRODUCCIÓN

Esta guía brinda recomendaciones a los patrocinadores y solicitantes[2] que han presentado información de biodisponibilidad (BD) para productos farmacéuticos en solicitud de nuevos fármacos en investigación (por sus siglas en inglés IND), solicitudes de nuevos fármacos (por sus siglas en inglés NDA) y suplementos de NDA. Además, contiene recomendaciones sobre el cumplimiento de los requisitos de BD establecidos en 21 CFR sección 320, que se aplican a las formas de dosificación administradas por vía oral. Estas formas de dosificación incluyen: cápsulas, soluciones, suspensiones (por ejemplo, fármacos de liberación inmediata (IR), productos farmacéuticos convencionales) y liberación modificada (por sus siglas en inglés MR)

[1] Esta guía ha sido elaborada por la Oficina de Farmacología Clínica con la colaboración de la Oficina de Calidad Farmacéutica del Centro de Evaluación e Investigación de Medicamentos de la Administración de Alimentos y Medicamentos.

[2] El término patrocinador se utilizará para referirse tanto a los patrocinadores como a los solicitantes.

(por ejemplo, productos farmacéuticos de liberación prolongada (ER) y de liberación retardada (DR)).

Esta guía también aplica para los productos farmacéuticos no administrados por vía oral, cuando sea conveniente basarse en medidas de exposición sistémica para determinar la BD de un fármaco (por ejemplo, sistemas de administración transdérmica y ciertos productos farmacéuticos vaginales, rectales y nasales). Asimismo, la guía ofrece recomendaciones sobre la realización de estudios de BD durante el periodo de investigación para un fármaco que se pretende presentar para su aprobación en una NDA y estudios de bioequivalencia (BE) durante el periodo posterior a la aprobación para determinados cambios en fármacos con una NDA[3] autorizada.

Esta guía no aborda información para demostrar BE para productos farmacéuticos en las solicitudes abreviadas de nuevos medicamentos (ANDA) y suplementos de ANDA. En agosto del 2021, la FDA emitió otro borrador de directrices sobre este tema titulado: *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.[4] Esta guía tampoco brinda recomendaciones sobre estudios realizados para respaldar la demostración de comparabilidad o biosimilitud para productos biológicos autorizados, en virtud de la sección 351 de la Ley de Servicios de Salud Pública (para más información, consulte las guías de la FDA tituladas: *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (diciembre de 2016) y, *Considerations in Demonstrating Interchangeability With a Reference Product* (mayo de 2019)).

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[3] La *bioequivalencia* (BE) se define en 21 CFR 3143(b).

[4] Cuando sea aprobada, esta guía representará el criterio actual de la FDA sobre este tema. Las directrices se actualizan periódicamente. Para obtener la versión más reciente de la guía, consulte la página web de guías de la FDA en https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Esta guía finaliza el estudio de la FDA titulado: *Bioavailability Studies Submitted in NDAs or INDs - General Considerations* (febrero, 2019). El borrador de febrero de 2019 de esta guía revisó y reemplazó el borrador de la guía *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - Consideraciones generales* (marzo de 2014). La FDA consideró los comentarios recibidos sobre la guía de marzo de 2014, al emitir el borrador de febrero de 2019 de esta guía. La FDA reconoce que esta guía no puede abordar todas las cuestiones relativas a la evaluación de los estudios de BD para IND y NDA. Por lo tanto, se insta a los patrocinadores a ponerse en contacto con la división de revisión correspondiente con preguntas específicas que no son abordadas en el presente trabajo.

El contenido de este documento no tiene fuerza y efecto de ley y no pretende que se vincule al público de ninguna manera, a menos que se especifique en un contrato. Este documento solo pretende aclarar al público los requisitos legales vigentes. Los documentos de orientación de la FDA, incluida esta orientación, deben considerarse únicamente recomendaciones, a menos que se citen requisitos reglamentarios o legales específicos. El uso de la palabra "debería" en las directrices de la Agencia significa que se sugiere o recomienda algo, pero que no se exige.

ANTECEDENTES

La determinación de la BD de las formulaciones es importante durante el ciclo de vida de los fármacos, ya que ayuda a la FDA a evaluar la seguridad y eficacia de un producto en un IND, NDA o suplemento de NDA. Para determinar la seguridad y eficacia de un fármaco de la indicación propuesta, la FDA revisa toda la información presentada, incluidos los datos de BD, las evaluaciones de exposición-respuesta y los resultados de los ensayos clínicos.

La BD se define como la velocidad y el grado de absorción del principio activo o la fracción activa de un fármaco y su disponibilidad en el lugar de acción.[5] En el caso de los fármacos que no están destinados a ser ingeridos por vía sanguínea, la BD se puede presentar a partir de mediciones científicamente válidas que reflejen la velocidad y el grado de disponibilidad del principio activo o la fracción activa en el lugar de acción del fármaco (consulte la sección III. *Study Design Considerations*).[6] Los datos de BD proporcionan una estimación de la cantidad de fármaco absorbido, así como información relacionada con la farmacocinética del medicamento, los efectos de los alimentos en la absorción de este y la proporcionalidad o linealidad de la dosis en la farmacocinética de los principios activos.

Los patrocinadores pueden determinar la BD de los fármacos administrados vía oral, comparando el perfil de exposición plasmática con el de un producto de referencia adecuado.[7] Se puede generar un perfil de exposición sistémico midiendo la concentración de principios activos o fracciones activas con el paso del tiempo y, cuando sea apropiado, metabolitos activos en muestras recolectadas de la circulación sistémica, con el paso del tiempo (consulte la sección III.A.8). Los perfiles de exposición sistémica reflejan tanto la liberación del principio activo de la sustancia farmacológica como las modificaciones presistémicas o sistémicas de este tras su liberación. La realización de un estudio de BD con un producto de referencia intravenoso (IV) ayuda a evaluar el impacto de la vía de administración sobre la BD y define la BD absoluta de la liberación del fármaco con la del producto farmacológico. La realización de un estudio de BD comparando una formulación con otra permite evaluar la BD relativa.

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[5] 21 CFR 314.3(b).
[6] 21 CFR 314.3(b).
[7] 21 CFR 320.25.

Para una evaluación de BD relativa, un producto de prueba podría dar lugar a diferentes perfiles y tiempo de concentración en plasma, en comparación con un producto de referencia debido a una velocidad o grado de absorción diferente. Estas diferencias pueden influir en la evaluación de la FDA y de los beneficios y riesgos de la nueva formulación o condición de administración. Por ejemplo, si el producto de prueba conduce a una exposición sistémica significativamente mayor que el producto de referencia, el producto de prueba podría generar problemas de seguridad asociadas con concentraciones sistémicas más altas. Si el producto de ensayo conlleva una exposición sistémica significativamente menor a la del producto de referencia, el producto de ensayo podría ser menos eficaz. Por tanto, cuando la variabilidad del producto de prueba es mayor que la del producto de referencia, tanto la seguridad como la eficacia del producto de prueba podrían verse afectadas. Este aumento de la variabilidad podría indicar que el rendimiento del producto de prueba no es comparable con el producto de referencia, y que tanto la eficacia y la seguridad del producto de prueba son demasiado variables para que el producto sea clínicamente válido.

A. Consideraciones generales de BD

Los estudios de BD que comparan dos formulaciones o dos condiciones de prueba suelen realizarse mediante un diseño cruzado. Sin embargo, desde el punto de vista científico, para un fármaco con una de vida media prolongada, un diseño paralelo podría ser más apropiado.[8]

Para determinar la BD de los nuevos fármacos presentados bajo un IND o un NDA, se pueden utilizar los principios de BE. La demostración de una BD equivalente o similar de dos productos durante el desarrollo de un nuevo fármaco podría ser necesaria para evaluar la seguridad o eficacia de un producto. Para más información, consulte la sección 505 de la Ley

[8] 21 CFR 320.26.

Federal de Alimentos, Medicamentos y Cosméticos de Estados Unidos (por sus siglas en inglés FD&C Act) (21 U.S.C. 355). En general, se debe utilizar un intervalo de confianza (IC) del 90% con límites de IC predefinidos, en el caso de la comparación de dos formas de dosificación durante el desarrollo del producto farmacéutico (por ejemplo, la formulación que se comercializará versus la formulación del ensayo clínico) o la interpretación del efecto de alimentos en un fármaco.

Cuando no se demuestre la similitud de la BD en una evaluación comparativa de esta, el patrocinador deberá demostrar que las diferencias en la velocidad y el grado de absorción no afectan significativamente a la seguridad y eficacia del fármaco basándose en los datos existentes en relación con la dosis-efecto o concentración-respuesta. En ausencia de esta evidencia, el patrocinador debe considerar la reformulación del producto de prueba, cambiando el método de manufactura por el producto de prueba u obtener datos adicionales sobre la seguridad o eficacia de dicho producto.

En algunos casos, los resultados de similitud en BD basados en la concentración máxima observada en el fármaco (C_{max}) del área bajo la curva de la concentración de fármaco (o metabolito) en sangre, plasma o sangre contra tiempo (por sus siglas en inglés AUC), entre el producto de prueba y el producto de referencia, podrían ser insuficientes para demostrar que no hay diferencia en cuanto a la seguridad o eficacia. Cuando las diferencias en la forma del perfil concentración-tiempo sistémico entre los productos de prueba y de referencia implican que el producto de prueba podría no producir la misma respuesta clínica que el producto de referencia (por ejemplo, el tiempo para alcanzar la concentración máxima del fármaco (T_{max}), en el caso de los productos analgésicos). En estos casos, un análisis de datos suplementarios (AUC parciales),

una evaluación de la exposición-respuesta o los estudios clínicos podrían ser científicamente más adecuados para evaluar las diferencias en la BD de los dos productos.

B. Cambios previos a la aprobación

En la BD relativa de las formulaciones utilizadas en el desarrollo de fármacos, se debe comparar: (1) las formulaciones de ensayos clínicos iniciales y finales; (2) las formulaciones utilizadas en ensayos clínicos y en los estudios de estabilidad, si son diferentes; (3) las formulaciones de ensayos clínicos y los productos farmacéuticos que se comercializarán, si son diferentes; (4) la equivalencia de las dosis de los productos; y (5) la comparación de dos productos diferentes como respaldo de una NDA descrita en el apartado 505(b)(2) de la Ley FD&C Act. A efectos de esta guía, en cada comparación, la nueva formulación, la formulación producida mediante un nuevo método de fabricación o la nueva dosificación son el *producto de prueba*, y la formulación anterior, el producto fabricado mediante el método de fabricación anterior o el producto con la dosificación anterior son el *producto de referencia*. Para más información, consulte la sección II A, *General BA Considerations; II.C, Postapproval Changes; and III.B.1, In Vitro Studies* en esta guía, sobre las consideraciones relacionadas con los cambios en los componentes, la composición o el método de fabricación, sugieren que se deben realizar más estudios *in vitro* (en vidrio*)* o *in vivo* (en el organismo vivo).

C. Cambios posteriores a la aprobación

En presencia de ciertos cambios importantes en los componentes, la composición, el lugar de fabricación o el método de fabricación de un fármaco posterior a su aprobación; el patrocinador debe demostrar la BE *in vivo* para el producto farmacéutico después del

cambio y compararlo con el fármaco antes del cambio.[9] Ciertos cambios posteriores a la aprobación que requieren estudios de BE deben ser presentados en un suplemento y aprobados por la FDA antes de distribuir el fármaco, con el cambio realizado.[10]

La información sobre los tipos de estudios de disolución recomendados *in vitro* e *in vivo* para demostrar la BE de los fármacos IR y MR aprobados como NDA para cambios específicos posteriores a la aprobación se proporcionan en las siguientes guías de la FDA:

- *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (November 1995)*
- *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (October 1997)*

Como alternativa, se podría utilizar un enfoque de evaluación y mitigación de riesgos de calidad para respaldar los cambios posteriores a la aprobación. Además, los patrocinadores deben discutir las propuestas de enfoques alternativos con la división de revisión correspondiente.

III. CONSIDERACIONES DEL DISEÑO DE ESTUDIO

Los patrocinadores deberán utilizar el método disponible que sea más preciso, susceptible y reproducible entre los que figuran en 21CFR 320.24(b) para medir la BD o demostrar el BE de un

[9] 21 CFR 320.21 y 320.22.
[10] Sección 506A(c)(2) Ley Federal de Alimentos, Medicamentos y Cosméticos de Estados Unidos (FD&C Act) (21 U.S.C. 356a(c)(2)); 21 CFR 314.70.

producto. [11] Se pueden utilizar varios métodos *in vivo* o *in vitro* para determinar la BD y establecer la BE. Estos métodos abarcan, por orden descendente, la precisión, sensibilidad y reproducibilidad, entre otros estudios farmacocinéticos (FC), pruebas *in vitro* que predicen la BD *in vivo* en humanos (estudios de correlación *in vivo-in vitro* (por sus siglas en inglés IVIVC)), estudios de farmacodinámica (FD), ensayos clínicos bien controlados que establezcan la seguridad y eficacia del fármaco, y otros estudios *in vitro* que la FDA considere apropiados.[12] Además, cuando los datos *in vivo* son apropiados para determinar la BD de un fármaco, la normativa proporciona directrices sobre los tipos específicos de estudios de BD *in vivo*.[13] Esta guía se centra, principalmente, en el uso de estudios *in vivo* para determinar la BD de un fármaco.

A. Estudios *in vivo*

1. Consideraciones generales

Para los estudios *in vivo*, la normativa permite el uso de medidas de FC en una matriz biológica accesible como la sangre, el plasma o el suero, para indicar la liberación de la sustancia farmacológica del medicamento en la circulación sistémica.[14] A efectos de esta guía, los términos para las matrices biológicas (es decir, sangre, plasma y suero) se utilizan indistintamente. Si no pueden realizarse mediciones seriadas del fármaco o sus metabolitos en plasma, suero o sangre, debe considerarse la medición de la excreción urinaria.[15]

Con frecuencia, la BD se basa en medidas de FC como el AUC para reflejar el *grado* de absorción sistémica y la (C_{max}) y (T_{max}) para reflejar la *velocidad* de absorción sistémica. Las

[11] 21 CFR 320.24(a).
[12] 21 CFR 320.24(b).
[13] 21 CFR 320.25 hasta 320.29.
[14] 21 CFR 320.24(b)(1)(i).
[15] 21 CFR 320.24(b)(l)(i).

comparaciones basadas en FC para describir la BD relativa suponen que la medición de la fracción activa en el lugar de acción no es posible y que existe alguna relación entre la concentración de la fracción activa en la circulación sistémica y la seguridad y eficacia del fármaco. Un estudio típico de FC para determinar la BD comparativa se realiza como un estudio cruzado. El diseño cruzado reduce la variabilidad en las medidas de FC que son causadas por factores específicos del sujeto, aumentando así la capacidad de identificar las diferencias en las medidas de FC que son causadas por diferentes formulaciones.

2. Estudio piloto

Si los patrocinadores lo desean, se puede realizar una prueba piloto con número reducido de sujetos, antes de proceder con un estudio de BD a gran escala. Los resultados de la prueba piloto pueden:

- Evaluar la variabilidad en las medidas FC.
- Determinar que el tamaño de la muestra alcance la potencia adecuada para realizar el análisis de BD en un estudio a escala real.
- Optimizar los intervalos de tiempo para la recolección de muestras.
- Determinar la duración del periodo de reposo farmacológico necesario entre tratamientos.

En cuanto a los productos IR, una programación cuidadosa de la toma de muestras iniciales de FC puede garantizar que la primera toma de muestras se produzca antes de la C_{max}, indicando así el protocolo óptimo de toma de muestras para un estudio a gran escala.[16] En algunas casos, los resultados de un ensayo piloto se pueden utilizar como base única para determinar la BD de un

[16] 21 CFR 320.25 hasta 320.27 (para información sobre lineamientos para la conducción y diseño de un estudio de biodisponibilidad o bioequivalencia *in vivo*).

fármaco, si el diseño y la ejecución del estudio son adecuados, y si un número suficiente de sujetos han completado el estudio con mediciones de FC evaluables.

3. Estudios a gran escala

En el apéndice A, se brindan recomendaciones generales para un estudio estándar de BD o BE basado en mediciones de FC. Asimismo, se recomiendan diseños de estudios cruzados no replicables para los estudios de BD de formas farmacéuticas IR y MR. Los patrocinadores tienen la opción de utilizar diseños replicados para los estudios de BD o BE, en los que el tratamiento de referencia se repite o tanto el producto de prueba como el de referencia se administran en múltiples ocasiones. Los diseños cruzados por réplicas se utilizan para estimar: (1) la varianza dentro de los parámetros propios del sujeto para el producto de referencia o para ambos, el producto de prueba y el de referencia; (2) el componente de varianza de interacción del sujeto por formulación. Estos diseños comprenden la variabilidad entre sujetos que puede complicar la interpretación de un estudio de BE en comparación con un enfoque cruzado sin réplicas.

Además del enfoque tradicional y el uso promedio de BE con diseños de réplica, se puede considerar el uso de un enfoque de BE a escala de referencia, utilizando un diseño de réplica. En otras palabras, se trata de un enfoque en el que los límites de aceptación de BE se adaptan a la variabilidad del producto de referencia. Normalmente, este enfoque de BE a escala de referencia se utiliza normalmente para fármacos con una alta variabilidad intrasujeto (mayor o igual al 30%) o fármacos con un índice terapéutico reducido.[17]

[17] Davit B, D Conner, 2010, Referencia-Scaled Average Bioequivalence Approach, en: I Kanfer, L Shargel, editores, Generic Drug Product Development – International Regulatory Requirements for Bioequivalence, Informa Healthcare, 271-272.

[18] Cuando se planifique el uso del enfoque de BE con escalado de referencia, se debe poner en contacto con la división de revisión correspondiente.

Para determinar la BD absoluta, los estudios de un solo período que utilizan un marcado isotópico son una alternativa científicamente aceptable.

4. Población de estudio

Generalmente, los estudios de BD se deberían llevar a cabo en sujetos en buen estado de salud, a partir de los 18 años o mayores; además, deben ser capaces de dar su consentimiento informado. Cuando las condiciones de seguridad imposibiliten el estudio en sujetos saludables, es preferible evaluar la BD de un fármaco en individuos con la enfermedad o afección que se está estudiando.[19] En estos casos, los patrocinadores deben procurar inscribir personas cuya enfermedad y tratamiento farmacológico tenga alta probabilidad de ser estable durante la duración del estudio. En los estudios de BD, deben participar hombres y mujeres, a menos que exista una razón específica para excluir algún género (por ejemplo, si el fármaco está indicado solo para uno de los géneros o existe un mayor potencial de reacciones adversas en uno de los sexos en comparación con el otro). Las mujeres que participen al inicio del estudio no deben: estar embarazadas, en periodo de lactancia ni quedar en estado de embarazo durante este.

5. Pruebas de dosis única y dosis múltiple (estado de equilibrio)

En conformidad con la normativa,[20] se recomienda estudios *in vivo* de dosis única para evaluar la BD de un fármaco, ya que suelen ser más sensibles que los estudios de estado de

[18] Jiang, W, F Maklouf, DJ Schuirmann, X Zhang, D Conner, LX Yu, R Lionberger, 2015, A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion, AAPS J, 17(4):891-901.
[19] 21 CFR 320.25(a).
[20] 21 CFR 320.25(a).

equilibrio al momento de evaluar la velocidad y el grado de liberación de la sustancia farmacológica del medicamento en la circulación sistémica. Se remite al patrocinador a la sección IV.C para una discusión sobre la realización de estudios para determinar la BD de un fármaco de un producto MR.

La normativa también proporciona directrices sobre el diseño de un estudio de BA *in vivo* de dosis múltiples y cuándo se requieran dichos estudios.[21] Si se realiza un estudio de dosis múltiple, el patrocinador debe dosificar el producto para alcanzar concentraciones equilibradas del fármaco.[22] Además, el patrocinador debe proporcionar pruebas de que se alcanzaron concentraciones estables del fármaco.

6. Metodología bioanalítica

Los patrocinadores deben usar el método bioanalítico para que los estudios de BD sean precisos, específicos, susceptibles y reproducibles.[23] La guía independiente de la FDA titulada: *Bionalytical Method Validation* (mayo de 2018) está disponible para ayudar a los patrocinadores a validar los métodos bioanalíticos.

7. *Administración en condiciones de ayuno o bajo alimentación*

El patrocinador debe determinar la BD del producto de prueba en condiciones de ayuno, ya que, generalmente, es un método más susceptible para evaluar las diferencias entre las formulaciones. También, deben evaluarse los efectos de los alimentos en la BD del producto de prueba.[24] Si la BD se determina usando un producto aprobado como referencia, el producto de

[21] 21 CFR 320.26.
[22] 21 CFR 320.27(c).
[23] 21 CFR 320.29 (para información de métodos bioanalíticos).
[24] Para más información consulte el borrador de la guía de la FDA titulado: *Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations* (February 2019). Cuando sea concluida, esta guía representará el criterio actualizado de la FDA sobre este tema.

referencia debe administrarse como se describe en la etiqueta. Si se anticipan problemas de tolerabilidad o situaciones adversas graves en condiciones de ayuno (ya sea para la prueba o el producto de referencia), el patrocinador debe realizar el estudio en condiciones de alimentación. Para más información, consulte el apéndice B.

8. Fracciones activas a medir

El principio activo que se libera de la forma de dosificación o su fracción activa o, en su caso, sus metabolitos activos, deben medirse en la matriz biológica obtenida durante el estudio de BD.

El perfil de concentración-tiempo del principio activo o de la fracción activa es más sensible a los cambios en la realización de la formulación. En cambio, el metabolito se ve más afectado por la formación, distribución y eliminación de metabolitos. Los siguientes son casos en los que un metabolito o metabolitos activos se deben someter a análisis de IC para la evaluación de BD:

- **Si el metabolito se forma por metabolismo presistémico (por ejemplo, metabolismo intestinal) y contribuye a la eficacia o seguridad:** en este caso, deben medirse los principios activo o las fracciones activas y el metabolito activo.
- **Cuando las concentraciones del principio activo o de la fracción activa sean demasiado bajas para permitir mediciones bioanalíticas confiables en la matriz biológica apropiada**: en este caso, debe medirse el metabolito en lugar del principio activo o la fracción activa.

9. Mediciones FC de exposición sistémica

Cuando estén disponibles, los patrocinadores deben usar medidas de exposición sistémica clínicamente relevantes para determinar la BA. Las medidas de exposición se definen en relación con las exposiciones máximas, parciales y totales del perfil concentración-tiempo del fármaco en la matriz biológica apropiada, como se describe, a continuación.

a. Exposición máxima

El patrocinador debe determinar la exposición máxima del fármaco midiendo C_{max}, la obtenida directamente de los datos de concentración sistémica del fármaco sin interpolación. La T_{max} puede proporcionar información importante sobre la velocidad de absorción. El primer punto de una curva de concentración-tiempo del fármaco basada en mediciones de sangre o plasma, a veces, es la concentración más alta, lo que suscita la preocupación de que el primer tiempo de muestreo fuera demasiado tardío para determinar con precisión la C_{max} y la T_{max}. Un estudio piloto cuidadosamente realizado puede ayudar a evitar este problema. Por ejemplo, la recogida de una muestra en un momento temprano para los productos IR, entre 5 y 15 minutos después de la dosificación, seguida de recolección de muestras adicionales (por ejemplo, de dos a cinco) en la primera hora después de la dosificación, podría ser suficiente para evaluar las concentraciones máximas tempranas.

b. Exposición total (grado de absorción)

Para los estudios de dosis única, el patrocinador debe calcular la exposición total teniendo en cuenta lo siguiente: el área bajo la curva de concentración-tiempo desde el tiempo cero hasta un momento determinado AUC_{0-t} de una matriz biológica apropiada, donde *t* es el último punto con una concentración medible.

- El área bajo la curva de la concentración en el tiempo desde el momento cero hasta

el infinito ($AUC_{0-\infty}$), a partir de una matriz biológica adecuada, donde $AUC_{0-\infty}$= $AUC_{0-t}+ Ct / \lambda z$. Ct es la última concentración medible del fármaco y λz es la constante de velocidad de eliminación terminal calculada mediante un método adecuado.

- Para fármacos con baja variabilidad intrasujeto (cuando esté disponible) en la distribución y aclaramiento (es decir, menor al 30%) y con una vida media prolongada, debe utilizarse un AUC reducido (para más información véase la sección VI.C).

Para los estudios en estado de equilibrio, el patrocinador debe calcular la exposición total utilizando el área bajo la curva de concentración-tiempo desde el tiempo cero hasta el tiempo TAU, en una matriz biológica apropiada mediante un intervalo de dosificación en estado de equilibrio (AUC_{0-TAU}), donde TAU es la duración del intervalo de dosificación.

c. Exposición parcial

Además de la exposición máxima y total, para ciertas clases de fármacos (por ejemplo, productos farmacéuticos analgésicos), una evaluación de la exposición parcial podría ser científicamente apropiada para apoyar la determinación de la BD relativa del fármaco. La FDA recomienda el uso del AUC parcial como medida de la exposición parcial. El tiempo para suspender el AUC parcial debe estar relacionado con una medida de respuesta clínicamente relevante. El patrocinador debe recolectar suficientes muestras cuantificables para permitir una estimación adecuada del AUC parcial. Además, los patrocinadores deben consultar a la división de revisión correspondiente las dudas sobre la idoneidad de la medida de respuesta o el uso de la exposición parcial.

10. Comparación de medidas de exposición a fármacos en estudios de BD

Para las comparaciones de BD, se recomienda un enfoque de IC. Asimismo, se sugiere la transformación logarítmica de las medidas de exposición antes de realizar el análisis estadístico. Esta guía recomienda el uso del enfoque de BE para comparar medidas de exposición sistémica para estudios de BD replicados y no replicados de productos IR y MR. Para obtener más información sobre el análisis de datos, consulte el anexo A y la guía de la FDA titulada: *Statistical Approaches to Establishing Bioequivalence* (febrero de 2001).

B. Otros enfoques para determinar la BD de un fármaco

En algunos casos, se recomiendan otros enfoques para determinar la BD de un fármaco. A continuación, se presentan algunas consideraciones generales relativas a estos enfoques.

1. *Estudios in vitro*

Bajo ciertas circunstancias, la BD se puede evaluar mediante enfoques *in vitro* (por ejemplo, la disolución y las pruebas de liberación del fármaco) durante las fases de preaprobación y postaprobación.[25] Las siguientes directrices de la FDA brindan recomendaciones sobre el desarrollo de la metodología de disolución, el establecimiento de requisitos y las aplicaciones reglamentarias de las pruebas de disolución:[26]

- *Pruebas de disolución de formas farmacéuticas orales sólidas de liberación inmediata (agosto de 1997)*

[25] 21 CFR 320.24(b)(5) y (6).
[26] Véase también el borrador de guía de la FDA titulado: *The Use of Physiologically Based Pharmacokinetic Analyses - Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls* (septiembre de 2020). Cuando sea concluida, esta guía representará el criterio actualizado de la FDA de la Agencia sobre este tema.

- *Formas de dosificación oral de liberación prolongada: Desarrollo, evaluación y aplicación de correlaciones in vitro/in vivo (septiembre de 1997)*
- *Exención de estudios de biodisponibilidad y bioequivalencia in vivo para formas farmacéuticas orales sólidas de liberación inmediata basadas en un sistema de clasificación biofarmacéutica (diciembre de 2017)*
- *Bioexenciones basadas en el sistema de clasificación biofarmacéutica (mayo de 2021)*
- *Pruebas de disolución y criterios de aceptación para fármacos en forma de dosificación oral sólida de liberación inmediata que contienen sustancias farmacológicas de alta solubilidad (agosto de 2018)*

2. Pruebas in vitro para predecir la BD in vivo en humanos

La IVIVC es un enfoque para describir la relación entre un atributo *in vitro* de una forma de dosificación (por ejemplo, la velocidad o el grado de liberación del fármaco) y una medida *in vivo* relevante (por ejemplo, la concentración plasmática del fármaco o la cantidad de fármaco absorbido). El modelo de esta relación facilita el desarrollo y la evaluación racional de las formas de dosificación de ER y, con menor frecuencia, de otras formas de dosificación. Una vez validada una IVIVC, la prueba *in vitro* sirve como sustituto para las pruebas de BD, así como herramienta para seleccionar las formulaciones y establecer los criterios de aceptación de disolución y liberación del fármaco.

En concreto, se recomienda la disolución *in vitro* y la caracterización de la liberación del fármaco para todas las formulaciones de productos de ER (incluidas las formulaciones de prototipo), principalmente, cuando se utilizan para definir las características de absorción *in vivo* para diferentes formulaciones de productos. Tales esfuerzos pueden permitir el establecimiento de una IVIVC. Cuando se establece una IVIVC o una relación *in vitro-in vivo* (IVIVR), la prueba

in vitro puede servir no solo como especificación de control de calidad para el proceso de fabricación, sino también como indicador de cómo se comportará el producto *in vivo*.[27]

Para más información sobre el desarrollo y la validación de una IVIVC, consulte la guía de la FDA titulada: *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (September 1997).* Los patrocinadores deben ponerse en contacto con la división de revisión correspondiente en relación con los enfoques para establecer IVIVC.

3. *Estudios de FD*

Se recomienda el uso de parámetros de FC porque suelen ser los más precisos, sensibles y reproducibles. Sin embargo, en los casos en los que no sea posible utilizar un criterio de valoración FC, deberá utilizarse un criterio de valoración FD bien justificado para determinar la BD o demostrar la BE.

4. *Estudios clínicos comparativos*

En pocos casos, la medición de los principios activos o de las fracciones activas en una matriz biológica accesible (es decir, el enfoque FC) o un enfoque FD no es posible para los fármacos administrados por vía oral; en estos casos, se pueden utilizar criterios de valoración clínicos.[28] Estos ensayos clínicos, generalmente, implican tamaños de muestras más grandes en comparación con los estudios FC y FD, debido a la variabilidad en la medición de los criterios de valoración,[29] ya que estos casos no ocurren muy a menudo, así que se espera que el uso de este enfoque sea poco frecuente (sección VI.D).

[27] 21 CFR 320.24(b)(1)(ii).
[28] 21 CFR 320.24(b)(4).
[29] 21 CFR 320.24(b)(4).

IV. EVALUACIÓN DE BD Y DEMOSTRACIÓN DE BE PARA DIVERSAS FORMAS DE DOSIFICACIÓN

Esta sección resume las recomendaciones para evaluar la BD y demostrar la BE basadas en formas de dosificación específicas. También, se describe cuándo los estudios de BD o BE deben llevarse a cabo (pre o postaprobación).

A. Soluciones y otras formas de dosificación solubilizadas

En el caso de soluciones orales, elixires, jarabes, tinturas u otras formas farmacéuticas solubilizadas, la BD *in vivo*, por lo general, es evidente; por tanto, se puede prescindir de exigir datos de BD *in vivo* para un producto basándose en otros factores de la solicitud.[30] Incluso cuando no se necesita un estudio comparativo, se requiere la caracterización de la farmacocinética del fármaco.[31] Además, se exime la realización de estudios de BA *in vivo* que comparen diferentes formulaciones de soluciones basándose en los siguientes supuestos: (1) la liberación de la sustancia farmacológica del producto farmacéutico es evidente por sí misma; (2) que las soluciones no contienen excipientes que afecten significativamente a la absorción del fármaco. Sin embargo, hay ciertos excipientes que pueden alterar la BD (por ejemplo, el sorbitol puede reducir la BD de los fármacos y la vitamina E puede aumentar la BD) en cantidades que, a veces, se utilizan en formas farmacéuticas líquidas orales. En estos casos, podría ser necesario determinar la BD *in vivo* del fármaco.[32] En el caso de las soluciones que contienen cosolventes o que están tamponados protegidos para mantener el fármaco en solución, puede producirse precipitación cuando la solución se expone al contenido gástrico. Los cambios en la formulación

[30] 21 CFR 320.24(b)(4).
[31] 21 CFR 314.50(d)(3).
[32] 21 CFR 320.22(b)(3)(iii).

de estos productos pueden provocar la precipitación del fármaco y, en estas ocasiones, podría ser necesario un estudio *in vivo*.[33]

B. Productos farmacéuticos IR

En este apartado, se incluyen las cápsulas, los comprimidos (incluidas las formas farmacéuticas convencionales, bucales, masticables, de desintegración oral y sublinguales) y las suspensiones.

1. Preaprobación: estudios de BD

Para los estudios de BD, la FDA recomienda un estudio de dosis única en ayunas.[34] En determinados casos, se podrían recomendar científicamente estudios de BD de dosis múltiples (véase la sección III.A.5) para evaluar la exposición sistémica del fármaco.[35] Las formas de dosificación no convencionales (por ejemplo, las formas de dosificación bucales, masticables, de desintegración oral y sublinguales) se deben administrar de acuerdo con el etiquetado propuesto. Además, el patrocinador debe determinar la BD de la forma farmacéutica no convencional intacta cuando se ingiere para evaluar el impacto de la ingestión accidental del producto intacto. El muestreo debe captar adecuadamente la T_{max} y la C_{max}, así como de la exposición total.

El patrocinador deberá evaluar la disolución *in vitro* de todas las suspensiones y formas farmacéuticas orales sólidas administradas por vía oral.

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[33] 21 CFR 320.22(b)(3)(iii).
[34] En general, véase: 21 CFR 320.26.
[35] Para más información sobre los estudios del efecto de los alimentos, consulte el borrador de la guía de la FDA titulado: *Assessing the Effects of Food on Drugs in INDs and NDAs - Clinical Pharmacology Considerations* (febrero de 2019). Cuando sea concluida, esta guía representará el criterio actualizado de la FDA sobre este tema. Véase también, en general, 21 CFR 320.27.

2. Cambios posteriores a la aprobación

En la guía de la FDA titulada: *SUPAC-IR: Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995), se brindan recomendaciones sobre los estudios de disolución *in vitro* y de BE *in vivo* para los cambios posteriores a la aprobación. En el caso de que se efectúen cambios posteriores a la aprobación, el patrocinador debe comparar los resultados de los estudios *in vitro* o *in vivo* entre los productos antes y después del cambio.

C. Productos farmacéuticos MR

Los productos MR incluyen productos ER y DR (por ejemplo, liberación controlada y liberación sostenida).[36]

Los productos ER son formas de dosificación diseñadas para ampliar o prolongar la liberación del principio activo o la fracción activa del fármaco. Cabe destacar que los productos ER pueden suspender la frecuencia de dosificación y las fluctuaciones de las concentraciones plasmáticas en comparación con un producto IR. Los productos ER pueden ser cápsulas, comprimidos, gránulos, pellets, perlas o suspensiones.

Los productos DR son formas de dosificación que liberan el principio activo o la fracción activa en un momento posterior al inmediatamente posterior a la administración (es decir, existe un desfase entre el momento de la administración y la primera concentración plasmática cuantificable). Normalmente, se utilizan recubrimientos (por ejemplo, recubrimientos entéricos)

[36] Para efectos de esta guía, los términos: *prolongado*, *controlado*, y *constante* se utilizan indistintamente

para retrasar la liberación del principio activo hasta que la forma farmacéutica haya pasado a través del medio ácido del estómago.

Si bien los productos farmacológicos DR se definen como productos MR, muchos productos DR se comportan como productos IR después de tener en cuenta el retraso; por tal motivo, la FDA considera que los requisitos y recomendaciones para el estudio BD de un producto DR son idénticos a los de un producto IR. En aquellos casos en que el producto DR dé lugar a un perfil *in vivo* complejo, se deberá contactar a la división de revisión correspondiente para obtener más información. El resto de esta sección se centra en las disposiciones relativas a los productos farmacológicos ER.

1. *Preaprobación: estudios de BD*

Los reglamentos contemplan el propósito y los requisitos de un estudio de BD para un producto ER y estipulan que: "el material o materiales de referencia para dicho estudio de BD se elegirán de tal manera que permitan una evaluación científica adecuada de las declaraciones de ER realizadas para el producto farmacéutico". [37] [38] Los productos de referencia apropiados deben ser uno de los siguientes o cualquier combinación de ellos:

- Una solución o suspensión del principio activo o de la fracción terapéutica.
- Un fármaco de liberación no controlada ya comercializado que contenga el mismo principio activo o fracción terapéutica y se administre de acuerdo con el etiquetado aprobado del fármaco de liberación no controlada.

[37] 21 CFR 320.25(f)(1).
[38] 21 CFR 320.25(f)(2).

- Un fármaco ER ya comercializado que contenga el mismo principio activo o fracción terapéutica y se administre de acuerdo con las recomendaciones de dosificación del etiquetado del fármaco ER ya comercializado.
- Un material de referencia distinto de los descritos anteriormente que sea apropiado por razones científicas válidas.[39]

Además, según la normativa, la finalidad de un estudio de BD *in vivo* de un fármaco para el que se hace una declaración de ER es determinar si se cumple todas las siguientes condiciones:[40]

i. El fármaco cumple las declaraciones de ER que se exigen.
ii. El perfil de BD establecido para el fármaco descarta la existencia de la absorción rápida.[41]
iii. La eficacia en estado de equilibrio del fármaco es equivalente a la de un fármaco comercializado en la actualidad de liberación prolongada o no prolongada que contenga el mismo principio activo o fracción terapéutica y que esté sujeto a un NDA.
iv. La formulación del fármaco proporciona un rendimiento FC uniforme entre las unidades de dosificación individuales.

Por lo tanto, basándose en los criterios expuestos anteriormente, se considerarán los perfiles FC individuales. Estas consideraciones pueden aplicarse más detalladamente a productos con características de liberación complejas.

[39] 21 CFR 320.25(f)(2).
[40] 21 CFR 320.25(f).
[41] 21 CFR 320.25(f)(l)(ii).

La FDA recomienda que se lleven a cabo los siguientes estudios de BD y de efecto alimentario para un fármaco ER presentado como NDA para los escenarios descritos, a continuación. En algunos casos, pueden evaluarse dosis no equivalentes de los productos ER e IR.[42] Para más información, contacte a la división de revisión correspondiente.

a. Una nueva formulación ER comparada con un producto IR previamente aprobado

- En el caso de los fármacos con farmacocinética lineal en el intervalo de dosificación terapéutica, un estudio en ayunas debe comparar el producto ER administrado como dosis única a la concentración más alta con el producto de referencia IR administrado sobre el mismo intervalo utilizado para el producto ER, para poder alcanzar la misma dosis total que el producto ER. Si por razones de seguridad no se puede utilizar la dosis más alta, se deberá utilizar una dosis más baja.

  Considere el siguiente ejemplo: se está desarrollando un producto ER de 150 miligramos (mg) administrado una vez al día (QD) versus un producto de referencia IR aprobado de 50 mg administrado tres veces al día (TID) o un producto de 75 mg administrado dos veces al día (BID). A efectos de BD relativa, el producto ER de 150 mg administrado como dosis única podría compararse con el producto de referencia IR de 50 mg administrado TID o con el producto de referencia IR de 75 mg administrado BID.
- En el caso de fármacos con farmacocinética no lineal en el intervalo de dosificación terapéutica, como mínimo, se deberá comparar una dosis única de las concentraciones más altas y bajas del producto de ER, con los productos de referencia de RI correspondientes, administrados durante el mismo período de tiempo que el intervalo de dosificación de ER. Si no se puede deducir la BD relativa de las concentraciones

[42] 21 CFR 320.25(f)(2)(i) y (iv).

intermedias de ER basándose en estudios previos, se deberá comparar un estudio de dosis única en ayunas de la concentración o concentraciones intermedias de ER con los productos de referencia de RI correspondiente administrados durante el intervalo de dosificación de ER.

- Si se están desarrollando varias concentraciones de ER y las concentraciones de ER no son proporcionalmente similares en cuanto a composición, se debe realizar un estudio de evaluación de equivalencia de concentración de dosis única en ayunas o un estudio de proporcionalidad de concentración de dosis para el producto ER. Como se describe en los siguientes ejemplos:
    - Si se están desarrollando tres concentraciones, 10, 25 y 50 mg, para una nueva forma de dosificación de ER, el estudio de equivalencia de concentración se debe realizar utilizando una concentración de 5×10 mg, 2×25 mg, y 1×50 mg para lograr la consistencia de la dosis.
    - Si se están desarrollando tres concentraciones, 10, 25 y 50 mg, para una nueva forma de dosificación de ER, el estudio de proporcionalidad de la concentración se debe realizar utilizando 1×10 mg, 1×25 mg y 1×50 mg.
- Cuando las concentraciones de los RE son proporcionalmente similares en cuanto a composición y las pruebas de liberación *in vitro* demuestran diferentes perfiles de velocidad de liberación, se debe realizar un estudio de evaluación de equivalencia de concentraciones de dosis única, en ayunas, concentración o un estudio de proporcionalidad de concentraciones de dosis para el producto RE.

- Se debe realizar un estudio del efecto de los alimentos con una dosis única y un alto

contenido de grasas en la concentración más alta del nuevo producto de ER (ER_{new})[43].

- Se deberá realizar un estudio en estado de equilibrio con la concentración más alta del producto ER en comparación con un producto de referencia IR ya aprobado y dosificado para alcanzar la dosis total equivalente del producto ER.

    b. Comparación del nuevo producto ER (ER_{new}) con un producto ER ya aprobado (ER_{old}) con un intervalo de dosificación diferente (es decir, donde ER_{new} y ER_{old} son intervalos de dosificación desiguales)

- Las recomendaciones para el desarrollo de un nuevo producto de ER dado de un producto de ER ya aprobado con un intervalo de dosificación diferente son las mismas que se describen en la sección anterior C.1.a. (es decir, el desarrollo de una nueva formulación de ER dado un producto de IR ya aprobado), excepto por la elección del producto de referencia. En este caso, el producto de referencia podría ser el producto ER_{old} o el IR ya aprobado.

    c. Comparación del nuevo producto ER (ER_{new}) con un producto ER ya aprobado (ER_{old})con el mismo intervalo de dosificación.

- El patrocinador debe realizar un estudio de BE de dosis única, en ayunas, sobre la concentración más alta del producto ER_{new} en comparación con el producto ER_{old}. Si los productos ER_{new} y ER_{old} tienen concentraciones diferentes, el patrocinador debe comparar los productos ER_{new} con los ER_{old} utilizando las concentraciones más altas de estos productos y la misma dosis molar.

[43] Para más información, consulte el borrador de la guía de la FDA titulado: *Assessing the Effect of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations (Febrero de 2019)*. Cuando sea concluida, esta guía representará el criterio actualizado de la FDA sobre este tema.

- Se debe realizar un estudio del efecto de los alimentos con una dosis única y un alto contenido de grasas utilizando la concentración de ER_{new} más alta.
- Cuando las composiciones de las concentraciones de ER_{new} no son proporcionalmente similares, se debe realizar un estudio de evaluación de concentración de dosis única, en ayunas o un estudio de proporcionalidad de concentración de la dosis para el nuevo producto ER_{new}.
- Si los perfiles FC de los dos productos ER son diferentes (por ejemplo, si la forma del perfil de tiempo contra la concentración es diferente), la demostración de BE entre los productos ER nuevos y antiguos podría no ser suficiente para asegurar que no hay diferencia en seguridad o eficacia. Científicamente, podrían recomendarse más estudios clínicos para garantizar que los dos productos tienen el mismo efecto clínico y perfil de seguridad.

2. Cambios posteriores a la aprobación

La guía de la FDA titulada: *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (octubre de 1997) brinda algunas recomendaciones sobre los tipos de disolución *in vitro* y estudios de BE *in vivo* para los productos farmacéuticos MR y los ER, para respaldar los cambios específicos posteriores a la aprobación. Para los cambios posteriores a la aprobación, la FDA recomienda que el patrocinador realice comparaciones *in vitro* o *in vivo* entre el producto fabricado antes del cambio y el fabricado después del cambio.

V. INFORMACIÓN ADICIONAL SOBRE LOS ENFOQUES IN VITRO

A. Consideraciones generales

Las regulaciones indican que, si se requieren datos *in vivo* de BD o BE, para un producto, el patrocinador puede solicitar una exención de estos requisitos, bajo ciertas circunstancias. [44] [45] Por ejemplo, en algunos casos, la BD o BE *in vivo* es evidente en función de determinadas características del producto farmacéutico[46] y no se requieren datos *in vivo* adicionales. En otros casos, el requisito de datos *in vivo* de BD o BE puede no exigirse y, en su lugar, se pueden aceptar datos *in vitro*.[47] Por ejemplo, el requisito de datos *in vivo* no se exigirá para diferentes concentraciones de un fármaco IR cuando: (1) el fármaco está en la misma forma farmacéutica, pero en una concentración diferente; (2) esta formulación de concentración diferente es *proporcionalmente similar* en sus ingredientes activos e inactivos a otro fármaco para el que el mismo patrocinador ha obtenido la aprobación; (3) la formulación de la nueva concentración cumple con una prueba *in vitro* adecuada, tal como se indica en las regulaciones.[48] [49] Además, para obtener una exención para concentraciones más altas, el patrocinador debe demostrar que la farmacocinética en el rango de dosis terapéutica es lineal. Las características que muestran que las formulaciones son *proporcionalmente similares* incluyen:

- Todos los principios activos e inactivos se encuentran en porciones idénticas entre las distintas dosis (por ejemplo, un comprimido de 50 mg contiene exactamente la mitad de

[44] 21 CFR 320.22 (a).
[45] Según 21 CFR 320.22; además, de la exención de un requisito de BD o BE *in vivo*, bajo determinadas circunstancias, la BD o BE pueden evaluarse usando enfoques *in vitro*, según 21 CFR 320.24(b)(6). Los principios científicos descritos en esta guía con respecto a la exención de un requisito *in vivo* también se aplican a la consideración de datos *in vitro* según esa regulación. En tales casos, no se exenta de un requisito de datos *in vivo*, sino que la FDA determina que los datos *in vitro* son el método más preciso, susceptible y reproducible para establecer la BD o BE, tal como se exige en 21 CFR 320.24(a). No obstante, para facilidad del lector, esta guía se refiere a la decisión de exentar un requisito de BD o BE *in vivo* conforme a 21 CFR 320.22 o a la decisión de aceptar datos de BD o BE *in vitro* conforme a 21 CFR 320.24(a) como una "exención".
[46] 21 CFR 320.22(b).
[47] 21 CFR 320.22(d).
[48] 21 CFR 320.22(d)(2).
[49] Para más información sobre una exención, ver también 21 CFR 322.22(d)(3) y (4). Asimismo, la FDA, por motivos justificados, podría exentar o, en el caso de las NDA, aplazar un requisito de presentación de pruebas de BD o BE *in vivo* si la exención o el aplazamiento son compatibles con la protección de la salud pública. Véase 320.22(e).

los principios activos que un comprimido de 100 mg y el doble de principios activos que un comprimido de 25 mg).

- En el caso de los principios activos de gran potencia, cuando la cantidad de principio activo en la forma farmacéutica es relativamente baja (es decir, la cantidad de principio activo es inferior al 5 % del peso del núcleo del comprimido o del peso del contenido de la cápsula), entonces: (1) el peso total de la forma farmacéutica es prácticamente el mismo para todas las concentraciones (es decir, dentro de más o menos el 10% del peso total de la concentración utilizada en el estudio BD); (2) se utilizan los mismos ingredientes inactivos para todas las concentraciones; (3) el cambio en cualquier concentración se obtiene alterando la cantidad de los ingredientes activos y uno o más de los ingredientes inactivos.
- Los comprimidos bicapa se consideran una formulación única, aunque consten de dos capas separadas con composiciones diferentes. Para evaluar la similitud proporcional de las distintas concentraciones de los comprimidos bicapa, todos los componentes de ambas capas deben ser proporcionalmente similares. El hecho de que solo una capa sea proporcionalmente similar y la otra no lo sea indica que los productos (es decir, el comprimido completo) *no* son proporcionalmente similares.
- Los ingredientes activos e inactivos no se encuentran en proporciones idénticas entre las diferentes concentraciones, como se ha indicado anteriormente, pero las proporciones de los ingredientes inactivos con respecto al peso total de la forma farmacéutica se encuentran dentro de los límites definidos por las directrices SUPAC-IR y SUPAC-MR

de la FDA para la industria, hasta inclusive los cambios de nivel II. [50] [51]

Los patrocinadores deben ponerse en contacto con la división de revisión correspondiente y proporcionar una justificación adecuada, si pretenden demostrar que un producto es proporcionalmente similar a otro producto farmacéutico que utiliza otro enfoque.

B. Estudios *in vitro* realizados con ayuda de BD

La FDA puede determinar que un enfoque *in vitro* es el método más preciso, susceptible y reproducible para determinar BD.[52] A continuación, se proporcionan recomendaciones adicionales sobre la realización de tales estudios.

1. Formulaciones de IR (cápsulas, tabletas y suspensiones)

Los datos *in vitro* se pueden utilizar para comparar formulaciones de productos farmacológicos en determinadas circunstancias. Si un patrocinador busca determinar la BD de formulaciones IR para cápsulas, tabletas y suspensiones usando datos *in vitro*, la FDA recomienda que los patrocinadores generen perfiles de disolución para todas las concentraciones usando un método de disolución apropiado (para más información sobre IVIVC, consulte III.B.2). Si los resultados indican que las características de disolución del producto no dependen del pH o de la concentración del producto, los perfiles de disolución en un medio suelen ser suficientes para no tener que evaluar la BD *in vivo.* Si no se cumplen estos criterios, el promotor deberá recoger datos de disolución en al menos tres medios (por ejemplo, pH 1.2; 4.5 y; 6.8). Se

[50] *SUPAC IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (noviembre de 1995)
[51] *SUPAC MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (*octubre de 1997)
[52] 21 CFR 320.24(b)(5) y (6).

deben utilizar pruebas de similitud para comparar los perfiles de disolución de las diferentes concentraciones del producto (para más información consulte la guía de la FDA titulada: *Dissolution Testing of Immediate Release Solid Oral Dosage Forms (*agosto de 1997)).

a. Sobreencapsulamiento de formulaciones de ensayos clínicos

El sellado de los productos farmacéuticos utilizados en ensayos clínicos se puede realizar mediante la sobreencapsulación de la forma farmacéutica. El patrocinador debe evaluar el impacto de esta sobreencapsulación en la liberación del principio activo del producto farmacéutico. La disolución se puede utilizar para evaluar el impacto de la sobreencapsulación, siempre que: (1) no se añadan a la cápsula otros excipientes, además de los que ya están en la forma farmacéutica; (2) los perfiles de disolución entre los productos sobreencapsulados y no sobreencapsulados sean comparables en tres medios a pH 1.2; pH 4.5 y; pH 6.8. No obstante, si se añaden otros excipientes, se deberá realizar un estudio *in vivo*, a menos que el patrocinador pueda justificar por qué los excipientes añadidos no alteran la BD del producto sobreencapsulado. Estas recomendaciones se aplican por igual tanto al producto farmacéutico investigado como a cualquier producto utilizado para comparar o como referencia en el mismo estudio clínico. Se podrían añadir enzimas al medio de disolución para comprender mejor el efecto de la sobreencapsulación en la liberación del fármaco.

b. Escalado y cambios posteriores a la aprobación

Una vez aprobados, los productos farmacéuticos pueden sufrir cambios en su formulación o fabricación por diversas razones. Los cambios de formulación pueden producirse en los componentes y la composición, y los cambios de fabricación pueden producirse en el escalado, el lugar de fabricación, el proceso de fabricación o el equipo. Dependiendo del posible impacto del cambio de fabricación en la liberación del ingrediente activo del producto farmacéutico y la BD

del ingrediente activo, ciertos cambios de fabricación para productos IR pueden ser aprobados basándose únicamente en la similitud de los perfiles de disolución entre la formulación después del cambio y la formulación antes del cambio.[53] [54] En la guía de la FDA titulada: *SUPAC IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (octubre de 1997). Los principios descritos en esta guía se pueden aplicar a los cambios previos a la aprobación, como cuando la formulación que se va a comercializar varía de la formulación del ensayo clínico.

2. Formulaciones de MR

El uso de datos *in vitro* podría ser aceptable para fármacos MR con cambios específicos posteriores a la aprobación.[55] La información específica sobre el empleo de datos *in vitro* para cambios posteriores a la aprobación de fármacos MR se describe en la guía de la FDA titulada: *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (octubre de 1997). Los principios descritos en la guía también se podrían aplicar a los cambios previos a la aprobación. A continuación, se presentan algunas consideraciones adicionales para el uso de datos *in vitro* con ayuda de la determinación de la BD de un fármaco.

a. Cápsulas de gránulo

[53] Para más información sobre la presentación de un suplemento para su previa aprobación por la FDA, consulte: 21 CFR 320.21(c)(1), 314.70(b)(2)(d).
[54] Para más información sobre dispensas de pruebas de biodisponibilidad *in vivo* o bioequivalencia, consulte: 21 CFR 320.22(d).
[55] 21 CFR 320.24(b)(6).

Según 21 CFR 320.24(b)(6), los estudios de BD *in vivo* para concentraciones mayores de cápsulas con gránulo (por ejemplo, una concentración que se desarrolla después de los estudios iniciales de BD de concentraciones menores) podrían no ser necesarios basándose en (1) los datos clínicos de seguridad o eficacia de la dosis propuesta y la necesidad de la concentración mayor; (2) la linealidad de la farmacocinética en el rango de dosis terapéutica; (3) si se utilizaron los mismos procedimientos de disolución para todas las concentraciones y se obtuvieron resultados de disolución similares. La prueba de similitud f2 puede utilizarse para demostrar perfiles similares entre las distintas concentraciones del producto. El patrocinador puede determinar la BD *in vivo* de una o más concentraciones inferiores comparando los perfiles de disolución y realizando un estudio de BD *in vivo* solo con la concentración más alta (a menos que, por razones de seguridad, se impida la administración de la concentración más alta a los sujetos). Los perfiles de disolución para cada concentración se deben generar utilizando el método de disolución recomendado. Si el método de disolución no se ha finalizado, los perfiles de disolución se deben generar en, al menos, tres medios (por ejemplo, pH 1.2; 4,5 y 6.8).

b. Otras formas de dosificación de MR

Para otras formas de dosificación MR, el promotor debe realizar un estudio de BD *in vivo* empleando la concentración más alta. El patrocinador puede determinar la BD para concentraciones menores comparando los perfiles de disolución mediante la evaluación f2 cuando el producto farmacéutico se encuentra en la misma forma farmacéutica, pero en una concentración diferente y: (1) el fármaco presenta una farmacocinética lineal; (2) las distintas concentraciones son proporcionalmente similares en sus principios activos e inactivos; (3) el mecanismo de liberación del fármaco es el mismo.[56] Si las formulaciones de todas las

[56] 21 CFR 320.24(b)(6).

concentraciones no son proporcionales desde el punto de vista de la composición, se pueden presentar datos *in vitro* para las concentraciones intermedias, si se aceptan los siguientes datos: (1) datos de BD o BE, según corresponda, tanto para la concentración más alta como para la más baja; (2) comparaciones de perfiles de disolución multimedia *in vitro* utilizando la evaluación f2. Por otro lado, se pueden conceder exenciones para concentraciones menores que no sean proporcionales a la concentración más alta, si se ha establecido un espacio seguro de disolución para el fármaco mediante IVIVC o IVIVR combinados con BE virtual.[57]

Los perfiles de disolución para cada concentración deben generarse utilizando el método de disolución recomendado. Si el método de disolución no se ha finalizado, los perfiles de disolución deben generarse en, al menos, tres medios (por ejemplo, pH 1.2; pH 4.5 y pH 6.8). Estos perfiles se deben generar en los productos de prueba y de referencia de todas las concentraciones utilizando las mismas condiciones de prueba de disolución.

VI. TEMAS ESPECIALES

A. Enantiómeros versus racematos

Durante el desarrollo de un fármaco racémico, el racemato se debe medir en estudios de BD utilizando un ensayo aquiral. También, podría ser importante medir los enantiómeros individuales del racemato para caracterizar la farmacocinética de los enantiómeros. Para el desarrollo de un enantiómero específico, debe evaluarse la inversión quiral.

La medición de enantiómeros individuales en BD solamente se recomienda cuando se cumple con las siguientes condiciones:

[57] 21 CFR 320.24(b)(6).

- Los enantiómeros presentan diferentes características de FD.
- Los enantiómeros presentan diferentes características de FC.
- Las actividades primarias de eficacia y seguridad residen en el enantiómero menor.
- Al menos uno de los enantiómeros presenta una absorción no lineal (expresada por un cambio en la relación de concentración del enantiómero con el cambio en la velocidad de entrada del fármaco).

En estos casos, el patrocinador debe aplicar los criterios de BE a los enantiómeros por separado.

B. Fármacos con mezclas complejas como principios activos

Algunos fármacos pueden contener sustancias farmacológicas complejas (es decir, sustancias o principios activos, los cuales son mezclas de múltiples componentes de origen sintético o natural). La composición química o la actividad biológica de algunos o todos los componentes de estas sustancias farmacológicas complejas pueden no estar completamente caracterizadas. Además, la cuantificación de todos los componentes activos o potencialmente activos en los estudios de BD podría no ser posible. En estos casos, los patrocinadores deben utilizar un número selecto de componentes en los estudios de BD. Generalmente, los criterios para seleccionar los componentes deben incluir la cantidad de la fracción en la forma farmacéutica, los niveles plasmáticos o sanguíneos de la fracción y la actividad biológica de la fracción. Cuando los enfoques de FC no son viables para evaluar la velocidad y el grado de absorción de una sustancia farmacológica de un producto farmacéutico, el patrocinador puede considerar enfoques de FD, clínicos o *in vitro*.[58] En casos como estos, los patrocinadores deben

[58] 21 CFR 320.24(b).

consultar a la división de revisión correspondiente sobre el enfoque y las fracciones para realizar estudios de BD.

C. Fármacos de vida media prolongada

En un estudio de BD o FC que incluya un producto oral IR con una vida media prolongada (es decir, mayor o igual a 24 horas), la caracterización de la vida media del producto debe incluir el muestreo de sangre durante un período de tiempo adecuado. Para determinar la BD de un medicamento que contiene un fármaco con una vida media prolongada, se debe realizar un estudio cruzado de dosis única, si se utiliza un período de lavado adecuado. Si el estudio cruzado es problemático, debe utilizarse un estudio con un diseño paralelo. Para un estudio cruzado o paralelo, el tiempo de recolección de la muestra debe asegurar que el medicamento se mueva completamente a través del tracto gastrointestinal para que la absorción de la sustancia farmacológica (C_{max}) y un AUC reducido adecuadamente (es decir, para medicamentos que no exhiben cinética flip-flop y medicamentos que no tienen alta variabilidad intrasujeto) puedan ser utilizados para caracterizar las exposiciones máxima y total al fármaco, respectivamente. En estos casos, el patrocinador debe consultar a la división de revisión correspondiente sobre la duración del muestreo y la elección de las medidas de FC para determinar la BD.

D. Medicamentos de administración oral destinados a la acción local

La determinación de la BA cuando la sustancia farmacológica produce sus efectos por acción local en el tracto gastrointestinal puede lograrse utilizando la farmacocinética, un criterio de valoración aceptable para la FD, estudios clínicos de eficacia y seguridad o estudios *in vitro*

adecuadamente diseñados y validados, según convenga.[59] En estos casos, los patrocinadores deben consultar a la división de revisión correspondiente sobre el enfoque para evaluar la BD.

E. Medicamentos combinados y coadministrados

Dos o más principios activos se pueden formular como un solo medicamento, que a efectos de este documento de orientación se denomina producto de combinación fija. Por lo general, el objetivo de un estudio de BD in vivo con un producto de combinación fija es comparar la velocidad y el grado de absorción de cada principio activo o fracción terapéutica en el medicamento combinado con la tasa y el grado de absorción de cada principio activo o fracción terapéutica administrados como preparaciones separadas de un solo ingrediente.[60]

Se recomienda un estudio cruzado de dos grupos, de dosis única, en ayunas, de la combinación fija versus los medicamentos de un solo ingrediente administrados simultáneamente o un producto de combinación aprobado que contenga los mismos ingredientes activos. Este estudio debe utilizar la concentración más alta de la combinación fija con dosis iguales de los medicamentos individuales. También, se podrían considerar algunos diseños de estudio alternativos dependiendo de la situación específica. Por ejemplo, cuando no hay interacciones farmacológicas entre los componentes de una combinación fija formada por dos componentes, podría ser apropiado un diseño de estudio de tres grupos que compare el producto farmacológico combinado versus los productos farmacológicos de un solo ingrediente administrados por separado.

Además, la evaluación del efecto de una alimentación alta en grasas sobre el nuevo fármaco puede ser útil para apoyar el etiquetado de la combinación fija. Se debe utilizar un

[59] 21 CFR 320.24.
[60] 21 CFR 320.25(g).

diseño de estudio de dosis única, con alto contenido en grasas y efecto de los alimentos.

Los patrocinadores deben consultar con la división de revisión correspondiente para discutir su situación.

Los estudios de BD para el producto de combinación fija deben incluir la medición de las concentraciones sistémicas de cada ingrediente activo. El enfoque IC para la evaluación BD debe aplicarse a cada unidad medida de la combinación fija y su producto de referencia.

En casos específicos, los fármacos se administran en conjunto (pero no están coformulados) con el objetivo de aumentar la exposición de uno de los fármacos (es decir, el fármaco sujeto). El segundo fármaco de *refuerzo* no está destinado a tener un efecto terapéutico directo y se administra únicamente para aumentar la exposición sistémica del fármaco sujeto. Cuando tanto el fármaco sujeto como el de refuerzo son nuevas unidades moleculares, la BD de cada uno debe determinarse individualmente y cuando se administran en combinación. Si se produce un cambio en la formulación del fármaco sujeto que haga necesario un estudio de BD, el fármaco sujeto se deberá administrar con el fármaco de refuerzo tanto para los productos posteriores al cambio como para los anteriores a este. Las medidas FC correspondientes, incluyendo los IC, deben ser determinadas y reportadas para el fármaco sujeto. No se recomienda medir las concentraciones del fármaco de refuerzo. Asimismo, los estudios de BD para el fármaco de refuerzo se deben realizar solo con el fármaco de refuerzo; el fármaco sujeto no debe dosificarse con el fármaco de refuerzo. Cuando la combinación (no coformulada) incluya una nueva unidad molecular y un fármaco de refuerzo aprobado, solo se evaluará la concentración del nuevo fármaco, ya que se asume que la BD del producto de refuerzo aprobado ha sido evaluada previamente.

TECHNICAL GUIDE FOR THE SUBMISSION AND EVALUATION OF COMPARATIVE DISSOLUTION PROFILES STUDIES

Ministry of Health
Dirección de Regulación de Productos de Interés Sanitario
Record Unit
16th St., 6th and 8th Ave., North Bldg., 2nd Floor, San José Costa Rica
Tel. Fax: 22227887. Email: ms.registros@misalud.go.cr
Bioequivalence Process, web site:https://www.ministeriodesalud.go.cr/index.php/regulacion-de-la-salud?layout=edit&id=60
Technical consultations, online form: https://www.ministeriodesalud.go.cr/index.php/regulacion-de-la-salud?layout=edit&id=62
Virtual consultations, appointments, and scheduling: citas.bioequivalencia@misalud.go.cr
December 2022

1. OBJECTIVE

To define the general guidelines to comparative dissolution profile studies provided during the inscription process, renewal process, or post-registration changes that require it (*Guía Técnica para la aplicación de cambios postregistro de medicamentos con equivalencia terapéutica*) (12), in compliance with the provisions of the Executive Decree No. 32470-S, *Reglamento para el registro Sanitario de los Medicamentos que requieren demostrar Equivalencia Terapéutica*, published in La Gaceta Nº 149, on August 4th, 2005 (1).

2. SPECIFIC OBJECTIVES

To establish standard experimental conditions for comparative dissolution profile studies as part of the regulatory requirements for therapeutic equivalence.

To set forth methodological aspects and standardized statistical criteria for the analysis of experimental data of the comparative dissolution profile studies.

To detail guidelines for the submission of the results of comparative dissolution profile studies in support of demonstrating drug dissolution similarity.

3. JUSTIFICATION

The absorption of the active ingredient of a dosage form, after the oral administration depends on:

a. The release of the active ingredient from a dosage form.
b. The dissolution of the active ingredient in digestive juices.
c. The permeability of the active ingredient through the gastrointestinal tract.

Due to the importance of the first criteria stated as depicted above, the “in vitro”

dissolution test could guide the behavior of the product "in vivo," in its research and development. The justification for “in vitro” dissolution studies is based upon the fact that, to achieve an appropriate drug absorption, it is required such to be dissolved in the biological fluid of the absorption site, regardless of the absorption mechanism through which this occurs.

4. SCOPE

This guide applies to all registration or renewal procedures for drugs in oral pharmaceutical form, containing any of the active ingredients indicated in the lists issued by the Consejo Técnico de Inscripciones (Technical Registration Council) (2 and 3). Furthermore, this guide applies to post-registration change procedures for drugs with therapeutic equivalence approved by this Ministry during validity of the sanitary registration (12).

5. GUIDELINES FOR COMPARATIVE DISSOLUTION PROFILES STUDIES

5.a. **Generalities**

During drug development, a dissolution testing is employed as a tool to spot factors in the formulation that influence and may have a critical effect on the bioavailability of the active ingredient.

In case the results of “in vitro” dissolution comparison biobatch chosen for this study do not demonstrate similarity; however, bioequivalence is concluded in the "in vivo" studies. The latter prevails as evidence of the demonstration of therapeutic equivalence. The possible causes of the in vivo-in vitro discrepancy should be addressed and fully justified by those conducting the research and development of the product in the final report of the study (10).

On the other hand, during drug development, the dissolution test is used as a tool to

identify the formulation factors that influence and may have a crucial effect on the bioavailability of the drug.

Once the composition and manufacturing process are defined, a dissolution test is employed in the quality control of scale-up and production batches to ensure batch-to-batch consistency and similar dissolution profiles. In some cases, a comparative dissolution profile test should be used for the waiver of a bioequivalence study; for instance, lower potencies of the same product (1). Therefore, dissolution profile studies can serve various purposes:

1) Test Quality Product:
    - To glean information on test batches used in bioavailability/bioequivalence studies and pivotal clinical studies, which support quality control specifications.
    - To be used as a tool in quality control to demonstrate consistency in manufacturing.
    - To glean information on the in vitro performance of the reference product used in bioavailability/bioequivalence studies and pivotal clinical studies.
2) Subrogated Bioequivalence Inference:
    - In certain cases, to demonstrate similarity between different formulations of an active ingredient and the reference drug (bioassays, e.g., variations, formulation changes during development, in vivo-in vitro correlation) (11).
    - To look into the batch-to-batch consistency of the (test and reference) products to be used as a basis for the selection of the appropriate biobatch with the best profile for the “in vivo” study.

Test methods should be developed product-related and based upon general requirements and/or specific pharmacopoeia (official books). In case these requirements prove to be unsatisfactory and/or do not reflect "in vivo" dissolution (i.e., biorelevance), it should be

considered alternative methods that prove to be discriminatory and able of detecting differences between batches with potentially acceptable and unacceptable "in vivo" yields of product. (10)

The comparative dissolution profile study should be devising to assess the behavior of equivalence pharmaceutical products to enable discrimination of the differences between the two tested products.

If possible, dissolution tests should be performed under simulated physiological conditions. This allows interpretation of dissolution data in relation to potential in vivo performance of the product. However, duly justified changes in the simulation of gastrointestinal conditions should be made in routine quality dissolution tests when strict adherence to the conditions assessed in the study protocol is not possible (9).

Due to the pH, the temperature, agitation, composition, and volume of the dissolution medium, are variables that significantly perturb the "in vitro" behavior of the drug, the study design should be matched to physiological conditions.

The dissolution equipment accepted for this kind of studies are United States Pharmacopeia (USP) section I and II. The features and specifications of this equipment should be standardized to control the physical variables that may affect the results; for instance, vibrations and other factors that affect the hydrodynamic properties. Standardization includes the equipment qualification and calibration process.

The dissolution method employed to perform the “in vitro” study should be validated in accordance with the requirements of the regulations on this area and their updates (5).

5.b. Experimental Conditions to Perform “In Vitro” Dissolution Profile Studies

"In vitro" dissolution studies of the reference and test product must be carried out under the following conditions:

5.b.1. **Equipment**

The basket apparatus, USP section I, it is recommended for capsules and other products with a tendency to float.

The paddle apparatus, USP section II, it is recommended for tablets, unless due to the way they disintegrate, a buildup of the particles is observed at the bottom of the beaker; in the latter case, the basket apparatus can be used.

The dissolution apparatus to be used must comply with the specifications and requirements set forth in USP Chapter <711> (6) and be qualified and calibrated.

5.b.2. **Agitation:** 75-100 r.p.m. if apparatus I is used; and 50-75 r.p.m. if apparatus II is used. In the study protocol, the value used must be duly justified.

5.b.3. **Volume:** 900 ml. Under certain debarments where a different volume is justified, as long as it is not less than 500 ml.

5.b.4. **Temperature:** 37ºC ± 0,5ºC. The value used should be duly justified in the study protocol.

5.b.5. **Number of Units to be Assessed:** 12 units.

5.b.6. **Dissolution Media:**

For the purpose of determining similarity, the "in vitro" dissolution study should be conducted in each of the following media:

5.b.6.1. HCI solution at pH 1.2. Prepared according to USP specifications for simulated gastric fluid without enzymes (SGF w/o enzyme).

5.b.6.2. Acetate buffer solution at pH 4.5. Prepared according to USP.

5.b.6.3. Phosphate buffer solution at pH 6.8. Prepared according to USP specifications for Simulated Intestinal Fluid without Enzymes (SIF w/o enzymes).

The addition of surfactants is not accepted (surfactants). In case of gelatin capsules or gelatin-coated tablets, the use of enzymes may be accepted. (10)

The use of water as the dissolution media is not recommended because test conditions such as pH and surface tension may vary depending on the water source and may switch during the dissolution test itself, due to the influence of active and inactive ingredients. (10)

5.b.7. **Sampling Times:**

The frequency and total sampling time for both, the test and reference products, must be such that an appropriate dissolution profile enables the similarity criteria to be applied. Sampling times should be exactly the same for both products; in addition, it should be sufficient to obtain consistent dissolution profiles at least every 15 minutes. On the other hand, more frequent sampling is recommended during the period of greatest change in the dissolution profile.

For fast dissolving products, where complete dissolution occurs within 30 minutes, it may be vital to generate a suitable profile by sampling at 5 or 10-minute intervals. (10)

A "quite fast" dissolving drug is considered when more than 85% of the amount indicated on the label dissolves in 15 minutes. In cases where the above is evidenced, both for the test and

reference product, the similarity of dissolution profiles can be accepted as demonstrated without any statistical calculation (F2). (10)

In addition, the absence of relevant differences (similarity) should be demonstrated in cases where more than 15 minutes, but not more than 30 minutes, are required to achieve near complete dissolution (at least 85% of the stated amount). F2 tests or other suitable tests should be used to demonstrate similarity of the test and reference drug profile.

The interpretation that dissolution profile differences imply or have clinical/therapeutic relevance is not acceptable, as these studies are only in vitro, they do not demonstrate an in vitro/in vivo correlation. (10)

The following times are recommended:

5.b.7.1. Immediate-Release Dosage Forms 10, 15, 20, 30, 45 and 60 minutes.

5.b.7.2. 12 hours Extended-Release Dosage Forms: 1, 2, 4, 6 and 8 hours.

5.b.7.3. 24 hours Extended-Release Dosage Forms: 1, 2, 4, 6, 8 and 16 hours.

In the study protocol, values different from those indicated should be duly justified. Likewise, calculations should only consider one more sample after each product (test and reference) is 85% dissolved. Calculations should include the first sampling time.

5.b.7.4. Enteric-Coated Products

The recommended conditions are acidic medium (pH 1.2) for 2 hours and buffer solution medium at pH 6.8. Both products must be subjected to the dissolution test in the acid phase and comply with the official specifications for this kind of products. (9)

For the comparative dissolution profile conducted with phosphate buffer solution at pH 6.8, it is recommended sampling times of 10, 15, 20, 30, 45, and 60 minutes.

In the study protocol, values different from those indicated should be duly justified. Likewise, calculations should only consider one more sample after each product (test and reference) is 85% dissolved. Calculations should include the first sampling time.

6. ASSESSMENT RESULTS

The results will be considered valid if the following conditions are compiled:

a. The data used to obtain the dissolution profile curve should be expressed as percentage (to at least one decimal place) of the amount declared on the label.
b. The percentage dissolved, at the same sampling time, of at least 3 points of the curve for each product, excluding time zero, is used.
c. Only one additional value is used after 85% dissolution of both products.
d. The coefficient of variation of the average of the results for each time should not be more than 20% for the first value used in the formula and should not be more than 10% for the following values.
e. The comparative analysis of the dissolution profiles should be carried out using the similarity factor (f2) and the difference factor (f1), which are calculated with the following equations:

$$f2 = 50LOG\left\{\left[1 + \frac{1}{n}\sum_{t=1} n(Rt - Tt)^2\right]^{-0.5} x\ 100\right\}$$

Where: R_t and T_t are the average values of the accumulated percentage of dissolved active ingredient (12 units), at time t, the reference product and the test product, respectively.

$$f1 = \left\{ \left[\sum_{t=1} n|Rt - Tt| \right] \Big/ \left[\sum_{t=1} n\, Rt \right] \right\} x100$$

Where n is the number of sampling times, R_t is the dissolution value of the reference product at time t and T_t is the dissolution value of the test product at time t. (9)

f. Assessment Criteria

The similarity of the dissolution profiles obtained under the conditions outlined in the previous sections is assessed bearing in mind the following criteria:

An f2 value of 50 or more (50-100) reflects the similarity of the two curves; in that way, the equivalence of the "in vitro" performance of the two products.

The difference factor calculates the percentage difference between two curves at each time and it is a measure of the relative error between two curves. Such difference is assessed bearing in mind the following criteria:

A value of f1 from 0 to 15 indicates that there is no significant difference between the two curves.

When the $f2$ statistic is not appropriate, similarity can be compared using model-independent or model-dependent methods; for example, multivariate statistical comparison of Weibull function parameters, or percent dissolved at different times or sampling points, would be alternative methods to the $f2$ statistic for demonstrating dissolution similarity, which may be acceptable, if statistically valid and duly justified.

In these cases, the acceptance limits of similarity should be pre-defined and justified within the protocol and should not be higher than 10% of difference. Besides, the dissolution variability of the test and reference product data should also be similar.

A lower variability of the test product may be acceptable. Evidence should be provided regarding that the statistical software used in the study, has been validated.

7. DOCUMENTATION TO BE SUBMITTED:

The manufacturer or holder of the drug must submit the requirements set forth in the Executive Decree 32470-S (1), for the assessment of the comparative dissolution profile studies report.

The comparative dissolution profile study and its results must be presented in a final report, which must be submitted with the "

"attached to this Guide duly completed. Besides, it has to indicate the page number(s) of the final report, in which the following sections are found:

a) Title of the study
b) ID number of the protocol conducted.
c) Name, address, and telephone number of the center(s) where the study was conducted.
d) Name, title, address, e-mail address, and telephone number of the following persons:
    i. Lead investigator (study leader)
    ii. Collaborating investigators (if additional personnel collaborated)
    iii. Author(s) of the report
    iv. Promoter (sponsor)
    v. Designated supervisor (study auditor)
e) Period in which the study was carried out (dates)
f) Certification document of the designated supervisor regarding the authenticity of the final report as a whole.

g) Description of reference and test products:

   i. International Nonproprietary Name (INN), or in its absence, another internationally accepted generic name.
   ii. Chemical name
   iii. Trade name
   iv. Qualitative-quantitative composition of the test product
   v. Qualitative composition of the reference product
   vi. Batch number and batch size
   vii. Pharmaceutical form
   viii. Release form
   ix. Administration route
   x. Storage conditions
   xi. Expiration date
   xii. Manufacturing laboratory and country of origin

h) Summary of the procedures carried out for the study.

i) Decision-making criteria

j) Comparative study results of dissolution profiles. For each time interval, the following information should be submitted in tabular form:

   i. Number of units of each product used.
   ii. The percentage dissolved of what is labeled for each unit (to at least one decimal place).
   iii. Average percent dissolved.
   iv. Variation coefficient

k) Statistical analysis and values of f1 and f2 in the different media.

l) Conclusions

m) Bibliography

n) Annexes:

i. Analytical procedure validation report (5)

ii. Evidence of analytical results: Chromatograms, spectrophotometry data, among others.

iii. Certificate(s) of analysis of the reference product and the original proposed product, with the following information:

- It contains the same active ingredient as the reference product; nonetheless, the excipients or pharmacologically inactive ingredients may vary as long as they do not have an effect on the safety and efficacy of the product.
- It is identical to the reference product in concentration or content of active ingredient per dosage unit, pharmaceutical form, and administration route.
- It meets the same specifications of identity, concentration, purity, and quality of the reference product.

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La Uruca, San José, Costa Rica, Thursday, August 4th, 2005

EXECUTIVE BRANCH

DECREES

N° 32470-S

PRESIDENT OF THE REPUBLIC

AND THE MINISTER OF HEALTH

Pursuant of the powers conferred by Articles 140, paragraphs 3) and 18), of the Political Constitution; 28th second paragraph of Law No. 6227, May 2nd, 1978, General Law on Public Administration; 1º, 2º, 4º, 113 of Law N° 5395, October 30th, 1973, General Health Law; 1º, 2º and 6º of Law N° 5412, Organic Law of the Ministry of Health; and Law No. 7472, Law for the Promotion of Competition and Effective Defense of the Consumer.

Deeming

1º - It is an essential function of the State to ensure the protection of the health of the population.

2º - General Health Law establishes that a drug may legally be destined to trade, public use, and consumption, when it satisfies the regulatory requirements, or the pharmacopoeia officially declared by the Executive Branch regarding its identity and qualities, safety, and efficacy.

3º - Law for the Promotion of Competition and Effective Defense of the Consumer establishes the commitment of the Administration to rationalize the procedures for the sanitary registration of pharmaceutical products.

4º - Executive Decree Nº 28466-S, Regulatory Registration, Control, Importation, and Advertising of Medicines, establishes that it is mandatory for Multi-origin Pharmaceutical Products of Health Risk to demonstrate bioequivalence. Therefore:

The following,

REGULATION FOR THE SANITARY REGISTRATION

OF DRUGS THAT REQUIRE DEMONSTRATING

THERAPEUTIC EQUIVALENCE

CHAPTER I

General Provisions

Article 1º- The aim of the present Regulation is to establish the guidelines to be complied with in terms of therapeutic equivalence, innovative and multi-origin drugs of alternative origin that require it in order to carry out the sanitary registration process. These guidelines are complementary to the requirements established in the current sanitary registration regulations.

Article 2º- This regulation is applicable to all multi-origin and innovative pharmaceutical

products of alternative origin that require proof of therapeutic equivalence based on the health risk criteria expressed in the prioritized list that will be published for that purpose.

Article 3º- All multi-origin or innovative pharmaceutical product of alternative origin included in the prioritized list, must additionally present for its sanitary registration or renewal, the requirements established in this regulation.

Article 4º- For the purposes of these regulations, the following definitions are adopted:

1) **Health Authority:** Legally empowered entity responsible for regulating the quality, safety, and efficacy of medicines in each country. This includes reviewing studies, reviewing the conclusions of the studies, defining which laboratories can perform bioequivalence studies, and conducting inspections and audits.

2) **Bioequivalence:** Relationship between two pharmaceutical products that are pharmaceutically equivalent and whose bioavailability in terms of rate and extent, after being administered at the same molar dose and under the same conditions, are similar to such a manner that their effects would be similar.

3) **Good Clinical Practices:** Regulations that should rule the design, direction, conduct, compliance, monitoring, auditing, recording, and analysis and information of clinical trials to ensure that the data and results obtained are correct and reliable and that the rights, integrity, and confidentiality of trial subjects, are protected.

4) Good Laboratory Practice (GLP): A set of rules, operating procedures, and standardized practices appropriate to ensure that the data generated by the laboratory participating in the bioequivalence study are reproducible, complete, and of high quality.

5) **Research Center:** Private or public entity accredited by the competent authority in the country of origin and recognized by the Ministry, in order to perform bioequivalence studies.

6) **Therapeutic Equivalence:** Condition that occurs between two pharmaceutical products when they are pharmaceutically equivalent and after the administration in the same molar dose, their effects with respect to efficacy and safety, will be essentially the same, when administered to patients through the same route and under the conditions specified in the labeling.

7) **Pharmaceutical Equivalent:** A drug that contains identical amounts of the same active ingredients of the product to which it is equivalent, in identical dosage form, meets similar or comparable standards and it is administered by the same route; however, it does not necessarily have the same excipients or the same manufacturing process.

8) **Therapeutic Equivalent:** Pharmaceutical Equivalent that should produce the same clinical effects and have the same safety profile as the product to which it is equivalent, when administered according to the specified conditions in their labeling.

9) **Prioritized List:** Document issued by the Ministry in which, considering health risk criteria, the products to which the provisions contained in this regulation shall be applied, are classified.

10) **Drug or Pharmaceutical Product:** Any substance of natural, synthetic, or semi-synthetic origin and any mixture of these substances or products employed for diagnostic purposes, prevention, treatment and relief of diseases, unusual symptoms, or physical states, as well as to restore or modify organic functions in humans or animals.

11) **Ministry:** Costa Rica Ministry of Health

12) **WHO:** World Health Organization

13) **Origin Country:** Country where the product is manufactured. In the case of being manufactured by third parties or between subsidiaries, it may also be in the country where the owner or representative of the marketing product is located.

14) **Dissolution Profile:** Curve that features the dissolution process when the amount or percentage of the drug dissolved is represented graphically dissolved versus time.

15) **Product, Pharmaceutical Product, or Interchangeable Drug:** Product that is therapeutically equivalent to the reference product; moreover, it can be interchanged in clinical practice.

16) **Reference Product:** Pharmaceutical product defined by the Ministry, and which test drug is intended to demonstrate to be therapeutically equivalent.

17) **Health Risk Product:** Pharmaceutical product that meets one or more of the health risk criteria defined by the Ministry.

18) **Pharmaceutical Product or Innovative Drug:** Pharmaceutical product first authorized for marketing, in the first country of origin, on the basis of their country of origin, based on its documentation of efficacy, safety, and quality.

19) **Innovative Product of Alternative Origin:** Innovative product that is not manufactured in the first country of origin.

20) **Market Leader Product:** Product that has demonstrated quality, safety, and efficacy and it is the most widely used in Costa Rica.

21) **Multi-origin pharmaceutical product:** Pharmaceutical equivalent that may or may not be a therapeutic equivalent.

22) **Regulation:** Regulation for the sanitary registration of drugs requiring proof of therapeutic equivalence.

23) **Health Risk:** Estimation of the probability that a pharmaceutical product represents a health risk, considering its bioequivalence, as well as epidemiological, clinical, pharmacokinetic, physicochemical criteria, and those associated with its pharmaceutical form.

CHAPTER II

Therapeutic Equivalence of Drugs

Article 5º - Any multi-origin or innovative product of alternative origin that according to sanitary criteria is classified as a health risk and it is included in the prioritized list, must demonstrate therapeutic equivalence for its registration, through documentation related to in vivo and in vitro studies, as appropriate.

Article 6º - The Ministry will request in vivo therapeutic equivalence by following the pondering health risk through the publication of the prioritized list in the official newspaper *La Gaceta*.

Article 7º-The prioritized list shall consist of three sections:

1) Products that require to prove their bioequivalence through documentation of in vivo and in vitro studies. Such products may be considered therapeutic equivalents when they prove bioequivalence with documentation of in vivo and in vitro studies and comply with the provisions of this regulation.

2) Products which will be provisionally required to submit in vitro bioequivalence documents, but which afterward will demonstrate their in vivo bioequivalence. Such products cannot be considered therapeutic equivalents until they demonstrate in vivo bioequivalence and comply with the provisions of this regulation.

3) Products that require to demonstrate their bioequivalence solely through documentation of in vitro studies. The products included in this section may be deemed therapeutic equivalents when they demonstrate in vitro bioequivalence and comply with the provisions of this regulation.

Such list will be updated at least once a year, incorporating products not previously included in any of the three sections and gradually incorporating products from section 2 into section 1.

Article 8º- For the first-time, sanitary registration or renewal of multi-origin or innovative drugs of alternative origin that require showcasing therapeutic equivalence, the following conditions shall be met:

1) The proposed product should be a pharmaceutical equivalent of the reference product.

2) It should comply with the requirements of the Good Manufacturing Practices as established in the Costa Rican regulations or in WHO regulations that have the same level of requirement. For this purpose, a document issued by the sanitary authority of the country of origin of the manufacturer(s) of the proposed product must be submitted, indicating such condition.

3) It must demonstrate its in vivo and in vitro bioequivalence with respect to the reference

product, by submitting the documentation described in Chapter III of this Regulation and as established in the prioritized list and the Guide for post-registration changes.

4) The indications for the use of the proposed product should have been pre-approved for the reference product.

5) The safety information included in the labeling should be consistent and comprehensive with that of the reference product.

Article 9º- Any product that has been registered as therapeutic equivalents and that experiences a change that, according to the Post-Registration Change Guide, warrants the submission of new bioequivalence documentation, should submit the requirements outlined in Chapter III, also complying with the provisions of this regulation, the sanitary registration regulations, and the Post-Registration Change Guide.

Article 10. - The Ministry may issue a Certificate of Therapeutic Equivalence once it has verified the conditions outlined in this chapter. Such certificate shall be valid until the expiration date of the sanitary registration; however, it may be rendered null and void if at least one of the following situations is fulfilled:

1) The sanitary registration of the product is cancelled.
2) Any of the certifications of the Good Manufacturing Practices and Good Laboratory Practices, are suspended or revoked.
3) The existence of one or more alerts, technically proven, indicating a lack of equivalence of the product.
4) The existence of changes associated with the product that, according to the Post-Registration Change Guide, require the submission of new documentation to

demonstrate therapeutic equivalence according to current regulations.

5) The existence of impurities that may influence the safety and efficacy of the drug is verified.

Article 11. Only the products that have demonstrated their therapeutic equivalence according to the provisions of these regulations, may denote their character of therapeutic equivalents in the labeling.

CHAPTER III

Documents Required for Bioequivalence

Article 12. - To demonstrate the bioequivalence of a multi-origin product or an innovative product of alternative origin, the following documentation must be submitted to the Ministry:

1) Final report of the study used to obtain the bioequivalence certification, as per Annex I.
2) Document issued by the health authority, or the organization authorized for this purpose in the country of origin, certifying that the research center(s) involved comply with the Good Laboratory Practices regulations established in that country or with the regulations recommended by the WHO on this matter. If the country where the study was carried out does not issue the requested document, it will be allowed to present a Certificate issued by the sanitary authority of the country, where the centers involved in the study are located; indicating that they are authorized to carry out this kind of study.
3) Document issued by the sanitary authority or the authorized organization, for such purpose in the country of origin, certifying that the study was conducted in compliance with the regulations of the International Conference on Harmonization (ICH) on Good Clinical Practice, only in the case of in vivo bioequivalence studies. In case the country

where the study was conducted does not issue such document, it can be submitted a sworn statement from the lead investigator explicitly stating the following:

a) Protocol ID number
b) Sponsor's name
c) Protocol title
d) Name(s) of Research Center(s) involved.
e) Exact address, telephone(s), fax, and e-mail of the principal investigator.
f) Statement that the study was conducted in compliance with the International Conference on Harmonization (ICH) standards for Good Clinical Practice, only in the case of in vivo bioequivalence studies.

4) Document issued by the sanitary authority of the country of origin, certifying the drug concerned has demonstrated bioequivalence with respect to the product that such country has designated as reference, through in vivo and in vitro studies, as applicable, complying with the provisions of the prioritized list. In case the country where the study was conducted does not issue such document, it is allowed to present an affidavit from the principal investigator explicitly stating the following:

The fifth option corresponds to the leading product on the market that has proven its quality, efficacy, and safety.

a) Protocol ID number
b) Sponsor's name
c) Protocol title
d) Name(s) of Research Center(s) involved.
e) Exact address, telephone(s), fax, and e-mail of the principal investigator.

f) Statement that the subject drug has demonstrated bioequivalence with respect to the reference product, through in vivo and in vitro studies, as applicable, complying with the provisions of the prioritized list.

Such documentation should be submitted only once, regardless of whether it is a first-time registration or a renewal, provided that the subject drug has not undergone changes that require new studies to be conducted, in which case the provisions on post-registration changes should be complied with. In the case of manufacture by third parties, this documentation should be issued by the country of the product holder.

Except for the final report mentioned in item 1), all other documents required in this article should be submitted duly legalized if signed from abroad.

Article 13.-In the case that the reference product with which bioequivalence is demonstrated is not exactly the same as the one defined as such by the Ministry, the results of the comparative study of dissolution profiles between the two reference products shall also be submitted, in which it is explicitly concluded that there are no significant differences between the two drugs.

CHAPTER IV

Criteria for the Selection of the Reference Product

Article 14.-The Ministry shall select the reference product according to the following criteria in order of priority:

1) The first option should always be the innovative product manufactured in the first-country of origin, which has a complete dossier on its quality, efficacy, and safety,

provided that it is the same product registered and marketed in Costa Rica.

2) The second choice should always be the innovative product manufactured, registered, and marketed in Costa Rica.
3) The third choice shall be the innovative product manufactured in an alternative origin, registered, and marketed in Costa Rica.
4) The fourth choice and in case the above conditions are not met, the Ministry may choose as reference product the innovative product manufactured in the first country of origin or alternative origin, or the reference product suggested in the WHO lists, even if it has not been marketed in Costa Rica.
5) The fifth choice corresponds to the leading product on the market that has proven its quality, efficacy, and safety.

Article 15. - In case, the national reference product is no longer marketed in the country, the Ministry may choose a new reference product among all the products therapeutically equivalent to it, following the same order of priority of the previous article.

CHAPTER V

Waiver of Submission of Bioequivalence Requirements

Article 16. - The Ministry may waive the bioequivalence requirement if it is a product that does not require therapeutic equivalence studies, when it is demonstrated that:

1) It is a product to be administered as an aqueous solution intravenously that contains the same active ingredient in the same molar concentration as the reference product. These studies are also not required when the product is a pharmaceutical equivalent administered by other parenteral routes, as an aqueous solution and contains the same

active ingredients in the same molar concentration and the same or similar excipients in similar concentrations with respect to the reference product. Some excipients may be different, provided that the change does not affect the safety and efficacy of the product.

2) It is a pharmaceutically equivalent product in the form of a solution for oral administration containing the same active ingredient in the same concentration as the reference product. Containing only excipients that do not affect the gastrointestinal transit or the gastrointestinal permeability, as well as the absorption or stability of the active ingredient in the gastrointestinal tract.
3) It is a pharmaceutically equivalent product in powder form for reconstitution as a solution and meets one of the above criteria.
4) It is a pharmaceutical equivalent in gas form.
5) It is s pharmaceutical equivalent in the form of an aqueous solution for otic or ophthalmic use, containing the same active ingredient in the same molar concentration and essentially the same excipients in similar concentrations. Some excipients may be different, provided that the change does not affect the safety and efficacy of the product.
6) It is a pharmaceutical equivalent in the form of an aqueous solution for topical administration. It contains the same active ingredient in the same molar concentration and essentially the same excipients in similar concentrations.
7) It is a pharmaceutical equivalent in spray or nebulizer for inhalations or nasal spray, in solution form administered with or without essentially the same device, containing the same active ingredient in the same concentration and necessarily the same excipients in comparable concentrations. In addition, the product may include different excipients, provided that the change does not affect the safety and efficacy of the product.

For paragraphs 5), 6) and 7) of this article, the applicant is required to demonstrate excipients in the product are the same and are in similar concentrations to those in the reference product. In case this information cannot be provided by the applicant, it is required to conduct in vivo or in vitro studies to demonstrate that the differences in the excipients do not affect the performance of the product.

Article 17. - The Ministry may waive the requirement of in vivo bioequivalence for a particular product belonging to the prioritized list among those that require in vivo studies, if the pharmaceutical product:

1) It is a product to which an in vivo study exception applies based on the comparison of dissolution profiles for lower concentrations (potencies), as it meets all of the following criteria:
    1.1) It is a pharmaceutical product for oral use, in solid form and immediate release.
    1.2) It is a lower concentration product per dosage form than the product that has previously demonstrated in vivo bioequivalence.
    1.3) It has the same pharmaceutical form and is produced with the same origin, manufacturer, and holder with respect to another approved with in vivo bioequivalence studies.
    1.4) It demonstrates that there are no significant differences regarding to the approved product by presenting the results of a comparative dissolution profile study.
    1.5) It contains active ingredients that have a linear relationship of their bioavailability parameters within the therapeutic dose range.
    1.6) The pharmaceutical form does not have enteric coating or modified release.

1.7) It is a product to which an exception for in vivo studies based on the Biopharmaceutical Classification System.

CHAPTER VI

Final dispositions

Article 18. – Drugs previously registered with in vitro bioequivalence documentation will require at the moment of their renewal, and when required by the prioritized list, the submission of documentation demonstrating their in vivo bioequivalence. Moreover, drugs that are registered for first time and that require the submission of in vivo and in vitro bioequivalence documentation at that date, according to the prioritized list, should comply with such requirements from that first registration.

ANNEX I

Final report of in vivo and in vitro studies

Regardless of the kind and design of the bioequivalence study conducted, the results should be submitted in a final report. Likewise, information on the totality of data obtained should be reported. In the case of in vivo studies, it should be included waivers, withdrawals, discontinuations, as well as the due justification of missing data.

In case the submission of in vivo and in vitro study reports is required for a particular product and according to the prioritized list, these may be accepted separately.

Each page of the final report should be numbered and contain the following sections:

1. Study Title
2. ID Number of the protocol conducted.

3. Name, address, and telephone number of the center(s) where the study was conducted.
4. Name, title, address, and telephone number of the following persons:
    4.1. Principal investigator
    4.2. Collaborating researchers
    4.3. Author(s) of the report
    4.4. Promoter (sponsor)
    4.5. Assigned supervisor
5. Period in which the study was carried out.
6. Certification document of the assigned supervisor on the authenticity of the final report as a whole.
7. Description of the reference and test products: International Nonproprietary Name (INN). By contrast, another internationally accepted generic name and chemical name, trade name, qualitative, and quantitative composition of the test product, qualitative composition of the reference product, lot, dose, route of administration, reconstitution (if applicable), storage conditions, expiration date, manufacturer's laboratory, country of origin, total number of doses of each product administered in the study (if applicable).
8. Copy of the approval letter of the protocol by the independent Ethics Committee (if applicable).
9. Summary of the procedures carried out for the in vitro and in vivo study.
10. Decision-making criteria.
11. Results of the comparative study of dissolution profiles
12. Results (in vivo studies only):
    12.1. Sequence and period of administration per subject
    12.2. Data by subject and by study product

12.3. Individual and average pharmacokinetic parameters

12.4. Individual curves, averages, and charts

13. Pharmacokinetic analysis (in vivo studies only).

14. Statistical analysis

15. Conclusions

16. Bibliography

17. Annexes:

17.1. Analytical procedure validation report

17.2. Individual chromatograms (if applicable)

17.3. Clinical laboratory tests, reference values and specific tests (if applicable).

17.4. Certificate(s) of analysis of the reference product and the proposed product demonstrating the pharmaceutical equivalence between the two, for which the latter must be demonstrated:

17.4.1. It contains the same active ingredient as the reference product. However, the excipients or pharmacologically inactive ingredients may vary as long as they do not have an effect on the safety and efficacy of the product.

17.4.2. It is identical to the reference product in concentration or content of active ingredient per dosage unit, pharmaceutical form, and route of administration.

17.4.3. It meets the same specifications of identity, concentration, purity, and quality of the reference product.

Article 19. Valid six months after its publication.

Issued at the Presidency of the Republic, San José, on the fourth day of February of the year two thousand and five.

ABEL PACHECO DE LA ESPRIELLA. - The Minister of Health, Dra. María del Rocío Sáenz Madrigal. – first time. – (O. C. Nº 184). - C-207595. - (D32470-60180).

Nº 32474-MINAE

THE PRESIDENT OF THE REPUBLIC

AND THE MINISTER OF ENVIRONMENT AND ENERGY

Pursuant to Article 140, paragraphs 3) and 18) and 146 of the Constitution, and Article 28 of the General Law on Public Administration No. 6227.

Deeming:

1º - The Minister of the Environment and Energy is the rector of the State in charge of the Natural Resources, Energy, and Mining Sector. Therefore, of issuing environmental policies, regulations, and administration of everything related to the environment, wild areas protection, biological corridors, conservation and management of wildlife, biodiversity, marine resources in protected wild areas, among others.

2º - That the Marviva Costa Rica Association was legally constituted under the laws of Costa Rica and is registered in the Public Registry, Section of Associations under file number fifteen thousand eighty-eight, legal ID number three-zero zero two-three four one one one five.

Republic of Costa Rica
Ministry of Health
Directorate of Health Regulation

BIOEQUIVALENCE DOSSIER

INSTRUCTIONS FOR SUBMISSION AND VERIFICATION OF CONTENTS

The Regulation for the Sanitary Registration of Medicines that Require Therapeutic Equivalence (Decree 32470-S) sets forth requirements for those multi-origin (generic) or innovative medicines of alternative origin, which comprise in their formulation one or more of the active ingredients included in the *List of Active Ingredients with High Health Risk* in force and according to *Cumulative Schedule*, should submit the bioequivalence study along with the comparative dissolution profile study.

For the due process, the aforementioned Regulation requests a compendium of documents necessary to evaluate the Therapeutic Equivalent status of the processed product regarding to the official reference product.

This compendium corresponds to the item entitled “Documentación de Equivalencia Terapéutica” included in the list of items in the Checklist (*Lista de Chequeo: Documentos presentados, para el registro sanitario de medicamentos)* in force, that is enclosed with the application for sanitary registration or renewal *(Formulario de Solicitud de Registro Sanitario de Medicamentos),* and available on the official website.

This guideline is intended to enable the preparation and joint standardized submission of the technical and legal documentation of comparative bioequivalence studies and dissolution profiles and has named this compendium "*Dossier's Bioequivalence*."

Therefore, the Dossier comprises the specific legal and technical documentation that must be submitted regarding Therapeutic Equivalence, as part of the Registration Dossier, renewal of the sanitary registration, or the submission of a new bioequivalence study, based upon subsequent changes to the registration of a product previously approved as Therapeutic Equivalent by the Ministry of Health, as provided in the Therapeutic Equivalence Regulation.

The instructions for processing a request for waiver of the bioequivalence study for aqueous solutions, according to the provisions of the Therapeutic Equivalence Regulation in force, or by biowaivers according to the Biopharmaceutical Classification System, are not the subject of these instructions.

Contents of the Instructions:

1. Bioequivalence Dossier Structure

It is organized in different sections and includes two kinds of documents:

1.1 Specific Bioequivalence Dossier documents:

They are crucial documents and specifically requested by the Therapeutic Equivalence Regulations, which are of a legal and technical nature regarding the study submitted and the quality of the data produced.

1) Bioequivalence Study Results Evaluation and Reporting Form (in Spanish as FOREBI) and attached documents.
2) Comparative Dissolution Profile (CDP) Submission and Evaluation Forms
3) Good Laboratory Practices Certificate(s)
4) Good Clinical Practice Certificate(s)
5) Bioequivalence Certificate in the country of origin of the in-process product
6) Declaration of the Supervisor on the authenticity of the Final Report of the study
7) Approval Letter of the protocol by the Independent Ethics Committee
8) Analysis Certificate of the test product and the reference product corresponding to the batches utilized in the bioequivalence study.
9) Therapeutic Equivalency Fee Payment Voucher

1.2 Referenced documents to the processing file:

These are documents already requested by the regulations of the general registration or renewal procedure, should be identified by the interested party, the official who verifies the documentation, and the evaluator, as original documents organized in the Dossier of the corresponding procedure. Notwithstanding, these documents also include data requested by the Therapeutic Equivalence Regulation; therefore, they are part of the information in the Dossier.

For the purpose of preventing duplications in the documents requested, in sections of the Bioequivalence Dossier where documents of this nature are requested, a Reference Sheet should be included where the location data of the documents (Section, page number) in the File of the corresponding procedure, should be noted. Some examples of documents that can be referenced are as follows:

1) Dissolution Profile Studies (when submitted and approved by the Ministry, prior to the submission of the bioequivalence study).
2) Complete qualitative-quantitative formulation of in-process product
3) Labeling and insert project.
4) Monograph

1.3 Document Checklist:

To facilitate the organization and verification at the time of receiving the documentation at the Ministry of Health, the applicant should include as the cover page of the Bioequivalence Dossier a " Document Checklist" (see Annex 1 of these instructions), which consists of a list of the sections in which each administrative, technical, and legal document required by the Decree in force for the application for Therapeutic Equivalence should be included, which must be submitted independently of the *type of application for processing.*

2. General instructions for the submission of documentation.

The proper arrangement and compilation of the Dossier are crucial to evaluate the compliance with the requirements established by the Ministry of Health to support the Therapeutic Equivalence of a product. Likewise, all documentation submitted for a procedure related to the enrollment or renewal of the sanitary registration of a pharmaceutical product, the interested

party should follow the instructions on the documents in the Dossier, without excluding other provisions established by the Ministry of Health for related documents.

2.1 Legal Aspects

2.1.0 The evaluation of the request for Therapeutic Equivalence requires an integral technical-legal analysis of all the documents requested and submitted to demonstrate this condition, including the documentation submitted with the corresponding procedure dossier."

2.1.1 All information submitted should be considered as a sworn statement.

2.1.2 The Bioequivalence Dossier should be submitted only once, unless changes have been made to the conditions of the product subsequent to the bioequivalence study, which requires new studies, pursuant to the provisions established in the *Technical Guide for the Application of Post-Registration Changes in Immediate or Modified Release Forms of Therapeutically Equivalent Drugs*, 2011 and its updates.

2.1.3 All documents signed from abroad must be legalized or apostilled, in compliance with the General Law of Consular Service and Article 294 of the General Law on Public Administration, with the exception of the Form for the Report and Assessment of Results of Bioequivalence Studies (FOREBI) provided in Section 2 of the Dossier.

2.1.4 All documents should be submitted in Spanish, and if in another language, the translation must be attached to the original document. In case of legal documents, the translation must be official.

2.1.5 All official documents must be in force at the time they are submitted to the Ministry of Health. In case it does not have an effective date, the Ministry of Health will grant it 2 years from its issuance.

2.1.6 During the renewal of a specific product, it will be allowed for the applicant to make reference to current legal documents on file with this Ministry and for which he/she has authorization of use. In this case, the applicant must attach a *Reference Sheet* in the corresponding Section of the Dossier, where the location of the original document (Name of the document, section, page number) is noted in the File of the corresponding procedure.

2.1.7 If the document has contact information containing telephone numbers, fax numbers, physical, and electronic addresses, such data must be updated, and its verification will be a responsibility shared by the Holder and its Legal Representative.

2.2 Aspects of Form

2.2.1 The Dossier must be placed as the final section of the set of documents that make up the Dossier of the corresponding procedure.

2.2.2 As in the case of the Dossier, it must have colored divider pages between its Sections, labeled with the number and name of the corresponding Section.

2.2.3 If the volume of documents in the Dossier exceeds the capacity of the press, the interested party may separate the Dossier from the Processing Dossier and place it in a folder with a two-hole press or double screw, cluster all of its pages, which must be numbered following the folio order of the corresponding Processing Dossier, and complying with points 2.2.1 and 2.2.2.

2.2.4 Any *Reference Sheet* included in the Dossier to direct the evaluator to attached documents in any section or Annex of the corresponding dossier be numbered within the total number of pages of the Dossier.

2.3. Technical Aspects

The content of any document must coincide with the requirement established by the Ministry of Health. Thereby, if the existing document contains data that partially conforms to the requested requirement and the interested party presumes that they can be fitted to the requirement by means of other additional explanatory documents. Such documents will be provided in the same section, preceded by an explanatory and detailed letter, directed to correct such divergences. The legal, technical, and scientific relevance of such documents and the explanation provided shall be determined by the Ministry of Health.

3. Specific Instructions for Each Section of the Checklist

Section 1. Dossier Document Checklist

a) Place the Documents Checklist sheet (see ANNEX 1 of these instructions) as the cover page, preceding all the documents of the Bioequivalence Dossier. This sheet must continue with the folio of the corresponding Processing Dossier and will be filled out by the official of the Ministry of Health who receives the documents.

Section 2. Form for the Reporting and Evaluation of Results of Bioequivalence Studies (FOREBI)

a) To dispose of this Section the FOREBI, in its printed format. This form has a group of

documents requested in sub-sections, which must be submitted according to the FOREBI instructions, and together with the Self-Checklist.

b) FOREBI has a second List of Documents to Verify requested in that form, which must also be applied by the official of the Ministry of Health who receives the documentation and must be placed as a cover page of that form (see FOREBI instructions).

c) For the Waiver of the bioequivalence study of lower potencies of a reference product to the higher potency authorized by this Ministry of Health as Therapeutic Equivalent, the following must be presented in this Section 2. of the Dossier:

1. For conventional or *immediate release oral formulations*:

1.1. . Copy of the *Certificate of Therapeutic Equivalence* issued by the *Ministry of Health,* for the product of higher potency.

1.2. *Form for the request of waiver of bioequivalence study of lower potency* of the same product, and the documents requested therein.

2. For *modified release* oral formulations (e.g., extended, delayed, extended, among others.): No waiver applies due to their features and composition with active ingredients of high health risk. Therefore, it should be submitted to the FOREBI complemented with the bioequivalence study for each potency or concentration.

<u>Section 3. Comparative Dissolution Profile (CDP) Study Submission and Evaluation Form(s)</u>

a) Attach in this Section of the Dossier the *Form(s)* mentioned with the CDP study(s) carried out according to the technical document, *Technical Guide for the presentation and assessment of Comparative Dissolution Profile* studies, in force. Both documents, Form, and Guide, are available on the bioequivalence site of the Ministry of Health website.

b) For products submitted for first time the Bioequivalence and CDP requirements, and according to the reference product of the bioequivalence study submitted with FOREBI (Section 2. of the Dossier), should be submitted in this section, according to the provisions of Decree 32470-S in force:

b.1. A *CDP study* between the in-process product and the official reference product in Costa Rica when the bioequivalence study has been conducted between both products.

b.2. *Two CDP studies:* one between the product in process and the official reference product in Costa Rica, and one CDP study between reference products, when the bioequivalence study and its reference product are those provided according to the regulations established by the Health Authority of another country. The studies should be submitted as indicated in point a).

c) For products that have a CDP study between the product in process and the official reference product in Costa Rica, previously approved by the Ministry of Health, the following must be presented in this section:

c.1. *Reference Sheet* in which it must be written the location data of the Ministry of Health Approval Document of the CDP study (site and page number of the folio) in the corresponding Processing Dossier.

c.2. A CDP study between reference products, when the bioequivalence study and its reference product, are established in accordance with the regulations established by a National Regulatory Agency of another country.

<u>Section 4. Complete qualitative-quantitative formulation of in-process product</u>

a) Attach in this section the *Reference Sheet* with the exact location of the original document in the corresponding processing dossier (location and page number of the folio).

b) The Qualitative-Quantitative formula should correspond to that of a *Pharmaceutical Equivalent* to the Reference Product of the bioequivalence study.

Section 5. Draft labeling, primary and secondary packaging, and insert

a) Attach in this section a *Reference Sheet* with the exact location of the document in the processing dossier (location and page number of the folio).

b) The labeling project of the in-process product as Therapeutic Equivalent, must include the printed phrase "Therapeutic Equivalent to the Official Reference Product."

c) All safety information included in the labeling and insert should be consistent and exhaustive with that of the official reference product.

Section 6. Monograph

a) Attach a Reference Sheet with the exact location of the document in the dossier of the corresponding procedure (location and page number of the folio).

b) The monograph of the processed product as a Therapeutic Equivalent must include:

   i. The phrase "Therapeutic Equivalent to the Official Reference Product."

   ii. The same approved indications and efficacy and safety information consistent and exhaustive, as those approved by this Ministry for the official reference product.

c) The interested party may access the monographs of the reference products in the bioequivalence site of the Ministry of Health's website.

d) The interested party should be aware that any approved update to the monograph of the official Reference Product implies an update to the monograph of all the products approved by the Ministry of Health as their Therapeutic Equivalents.

e) The monograph project must comply with the format required by the current drug registration regulations.

f) In the case of a renewal application for a product that has been previously registered without a monograph, the product must submit the monograph in this section of the Dossier.

Section 7. Good Laboratory Practice (GLP) Documents

Regarding the laboratory(ies), whether contracted or owned by the holder of the in-process product, involved in analytical aspects of the bioequivalence study, and as appropriate to the nature of the studies, at least the centers that perform the CDP, bioanalytical determinations, clinical biochemistry, among others:

a) Submit a document from the Health Authority or authorized organization in the country where the laboratory(ies) is (are) located, certifying that it complies with the GLP regulations established in that country, or with the regulations recommended by the WHO in this matter and including identification data such as:
Date of issue of the document, Laboratory Name, Current address, Country, Telephone, Fax, Email; Local or WHO regulations with which it complies; Name of the certifying health authority or authorized organization; Name and signature of the person responsible in the authority or organization, address, telephone numbers, and Official seals.

b) When the sanitary authority or the authorized agency in the country where the laboratory(ies) is (are) located, establishes that they do not issue the document of point a), a Certificate issued by this sanitary authority or the authorized agency must be presented,

where it certifies the authorization of the corresponding laboratory to carry out the kind of tests, and where it includes identification data such as:

Date of issue of the document; Laboratory Name, Current address, Country, Telephone, Fax, Email; Kind of studies authorized (Dissolution Profiles, bioanalytical determinations, clinical biochemistry, among others as appropriate); Name of the authorized health authority or organization, Name, and signature of the person in charge of the authority or organization, Official seals.

c) Enclose a Reference Sheet with the exact location of the respective document in the corresponding dossier, when the product being processed has a CDP study with respect to the official reference product, previously approved by the Ministry of Health, given that the document is requested in the Form for submission and assessment of the documentation of comparative dissolution profile studies.

Chapter V

Data Analysis

In this chapter, the results of the data analysis obtained from each of the research instruments are unveiled. Furthermore, this section enacts the interpretation and analysis of the results of the translated texts by implementing the translation techniques and procedures. According to The University of Pretoria (n.d.), “Data analysis is the most crucial part of any research. Data analysis summarizes collected data. It involves the interpretation of data gathered through the use of analytical and logical reasoning to determine patterns." The vitality of this process lies in the implementation of it the data collection is streamlined.

5.1 Analysis and Interpretation of the Results

To fulfill the objectives set out at the beginning of this research, it was necessary to conduct an in-depth analysis of each text to gather information related to the function of each text and its elements. These results were collected using different data collection instruments, including two procedures and a translation technique.

5.1.1 Text Analysis

First, the texts were analyzed using the model proposed by Peter Newmark. Subsequently, each of the elements of the texts was categorized with the aid of an analysis table. In this section, the nature of the texts was determined, and each of their components was classified. The results obtained by applying the translation procedures and techniques are shown below.

Table 5. Text Analysis Chart

Text analysis	**Documents from English into Spanish**	**Documentos del español al inglés**

Text Style	Descriptive	Descriptive
Text Function	Informative	Informative
Scale of Formality	Formal	Formal
Scale of Generality or Difficulty	Opaquely technical	Opaquely technical
Scale of Emotional Tone	Factual	Factual
Translation Method	Semantic/ Communicative	Semantic/ Comunicative

Table 5 shows the results obtained from the text analysis.
Source: Researcher's creation

5.1.2 Color Coding

This instrument aids in making plain to the readers the translation procedures applied in the translated text. To conduct this technique, eleven translation procedures were applied: punctuation changes, adaptation, literal translation, transposition, modulation, amplification, omission, explicitation, compensation, equivalence, and sentence inversion. Further, to better understand the equivalence between the original and the translated text, the texts were organized as follows: first, the original text, where all the omissions can be spotted, and then the translated text, where the other translation procedures can be observed. The chart below showcases the translation procedures with their respective colors to facilitate their identification.

Table 6. Color-coding Chart

Translation procedure	**Color Assigned**
Punctuation changes	

Adaptation	
Literal Translation	
Transposition	
Explicitation	
Amplification	
Compensation	
Omission	
Modulation	
Equivalence	
Sentence inversion	

Table 6 depicts the colors used to represent the different translation procedures found in the texts.
Source: Researcher's creation

5.1.2.1 Color Coding of English into Spanish Documents

Paragraph 1

BA is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, BA can be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action (see section III. Study Design Considerations). BA data provide an estimate of the amount of the drug absorbed as well as

information related to the pharmacokinetics of the drug, the effects of food on the absorption of the drug, and dose proportionality or linearity in the pharmacokinetics of the active moieties.

La BD se define como la velocidad y el grado de absorción del principio activo o la fracción activa de un fármaco y su disponibilidad en el lugar de acción. En el caso de los fármacos que no están destinados a ser ingeridos por vía sanguínea, la BD se puede presentar a partir de mediciones científicamente válidas que reflejen la velocidad y el grado de disponibilidad del principio activo o la fracción activa en el lugar de acción del fármaco (consulte la sección III. Study Design Considerations). Los datos de BD proporcionan una estimación de la cantidad de fármaco absorbido, así como información relacionada con la farmacocinética del medicamento, los efectos de los alimentos en la absorción de éste y la proporcionalidad o linealidad de la dosis en la farmacocinética de las fracciones activas.

Paragraph 2

Sponsors can determine the BA for orally administered drug products by comparing a plasma exposure profile to that of a suitable reference product. A systemic exposure profile can be generated by measuring the concentration of active ingredients and/or active moieties over time, and when appropriate, active metabolites over time in samples collected from the systemic circulation (see section III.A.8). Systemic exposure profiles reflect both the release of the drug substance from the drug product as well as presystemic or systemic modifications to the drug substance after its release. Conducting a BA study with an intravenous (IV) reference product helps assess the impact of the route of administration on BA and defines the absolute BA of the drug released from the drug product. Conducting a BA study comparing one formulation to another enables an assessment of relative BA.

Los patrocinadores pueden determinar la BD de los fármacos administrados vía oral, comparando el perfil de exposición plasmática con el de un producto de referencia adecuado. Se puede generar un perfil de exposición sistémico midiendo la concentración de principios activos y/o fracciones activas con el paso del tiempo y, cuando sea apropiado, metabolitos activos en muestras recolectadas de la circulación sistémica, con el paso del tiempo. (consulte la sección III.A.8). Los perfiles de exposición sistémica reflejan tanto la liberación de la sustancia farmacológica como las modificaciones presistémicas o sistémicas del mismo tras su liberación. La realización de un estudio de BD con un producto de referencia intravenoso (IV) ayuda a evaluar el impacto de la vía de administración sobre la BD y define la BD absoluta de la liberación del fármaco con la del producto farmacológico. La realización de un estudio de BD comparando una formulación con otra permite evaluar la BD relativa.

Paragraph 3

C. Postapproval Changes

In the presence of certain major changes in the components, composition, manufacturing site, or method of manufacture of a drug after its approval, the sponsor must demonstrate the in vivo BE for the drug product after the change compared to the drug product before the change. Certain postapproval changes that require BE studies must be submitted in a supplement and approved by the FDA before distributing a drug product made with the change.

Information on the types of recommended in vitro dissolution and in vivo studies for demonstrating the BE for IR and MR drug products approved as NDAs for specified postapproval changes is provided in the following FDA guidances:

C. Cambios posteriores a la aprobación

En presencia de ciertos cambios importantes en los componentes, la composición, el lugar de fabricación o el método de fabricación de un fármaco posterior a su aprobación; el patrocinador debe demostrar la BE in vivo para el producto farmacéutico después el cambio y compararlo antes del cambio. Ciertos cambios posteriores a la aprobación que requieren estudios de BE deben ser presentados en un suplemento y aprobados por la FDA antes de distribuir el fármaco, con el cambio realizado.

La información sobre los tipos de estudios de disolución recomendados in vitro e in vivo para demostrar la BE de los fármacos IR y MR aprobados como NDA para cambios específicos posteriores a la aprobación se proporciona en las siguientes guías de la FDA:

Paragraph 4

BA frequently relies on PK measures such as the AUC to reflect the extent of systemic absorption and the C_{max}, and T_{max} to reflect the rate of systemic absorption. PK-based comparisons to describe relative BA assume that measuring the active moiety at the site of action is not possible and that some relationship exists between the concentration of the active moiety in the systemic circulation and the safety and efficacy of the drug. A typical PK study to determine comparative BA is conducted as a crossover study. The crossover design reduces variability in PK measures that are caused by subject-specific factors, thereby increasing the ability to discern differences in PK measures that are caused by different formulations.

Con frecuencia, la BD se basa en medidas de FC como el AUC para reflejar el grado de absorción sistémico y la **(C_{max})** y **(T_{max})** para reflejar la *velocidad* de absorción sistémica. Las comparaciones basadas en FC para describir la BD relativa suponen que la medición de la fracción activa en el lugar de acción no es posible y que existe alguna relación entre la concentración de la fracción activa en la circulación sistémica y la seguridad y eficacia del

fármaco. Un estudio típico de FC para determinar la BD comparativa, se realiza como un estudio cruzado. El diseño cruzado reduce la variabilidad en las medidas de FC que son causadas por factores específicos del sujeto, aumentando así la capacidad de identificar las diferencias en las medidas de FC que son causadas por diferentes formulaciones.

Paragraph 5

In addition to the traditional approach and the use of average BE with replicate designs, the use of a reference-scaled BE approach using a replicate design can be considered. This is an approach in which the BE acceptance limits are scaled to the variability of the reference product. This reference-scaled BE approach is typically used for drugs with a high intrasubject variability (greater than or equal to 30 percent) or drugs with a narrow therapeutic index. The appropriate review division should be consulted when planning the use of the reference-scaled BE approach.

Además del enfoque tradicional y el uso promedio de BE con diseños de réplica, se puede considerar el uso de un enfoque de BE a escala de referencia, utilizando un diseño de réplica. En otras palabras, se trata de un enfoque en el que los límites de aceptación de BE se adaptan a la variabilidad del producto de referencia. Normalmente, este enfoque de BE con escalado de referencia se utiliza para fármacos con una alta variabilidad intrasujeto (mayor o igual al 30%) o fármacos con un índice terapéutico reducido. Cuando se planifique el uso del enfoque de BE con escalado de referencia, se debe poner en contacto con la división de revisión correspondiente.

Paragraph 6

5. Single-Dose and Multiple-Dose (Steady-State) Testing

Consistent with the regulations, this guidance generally recommends single-dose, in vivo studies to assess the BA of a drug because they are generally more sensitive than steady-state studies in assessing the rate and extent of release of the drug substance from the drug product into

the systemic circulation. The sponsor is referred to section IV.C for a discussion on the conduct of studies to determine the BA of a drug of an MR product.

5. Pruebas de dosis única y dosis múltiple (estado de equilibrio)

En conformidad con la normativa, se recomienda estudios *in vivo* de dosis única para evaluar la BD de un fármaco, ya que suelen ser más sensibles que los estudios de estado de equilibrio al momento de evaluar la velocidad y el grado de liberación de la sustancia farmacológica del medicamento en la circulación sistémica. Se remite al patrocinador a la sección IV.C para una discusión sobre la realización de estudios para determinar la BD de un fármaco de un producto MR.

Paragraph 7

8. Moieties to Measure

The active ingredient that is released from the dosage form or its active moiety and, when appropriate, its active metabolites, should be measured in the biological matrix collected during the BA study.

The concentration-time profile of the active ingredient or the active moiety is more sensitive to changes in performance of the formulation. In contrast, the metabolite is more affected by metabolite formation, distribution, and elimination. The following scenarios are instances when an active metabolite(s) should be subjected to CI analyses for BA assessment:

8. Fracciones activas a medir

El principio activo que se libera de la forma de dosificación o su fracción activa o, en su caso, sus metabolitos activos, deben medirse en la matriz biológica obtenida durante el estudio de BD.

El perfil de concentración-tiempo del principio activo o de la fracción activa es más sensible a los cambios en la realización de la formulación. En cambio, el metabolito se ve más afectado por la formación, distribución y eliminación de metabolitos. Los siguientes son casos en los que un metabolito o metabolitos activos se deben someter a análisis de IC para la evaluación de BD:

Paragraph 8

c. Partial exposure

In addition to peak and total exposure, for certain classes of drugs (e.g., analgesic drug products), an evaluation of the partial exposure could be scientifically appropriate to support the determination of the relative BA of the drug product. The FDA recommends the use of partial AUC as a partial exposure measure. The time to truncate the partial AUC should be related to a clinically relevant response measure. The sponsor should collect sufficient quantifiable samples to allow an adequate estimation of the partial AUC. Sponsors should consult the appropriate review division for questions on the suitability of the response measure or the use of partial exposure.

c. Exposición parcial

Además de la exposición máxima y total, para ciertas clases de fármacos (por ejemplo, productos farmacéuticos analgésicos) una evaluación de la exposición parcial podría ser científicamente apropiada para apoyar la determinación de la BD relativa del producto farmacéutico. La FDA recomienda el uso del AUC parcial como medida de la exposición parcial. El tiempo para suspender el AUC parcial debe está relacionado con una medida de respuesta clínicamente relevante. El patrocinador debe recolectar suficientes muestras cuantificables para permitir una estimación adecuada del AUC parcial. Además, los patrocinadores deben consultar a

la división de revisión correspondiente las dudas sobre la idoneidad de la medida de respuesta o el uso de la exposición parcial.

Paragraph 9

10. Comparison of Drug Exposure Measures in BA Studies

A CI approach is recommended for BA comparisons. Log-transformation of exposure measures before statistical analysis is recommended. This guidance recommends the use of the BE criterion to compare systemic exposure measures for replicate and non-replicate BA studies of both IR and MR products. For additional information on data analysis, refer to appendix A and to the FDA guidance entitled *Statistical Approaches to Establishing Bioequivalence* (February 2001).

10. Comparación de medidas de exposición a fármacos en estudios de BD

Para las comparaciones de BD, se recomienda un enfoque de IC. Asimismo, se sugiere la transformación logarítmica de las medidas de exposición antes de realizar el análisis estadístico. Esta guía recomienda el uso del enfoque de BE para comparar medidas de exposición sistémica para estudios de BD replicados y no replicados de productos IR y MR. Para más información sobre el análisis de datos, consulte el anexo A y la guía de la FDA titulada: *Statistical Approaches to Establishing Bioequivalence* (febrero de 2001).

Paragraph 10

2. In Vitro Tests Predictive of Human In Vivo BA

IVIVC is an approach to describe the relationship between an in vitro attribute of a dosage form (e.g., the rate or extent of drug release) and a relevant in vivo measure (e.g., the plasma drug concentration or the amount of drug absorbed). Modeling of this relationship facilitates the rational development and evaluation of ER dosage forms, and less commonly, of other dosage

forms. Once an IVIVC is validated, the in vitro test serves as a surrogate for BA testing as well as a tool to screen formulations and set the dissolution and drug-release acceptance criteria.

2. Pruebas in vitro para predecir la BD in vivo en humanos

La IVIVC es un enfoque para describir la relación entre un atributo *in vitro* de una forma de dosificación (por ejemplo, la velocidad o el grado de liberación del fármaco) y una medida *in vivo* relevante (por ejemplo, la concentración plasmática del fármaco o la cantidad de fármaco absorbido). El modelo de esta relación facilita el desarrollo y la evaluación racional de las formas de dosificación de ER y, con menor frecuencia, de otras formas de dosificación. Una vez validada una IVIVC, la prueba *in vitro* sirve como sustituto para las pruebas de BD, así como de herramienta para seleccionar las formulaciones y establecer los criterios de aceptación de disolución y liberación del fármaco.

Paragraph 11

Specifically, in vitro dissolution and drug-release characterization are recommended for all ER product formulations (including prototype formulations), particularly when used to define the in vivo absorption characteristics for different product formulations. Such efforts can enable the establishment of an IVIVC. When an IVIVC or in vitro-in vivo relationship (IVIVR) is established, the in vitro test can serve not only as a quality control specification for the manufacturing process but also as an indicator of how the product will perform in vivo.

En concreto, se recomienda la disolución *in vitro* y la caracterización de la liberación del fármaco para todas las formulaciones de productos de ER (incluidas las formulaciones de prototipo), principalmente cuando se utilizan para definir las características de absorción *in vivo* para diferentes formulaciones de productos. Tales esfuerzos pueden permitir el establecimiento de una IVIVC. Cuando se establece una IVIVC o una relación *in vitro-in vivo* (IVIVR), la prueba

in vitro puede servir no sólo como especificación de control de calidad para el proceso de fabricación, sino también como indicador de cómo se comportará el producto *in vivo*.

Paragraph 12

4. Comparative Clinical Studies

In limited cases, the measurement of the active ingredients or active moieties in an accessible biological matrix (i.e., the PK approach) or a PD approach is not possible for orally administered drug products; in such cases, clinical endpoints can be used. These clinical trials would generally involve larger sample sizes compared to PK and PD studies due to variability in the measurement of the endpoints. Because these circumstances do not occur very often, use of this approach is expected to be rare (section VI.D).

4. Estudios clínicos comparativos

En pocos casos, la medición de los principios activos o de las fracciones activas en una matriz biológica accesible (es decir, el enfoque FC) o un enfoque FD no es posible para los fármacos administrados por vía oral; en estos casos, se pueden utilizar criterios de valoración clínicos. Estos ensayos clínicos generalmente implican tamaños de muestras más grandes en comparación con los estudios FC y FD debido a la variabilidad en la medición de los criterios de valoración, ya que estos casos no ocurren muy a menudo, así que se espera que el uso de este enfoque sea poco frecuente (sección VI.D).

Paragraph 13

2. MR Formulations

The use of in vitro data could be acceptable for MR drug products with specific postapproval changes. Specific information on the use of in vitro data for postapproval changes to MR drug products is delineated in the FDA's guidance entitled *SUPAC-MR: Modified Release Solid Oral*

Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (October 1997). The same principles described in the guidance might also apply to pre-approval changes. Additional considerations for the use of in vitro data in support of determining a drug's BA are described below.

2. Formulaciones de MR

El uso de datos *in vitro* podría ser aceptable para fármacos MR con cambios específicos posteriores a la aprobación. La información específica sobre el empleo de datos *in vitro* para cambios posteriores a la aprobación de fármacos MR se describe en la guía de la FDA titulada: *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (octubre de 1997). Los principios descritos en la guía, también se podrían aplicar a los cambios previos a la aprobación. A continuación, se presentan algunas consideraciones para el uso de datos *in vitro* con ayuda de la determinación de la BD de un fármaco.

Paragraph 14

E. Combination and Co-administered Drug Products

Two or more active ingredients can be formulated as a single drug product, which is referred to for the purposes of this guidance document as a fixed combination product. Generally, the purpose of an in vivo BA study involving a fixed combination product is to compare the rate and extent of absorption of each active drug ingredient or therapeutic moiety in the combination drug product to the rate and extent of absorption of each active drug ingredient or therapeutic moiety administered concurrently as separate, single-ingredient preparations.

E. Medicamentos combinados y coadministrados

Dos o más principios activos se pueden formular como un sólo medicamento, que a efectos de este documento de orientación se denomina producto de combinación fija. Por lo general, el objetivo de un estudio de BD *in vivo* con un producto de combinación fija es comparar la velocidad y el grado de absorción de cada principio activo o fracción terapéutica en el medicamento combinado con la tasa y el grado de absorción de cada principio activo o fracción terapéutica administrados como preparaciones separadas de un solo ingrediente.

Paragraph 15

A two-arm, single-dose, crossover, fasted study of the fixed combination versus the single-ingredient drug products administered concurrently or an approved combination product containing the same active ingredients is recommended. This study should use the highest strength of the fixed combination with matching doses of the individual drug products. Certain alternative study designs could also be considered depending on the specific situation. For instance, when there are no drug interactions between the components of a fixed combination consisting of two components, a three-arm study design comparing the combination drug product versus the single-ingredient drug products administered separately could be appropriate.

Se recomienda un estudio cruzado de dos grupos, de dosis única, en ayunas, de la combinación fija versus los medicamentos de un solo ingrediente administrados simultáneamente o un producto de combinación aprobado que contenga los mismos ingredientes activos. Este estudio debe utilizar la concentración más alta de la combinación fija con dosis iguales de los medicamentos individuales. También, se podrían considerar algunos diseños de estudio alternativos dependiendo de la situación específica. Por ejemplo, cuando no hay interacciones farmacológicas entre los componentes de una combinación fija formada por dos componentes, podría ser apropiado un diseño de estudio de tres grupos que compare el producto farmacológico

combinado versus los productos farmacológicos de un solo ingrediente administrados por separado.

5.1.2.2 Color Coding of Spanish into English Documents

Paragraph 1

Durante el desarrollo de un medicamento la prueba de disolución es usada como una herramienta para identificar factores en la formulación que influyan y podrían tener un efecto crítico en la biodisponibilidad del principio activo.

En caso de que los resultados de la comparación de disolución “in vitro” del biolote elegido para este estudio, no demuestren similitud, pero se concluye bioequivalencia en los estudios “in vivo”, este último prevalece como evidencia de la demostración de equivalencia terapéutica. Las posibles causas de la discrepancia in vivo-in vitro deben abordarse y ser ampliamente justificadas por quienes realizan la investigación y desarrollo del producto, en el informe final del estudio (10).

Durante el desarrollo de un medicamento, se usa la prueba de disolución como una herramienta para identificar los factores de formulación que influyen y pueden tener un efecto crucial en la biodisponibilidad del medicamento.

During drug development, a dissolution testing is employed as a tool to spot factors in the formulation that influence and may have a critical effect on the bioavailability of the active ingredient.

In case the results of “in vitro” dissolution comparison biobatch chosen for this study do not demonstrate similarity; however, bioequivalence is concluded in the "in vivo" studies. The latter prevails as evidence of the demonstration of therapeutic equivalence. The possible causes

of the in vivo-in vitro discrepancy should be addressed and fully justified by those conducting the research and development of the product in the final report of the study (10).

On the other hand, during drug development, the dissolution test is used as a tool to identify the formulation factors that influence and may have a crucial effect on the bioavailability of the drug.

Paragraph 2

Tan pronto como se definan la composición y el proceso de fabricación, se utiliza una prueba de disolución en el control de calidad de la ampliación y de los lotes de producción para garantizar la consistencia entre lotes y que los perfiles de disolución sean similares. Además, en ciertos casos, se puede usar una prueba de perfiles de disolución comparativo para exención de un estudio de bioequivalencia, por ejemplo, potencias menores de un mismo producto (1). Por lo tanto, los estudios de perfiles de disolución pueden servir para varios propósitos:

1) Prueba de calidad del producto:

- Obtener información sobre los lotes de prueba utilizados en los estudios de biodisponibilidad/ bioequivalencia y estudios clínicos pivótales, que respalden las especificaciones de control de calidad.
- Para ser utilizado como una herramienta en el control de calidad para demostrar consistencia en la fabricación.
- Obtener información sobre el comportamiento in vitro del producto de referencia utilizado en los estudios de biodisponibilidad/ bioequivalencia y estudios clínicos pivótales.

Once the composition and manufacturing process are defined, a dissolution test is employed in the quality control of scale-up and production batches to ensure batch-to-batch

consistency and similar dissolution profiles. In some cases, a comparative dissolution profile test should be used for the waiver of a bioequivalence study; for instance, lower potencies of the same product (1). Therefore, dissolution profile studies can serve various purposes:

1) Test Quality Product:

- To glean information on test batches used in bioavailability/bioequivalence studies and pivotal clinical studies, which support quality control specifications.
- To be used as a tool in quality control to demonstrate consistency in manufacturing.
- To glean information on the in vitro performance of the reference product used in bioavailability/bioequivalence studies and pivotal clinical studies.

Paragraph 3

El estudio de perfiles de disolución comparativos debe ser diseñado para evaluar el comportamiento de productos equivalentes farmacéuticos de manera que permita discriminar las diferencias entre los dos productos ensayados.

En lo posible, las pruebas de disolución se deberán realizar simulando condiciones fisiológicas. Esto permite la interpretación de los datos de disolución en relación a un potencial rendimiento in vivo del producto. Sin embargo, pueden realizarse cambios debidamente justificados en la simulación de las condiciones gastrointestinales en las pruebas de disolución rutinarias de calidad, cuando no es posible una adherencia estricta a las condiciones evaluadas en el protocolo de estudio (9).

Debido a que el pH, la temperatura, la agitación, la composición y el volumen del medio de disolución son variables que afectan significativamente el comportamiento “in vitro” del medicamento, el diseño del estudio debe corresponderse a las condiciones fisiológicas.

The comparative dissolution profile study should be devising to assess the behavior of equivalence pharmaceutical products to enable discrimination of the differences between the two tested products.

If possible, dissolution tests should be performed under simulated physiological conditions. This allows interpretation of dissolution data in relation to potential in vivo performance of the product. However, duly justified changes in the simulation of gastrointestinal conditions should be made in routine quality dissolution tests when strict adherence to the conditions assessed in the study protocol is not possible (9).

Due to the pH, the temperature, agitation, composition, and volume of the dissolution medium, are variables that significantly perturb the "in vitro" behavior of the drug, the study design should be matched to physiological conditions.

Paragraph 4

Artículo 1º—El objetivo del presente Reglamento es establecer las directrices que deben cumplir en materia de equivalencia terapéutica, los medicamentos multiorigen e innovadores de origen alterno que así lo requieran para realizar el trámite de registro sanitario. Estas directrices son complementarias a los requisitos establecidos en la normativa de registro sanitario vigente.

Artículo 2º—El presente reglamento se aplica a todos los productos farmacéuticos multiorigen e innovadores de origen alterno que requieran probar su equivalencia terapéutica con base en los criterios de riesgo sanitario expresados en el listado priorizado que será publicado para tal efecto.

Artículo 3º—Todo producto farmacéutico multiorigen o innovador de origen alterno que se encuentre incluido en el listado priorizado, debe presentar para su registro sanitario o

renovación, además de los requisitos exigidos en la regulación vigente, los requisitos establecidos en el presente reglamento.

Article 1º- The aim of the present Regulation is to establish the guidelines to be complied with in terms of therapeutic equivalence, innovative and multi-origin drugs of alternative origin that require it in order to carry out the sanitary registration process. These guidelines are complementary to the requirements established in the current sanitary registration regulations.

Article 2º- This regulation is applicable to all multi-origin and innovative pharmaceutical products of alternative origin that require proof of therapeutic equivalence based on the health risk criteria expressed in the prioritized list that will be published for that purpose.

Article 3º- All multi-origin or innovative pharmaceutical product of alternative origin included in the prioritized list, must additionally present for its sanitary registration or renewal, the requirements established in this regulation.

Paragraph 5

1) **Autoridad sanitaria:** Entidad facultada legalmente que tiene la responsabilidad de regular sobre la calidad, seguridad y eficacia de los medicamentos en cada país. Esto incluye la revisión de los estudios, la revisión de las conclusiones de los estudios, la definición de qué laboratorios pueden hacer estudios de bioequivalencia y la realización de inspecciones y auditorías.

2) **Bioequivalencia:** Relación entre dos productos farmacéuticos que son equivalentes farmacéuticos y cuya biodisponibilidad en términos de tasa y grado, después de ser administrados a la misma dosis molar, bajo las mismas condiciones, son similares a tal grado, que sus efectos serían esencialmente los mismos.

1) Health Authority**:** Legally empowered entity responsible for regulating the quality, safety**,** and efficacy of drugs in each country. This includes reviewing studies, reviewing the conclusions of the studies, defining which laboratories can perform bioequivalence studies, and conducting inspections and audits.

2) Bioequivalence**:** Relationship between two pharmaceutical products that are pharmaceutically equivalent and whose bioavailability in terms of rate and extent, after being administered at the same molar dose and under the same conditions, are similar to such a manner that their effects would be similar.

Paragraph 6

6) **Equivalencia terapéutica:** Condición que se da entre dos productos farmacéuticos cuando son equivalentes farmacéuticos y después de la administración en la misma dosis molar, sus efectos con respecto a la eficacia y la seguridad, serán esencialmente los mismos, cuando es administrado a los pacientes por la misma vía y bajo las condiciones especificadas en el etiquetado.

7) **Equivalente farmacéutico:** Medicamento que contiene cantidades idénticas de los mismos principios activos del producto al que es equivalente, en idéntica forma farmacéutica, cumple con estándares similares o comparables y es administrado por la misma vía, pero no necesariamente tiene los mismos excipientes ni el mismo proceso de fabricación.

6) Therapeutic Equivalence**:** Condition that occurs between two pharmaceutical products when they are pharmaceutically equivalent and after the administration in the same molar dose, their effects with respect to efficacy and safety, will be essentially the same, when administered to patients through the same route and under the conditions specified in the labeling.

7) Pharmaceutical Equivalent**:** A drug that contains identical amounts of the same active ingredients of the product to which it is equivalent, in identical dosage form, meets similar or comparable standards and it is administered by the same route**;** however**,** it does not necessarily have the same excipients or the same manufacturing process.

Paragraph 7

8) **Equivalente terapéutico:** Equivalente farmacéutico que debe producir los mismos efectos clínicos y poseer el mismo perfil de seguridad que el producto al que es equivalente, cuando se administra según las condiciones especificadas en su rotulación.

9) **Listado priorizado:** Documento emitido por el Ministerio en el que, siguiendo criterios de riesgo sanitario, se clasifican los productos a los cuales se les aplicarán las disposiciones contenidas en el presente reglamento.

10) **Medicamento o producto farmacéutico:** Toda sustancia de origen natural, sintético o semisintético, y toda mezcla de esas sustancias o productos que se utilizan para el diagnóstico, prevención, tratamiento y alivio de las enfermedades, síntomas o estados físicos anormales, así como para restablecer o modificar funciones orgánicas en las personas o animales.

8) Therapeutic Equivalent**:** Pharmaceutical Equivalent that should produce the same clinical effects and have the same safety profile as the product to which it is equivalent, when administered according to the specified conditions in their labeling.

9) Prioritized List**:** Document issued by the Ministry in which considering health risk criteria, the products to which the provisions contained in this regulation shall be applied, are classified.

10) Drug or Pharmaceutical Product**:** Any substance of natural, synthetic, or semi-synthetic origin and any mixture of these substances or products employed for diagnostic purposes, prevention, treatment and relief of diseases, unusual symptoms, or physical states, as well as to restore or modify organic functions in humans or animals.

Paragraph 8

Artículo 9º—Todos aquellos productos que hayan sido registrados como equivalentes terapéuticos y que sufran cambios que, según la Guía de cambios post-registro, ameriten la presentación de nueva documentación de bioequivalencia, deberán presentar los requisitos descritos en el capítulo III, atendiendo también lo dispuesto en el presente reglamento, en la normativa de registro sanitario y en la Guía de cambios post-registro.

Artículo 10. — El Ministerio podrá emitir un Certificado de equivalencia terapéutica una vez que haya constatado las condiciones descritas en el presente capítulo. Dicho certificado será vigente hasta la fecha de vencimiento del registro sanitario, sin embargo éste podrá quedar sin efecto si se cumple al menos una de las siguientes situaciones:

Article 9º- Any product that has been registered as therapeutic equivalents and that experiences a change that, according to the Post-Registration Change Guide, warrants the submission of new bioequivalence documentation, should submit the requirements outlined in Chapter III, also complying with the provisions of this regulation, the sanitary registration regulations**,** and the Post-Registration Change Guide.

Article 10. - The Ministry may issue a Certificate of Therapeutic Equivalence once it has verified the conditions outlined in this chapter. Such certificate shall be valid until the expiration

date of the sanitary registration; however, **it may be rendered null** and void if at least one of the following situations is fulfilled:

Paragraph 9

7) Es un equivalente farmacéutico en aerosol o nebulizador para inhalaciones o rociador nasal, en forma de solución administrado con o sin esencialmente el mismo dispositivo, que contiene el mismo principio activo en la misma concentración y esencialmente los mismos excipientes en concentraciones comparables. El producto puede incluir diferentes excipientes, siempre que el cambio no afecte la seguridad y eficacia del producto.

Para los incisos 5), 6) y 7) del presente artículo, se requiere que el solicitante demuestre que los excipientes en el producto son esencialmente los mismos y están en concentraciones comparables a los del producto de referencia. En caso de que esta información no pueda ser proporcionada por el solicitante, se requiere que el solicitante lleve a cabo estudios in vivo o in vitro para demostrar que las diferencias en los excipientes no afectan el desempeño del producto.

7) It is a pharmaceutical equivalent in spray or nebulizer for inhalations or nasal spray in solution form administered with or without essentially the same device, containing the same active ingredient in the same concentration and necessarily the same excipients in comparable concentrations. In addition, the product may include different excipients provided that the change does not affect the safety and efficacy of the product.

For paragraphs 5), 6) and 7) of this article, the applicant is required to demonstrate excipients in the product are the same and are in similar concentrations to those in the reference product. In case this information cannot be provided by the applicant, it is

required to conduct in vivo or in vitro studies to demonstrate that the differences in the excipients do not affect the performance of the product.

Paragraph 10

6. Documento de certificación del monitor designado sobre la autenticidad del conjunto del informe final.
7. Descripción de los productos referencia y prueba: denominación común internacional (DCI), o en su defecto, otra denominación genérica internacionalmente reconocida y nombre químico, nombre comercial, composición cuali – cuantitativa del producto de prueba, composición cualitativa del producto de referencia, lote, dosis, vía de administración, reconstitución (si aplica), condiciones de conservación, fecha de vencimiento, laboratorio fabricante, país de origen, número total de dosis de cada producto administradas en el estudio (si aplica).

6. Certification document of the assigned supervisor on the authenticity of the final report as a whole.
7. Description of the reference and test products: International Nonproprietary Name (INN). By contrast, another internationally accepted generic name and chemical name, trade name, qualitative and quantitative composition of the test product, qualitative composition of the reference product, lot, dose, route of administration, reconstitution (if applicable), storage conditions, expiration date, manufacturer's laboratory, country of origin, total number of doses of each product administered in the study (if applicable).

Paragraph 11

Artículo 18. — Los medicamentos que se hayan registrado con documentación de bioequivalencia in vitro, requerirán al momento de su renovación y cuando el listado priorizado

así lo requiera, la presentación de documentación que demuestre su bioequivalencia in vivo. Asimismo, los medicamentos que se registren por primera vez y que requieran la presentación de la documentación de bioequivalencia in vivo e in vitro a esa fecha, según lo dispuesto en el listado priorizado, deberán cumplir con tales requisitos desde ese primer registro.

ANEXO I

Informe final de los estudios in vivo e in vitro

De forma independiente al tipo y diseño del estudio de bioequivalencia ejecutado, los resultados deben reportarse en un informe final.

Debe reportarse la información de la totalidad de datos obtenidos. En el caso particular de los estudios in vivo se deben incluir los abandonos, retiros, descontinuaciones, así como la debida justificación de datos faltantes

Article 18. – Drugs previously registered with in vitro bioequivalence documentation will require at the moment of their renewal, and when required by the prioritized list, the submission of documentation demonstrating their in vivo bioequivalence. Moreover, drugs that are registered for first time and that require the submission of in vivo and in vitro bioequivalence documentation at that date, according to the prioritized list, should comply with such requirements from that first registration.

ANNEX I

Final report of in vivo and in vitro studies

Regardless of the kind and design of the bioequivalence study conducted, the results should be submitted in a final report.

Likewise, information on the totality of data obtained should be reported. In the case of in

vivo studies, it should be included waivers, withdrawals, discontinuations, as well as the due justification of missing data.

Paragraph 12

El presente Instructivo está dirigido a facilitar a los interesados la preparación y presentación estandarizada y conjunta de la documentación técnica y legal de estudios de bioequivalencia y perfiles de disolución comparativos, y ha denominado a este compendio "Dossier de Bioequivalencia".

El Dossier reúne por tanto, la documentación legal y técnica específica que se debe presentar en materia de Equivalencia Terapéutica, como parte del Expediente de trámite de inscripción o renovación del registro sanitario, o bien, para la presentación de un nuevo estudio de bioequivalencia, motivado por cambios posteriores al registro, de un producto previamente aprobado como Equivalente Terapéutico por el Ministerio de Salud, según lo dispuesto en el Reglamento de Equivalencia Terapéutica.

This guideline is intended to enable the preparation and joint standardized submission of the technical and legal documentation of comparative bioequivalence studies and dissolution profiles and has named this compendium *"Dossier's Bioequivalence*."

Therefore, the Dossier comprises the specific legal and technical documentation that must be submitted regarding Therapeutic Equivalence as part of the Registration Dossier, renewal of the sanitary registration, or the submission of a new bioequivalence study based upon subsequent changes to the registration of a product previously approved as Therapeutic Equivalent by the Ministry of Health, as provided in the Therapeutic Equivalence Regulation.

Paragraph 13

2.1.5 Todo documento oficial debe estar vigente en su presentación al Ministerio de Salud. En caso no tener fecha de vigencia, el Ministerio de Salud le otorgará 2 años a partir de su emisión.

2.1.6 Durante la renovación de un producto específico, será permitido que el solicitante haga referencia a documentos legales vigentes que consten en archivos de este Ministerio y sobre los cuales tenga autorización de uso. En este caso el solicitante debe adjuntar en el Apartado correspondiente del Dossier, una Hoja de Referencia donde se anote la ubicación del documento original (Nombre del documento, Apartado o sección, número de página) en el Expediente del trámite que corresponda.

2.1.5 All official documents must be in force at the time they are submitted to the Ministry of Health. In case it does not have an effective date, the Ministry of Health will grant it 2 years from its issuance.

2.1.6 During the renewal of a specific product, it will be allowed for the applicant to make reference to current legal documents on file with this Ministry and for which he/she has authorization of use. In this case, the applicant must attach a Reference Sheet in the corresponding Section of the Dossier, where the location of the original document (Name of the document, section, page number) is noted in the File of the corresponding procedure.

Paragraph 14

2.3. Aspectos Técnicos

El contenido de todo documento debe coincidir con el requisito establecido por el Ministerio de Salud. En caso de existir en el documento datos que se ajustan parcialmente con el requisito solicitado y el interesado presume, que pueden ser ajustados al requisito mediante otros documentos explicativos adicionales, dichos documentos serán dispuestos en el mismo apartado,

antecedidos por una carta explicativa y pormenorizada, dirigida a subsanar tales divergencias. La pertinencia legal, técnica y científica de tales documentos y la explicación remitida, será la determinada por el Ministerio de Salud.

2.3. Technical Aspects

The content of any document must coincide with the requirement established by the Ministry of Health. Thereby, if the existing document contains data that partially conforms to the requested requirement and the interested party presumes that they can be fitted to the requirement by means of other additional explanatory documents. Such documents will be provided in the same section preceded by an explanatory and detailed letter, directed to correct such divergences. The legal, technical, and scientific relevance of such documents and the explanation provided shall be determined by the Ministry of Health.

Paragraph 15

a) Presentar un documento de la autoridad sanitaria o el organismo autorizado en el país donde se domicilia el laboratorio (s), en el que certifique que cumple con la normativa de BPL establecida en dicho país, o bien, con la normativa recomendada por la OMS en esta materia, y donde se incluya datos de identificación tales como:

   Fecha de emisión del documento; Nombre del Laboratorio, Dirección actual, País, Teléfono, Fax, Email; Normativa local o de la OMS con la que cumple; Nombre de la autoridad sanitaria o el organismo autorizado que certifica; Nombre y firma del responsable en la autoridad u organismo, domicilio, teléfonos, Sellos oficiales.

a) Submit a document from the Health Authority or authorized organization in the country where the laboratory (ies) is (are) located, certifying that it complies with the GLP

regulations established in that country, or with the regulations recommended by the WHO in this matter and including identification data such as:

Date of issue of the document, Laboratory Name, Current address, Country, Telephone, Fax, Email; Local or WHO regulations with which it complies; Name of the certifying health authority or authorized organization; Name and signature of the person responsible in the authority or organization, address, telephone numbers, and Official seals.

5.1.3 Glossary

The last instrument employed was a glossary to spot the most complex terminology utilized in the texts. To better comprehend the terminology in both texts English and Spanish, a glossary was devised for each language, each comprising 25 words in which the most relevant terms requiring further explanation were taken and thus deepen the meaning of some words and facilitate the understanding of these. Likewise, to aid the readers to grasp these terms the grammatical category and the definition is also determined.

5.1.3.1 Glossary from English into Spanish

Table 7. Glossary from English into Spanish

Documents from English into Spanish			
Source Language Term	**Target Language Term**	**Grammatical Category**	**Definition**
BE	Bioequivalencia	Sustantivo	Relación entre dos productos farmacéuticos que son equivalentes farmacéuticos y cuya biodisponibilidad en términos de

			tasa y grado, después de ser administrados a la misma dosis molar, bajo las mismas condiciones, son similares a tal grado, que sus efectos serían esencialmente los mismos
BD	Biodisponibilidad	Sustantivo	Cantidad y velocidad con la cuales un fármaco ingresa al organismo (se absorbe) y llega a estar disponible en el sitio de acción
In vivo	En el organismo vivo	Locución	Estudio que implica pruebas con sujetos vivos como animales, plantas o células. Se consideran los ensayos clínicos centrados en evaluar la seguridad y eficacia de un fármaco experimental en seres humanos
In vitro	En vidrio	Locución	Se refiere a una técnica para realizar un determinado experimento en un tubo de ensayo, o generalmente en un ambiente controlado fuera de un organismo vivo
PK	Farmacocinética	Sustantivo	Estudia el proceso que sigue el medicamento en el organismo desde el momento en que se ingiere o se aplica directamente en el torrente sanguíneo, hasta su excreción y eliminación del cuerpo

PD	Farmacodinámica	Sustantivo	Estudio de los efectos bioquímicos y fisiológicos de los fármacos y de sus mecanismos de acción y la relación entre la concentración del fármaco y el efecto de éste sobre un organismo
Enantiomer	Enantiómero	Sustantivo	Par de compuestos químicos cuyas estructuras moleculares tienen una relación de imagen especular no superponible entre sí
Chiral	Quiral	Adjetivo	Dicho de una estructura o de un objeto que no es superponible con su imagen especular
Racemate	Racemato	Sustantivo	Compuesto racémico o mezcla
Buffered	Tamponado	Adjetivo	Material para reducir los golpes o daños debido al contacto
Bilayer	Bicapa	Adjetivo	Doble capa molecular que forma la membrana plasmática
Scale-up	Escalado	Sustantivo	Aumento según una proporción fija
Full-Scale	A gran escala	Adjetivo	Implica el uso completo de los recursos disponibles
Bead	Perla	Sustantivo	Una forma de dosificación sólida en forma de una pequeña esfera
Swallowed	Ingerir	Verbo	Introducir por la boca para hacerlo llegar al estómago

Steady-state	Estado de equilibrio	Adjetivo	Estado o condición de un sistema o proceso que no cambia en el tiempo
Waive	Exentar	Verbo	Declarar la ausencia de responsabilidad
Chewable	Masticable	Adjetivo	Que se puede masticar
Granules	Gránulos	Sustantivo	Partícula de materia de pequeño tamaño
Active Moiety	Fracción activa	Sustantivo	Molécula o ion central de un fármaco, es decir, la molécula del fármaco sin ciertos apéndices que es responsable de la acción fisiológica o farmacológica de una sustancia farmacológica
Truncate	Suspender	Verbo	Detener o diferir por algún tiempo una acción u obra
Enroll	Incribirse	Verbo	Registrar o entrar en una lista, catálogo o rollo
Booster	Refuerzo	Sustantivo	Dispositivo auxiliar para aumentar la fuerza, potencia, presión o eficacia
Deemed	Considerar	Verbo	Llegar a pensar o juzgar
Lag	Desface	Sustantivo	Diferencia o desajuste entre dos acciones, situaciones o procesos

Table 7 renders the words included in the glossary from Spanish into English.
Source: Researcher's creation

5.1.3.2 Glossary from Spanish into English

Table 8. Glossary from Spanish into English

Documentos del español al inglés a español			
Término en el idioma de partida	**Término en el idioma de llegada**	**Categoría gramatical**	**Definición**
Espectrofotometría	Spectrophotometry	Noun	The quantitative measurement of properties (such as relative intensities) of light at different wavelengths of a particular spectrum
r.p.m.	Revolution per minutes	Noun	A measure of the frequency of rotation, specifically the number of rotations around a fixed axis in one minute
Farmacopea	Pharmacopoeia	Noun	Book describing drugs, chemicals, and medicinal preparations
Surfactantes	Surfactants	Noun	A surface-active substance
Tensoactivos	Surface-active	Adjective	Altering the properties and especially lowering the tension at the surface of contact between phases
Capa entérica	Enteric Coated	Adjective	Coated with a material that permits transit through the stomach to the small intestine before the medication is released

Bioexención	Biowaiver	Noun	In vivo bioavailability and/or bioequivalence studies may be waived (not considered necessary for product approval).
Subrrogar	Subrogated	Verb	To substitute (something or someone, such as a second creditor) for another with regard to a legal right or claim
Acetato	Acetate	Noun	Salt or ester of acetic acid
Fosfato	Phosphate	Noun	Salt or ester of a phosphoric acid
Cromatogramas	Chromatograms	Noun	Time-based graphic record (as of concentration of eluted materials) of a chromatographic separation
Bioensayos	Bioassays	Noun	Determination of the relative strength of a substance (such as a drug) by comparing its effect on a test organism with that of a standard preparation
Biorrelevancia	Biorelevance	Adjective	Release of a poorly soluble drug from hydrophobically modified poly (acrylic acid) in simulated intestinal fluids
Hidrodinámica	Hydrodynamic	Adjective	Relating to, or involving principles of hydrodynamics
Lote	Batch	Noun	Product designation or coding

Biolote	Biobatch	Noun	Batch of product formulated for the purpose of pharmacokinetic evaluation in a bioavailability/bioequivalence study.
Nebulizador	Nebulizer	Noun	Device for producing a fine spray of liquid, used for inhaling a medicinal drug
Biofarmacéutica	Biopharmaceutical	Adjective	Pharmaceutical derived from biological sources and especially one produced by biotechnology
Subsanar	Correct	Verb	To make or set right
Enzima	Enzyme	Noun	Proteins that are produced by living cells and catalyze specific biochemical reactions at body temperatures
Principio activo	Active Ingredient	Noun	Part of a substance or compound that produces its chemical or biological effect
Compendio	Compendium	Noun	List of a number of items
Filiales	Subsidiaries	Adjective	Relating to, or constituting a subsidy
Excipiente	Excipient	Noun	Inert substance that forms a vehicle (as for a drug)
Pivotal	Pivotal	Adjective	Vitally important

Table 8 portrays the words included in the glossary from English into Spanish.

Source: Researcher's creation

Chapter VI

Conclusions and Recommendations

In this very last chapter, the conclusions sketched out throughout the research process are tackled by assessing the results obtained in each of the preceding chapters to proceed to undertake a critical synthesis aimed at extracting the foremost achievements and accomplishments found. Likewise, it depicts the restatement of the research question. It portrays the recommendations and guidelines drawn from the analysis of the information deeming the findings obtained, which are given to complement the work outlined for future lines of research.

6.1 Purpose of the Conclusion

The conclusion of the present research intends to lay out the results obtained from the research lines to give responses to the objectives set. The core of this section is to provide a concise overview, spotlighting the key contributions of the study and showcasing the substantial outcomes found during the research process. It is pivotal to spotlight the development of this section; the information in the texts was analyzed in depth. Hereunder, the results are rendered following the specific objectives defined to develop greater coherence and clarity between the stated objectives and the results.

6.2 Conclusions

6.2.1 To translate some documents from Spanish into English and for English into Spanish for CALOX of Costa Rica, S.A.

The following conclusions were reached after analyzing the documents provided by CALOX of Costa Rica.

The first objective of this research was accomplished through an exhaustive analysis of the Source Texts and ensuring their full comprehension and interpretation of the Target texts. The analysis of these documents included the elements as the different kinds of stylistic scales between them, the scale of formality, the scale of generality or difficulty, and the scale of emotional tone; it also includes the text style and the text function, as well as the translation method employed.

Through the use of the text analysis chart, the following was concluded: the style of the texts was classified as descriptive because the function of the texts was oriented to explain the use of the drugs, define certain pharmacological and chemical terminology, and inform the readers, such as detailing legal procedures required for the approval of pharmaceutical products. Considering these aspects, it was deemed that the text function was categorized as informative.

On the flip side, the scale of formality was classified as formal, considering that all the texts studied were scientific, medical, chemical, and legal. Therefore, the language utilized established a high degree of formality. As for the scale of generality and difficulty of the texts, both were qualified as Opaquely Technical since deeming all aspects of the level of difficulty was comprehensible only to experts in the field of pharmacology. Consequently, the emotional tone scale was categorized as factual because the core was to inform the reader about some particular subjects and areas. Similarly, it was determined that the kind of translation used were semantic and communicative. Due to the nature of all the texts, it was necessary to use a translation faithful to the original. Therefore, the determination of all these aspects of the text analysis chart and the knowledge of each of them helped to generate a complete translation and successfully convey the message of the original texts, yielding an accurate and cohesive translation.

6.2.2 To apply various translation techniques to the documents to achieve accurate target texts.

As a result of the use of the different translation techniques and procedures for the documents provided by CALOX of Costa Rica S.A., a reliable, accurate, and natural translation was obtained in the Target Language. In addition, it was ascertained that the eleven procedures (punctuation changes, adaptation, literal translation, transposition, modulation, amplification, explicitation, compensation, omission, equivalence, and sentence inversion) were successfully applied in the translation process. Nonetheless, the use of these varied in each language due to the needs of each text. Therefore, the results were different for each language. The results obtained by implementing the color-coding technique are shown below.

When translating the texts in both languages, it was deduced that the translation procedure that was used most was the literal translation since the texts had a scale of generality and difficulty opaquely technical that entailed many technical terms, thereby requiring the application of semantic translation, i.e., in order to convey the message to the Target Text audience successfully, the translations were sought to remain as faithful as possible to the original. Also, due to the documents' medical, legal, scientific, and chemical nature, the translation was produced accurately to preserve the original text's message and avoid confusion. Therefore, the procedure that best fitted these necessities was the literal translation since it made it possible to uphold the authenticity and essence of the original.

Transposition was one of the most frequently requested procedures in both languages; this procedure was used to replace some parts of the Source Language sentence with completely different ones in the Target Language, but always keeping the meaning of the original one. This procedure was implemented to replace some parts of the sentence in the Source Language with

completely different ones in the Target Language, but always conserving the meaning of the original. This was used at the grammatical level for those parts of sentences that implied a change in the structure of the sentence elements. The most common kind of transposition employed was word-order transposition, followed by the transposition from plural to singular; using this procedure made it possible to generate greater coherence in the sentences.

The equivalence procedure was primarily used to translate the names of laws, institutions, procedures, formulas, chemicals, and pharmaceutical terms since many of these elements demanded their exact equivalent in the Target Language, which was correctly transferred into the Target Language. This procedure was used especially in translating documents from English to Spanish because many abbreviations were repeated throughout the text. This procedure allowed a better interpretation of the elements in the target language.

Modulation was applied in those parts of the translation where a change of point of view was required in the original message to transmit the complete essence of the message in the language. However, to resort to this procedure required an absolute knowledge of the subject, as its use required a variation in the vocabulary of the sentences or phrases, always seeking to maintain the main idea of the original and taking care not to lose the meaning. In the translation, modulations were asked to appreciate those parts of the text that needed to be conveyed more naturally in the target language. Likewise, the type of modulation most frequently used was the change from the passive voice.

On the other hand, the omission procedure was most frequently observed in the translation of the documents from Spanish to English, where elements such as articles and prepositions were omitted because they were not required in the Target Text; the use of these elements did not

hinder the meaning of the original. In addition, this procedure was applied to streamline the message and avoid redundancies and unnecessary vocabulary in the target language, which, as shown in Chapter V, was used appropriately.

Because the complexity of texts was too complex, it was necessary to resort to the procedures of explications and amplification to communicate the message in the clearest and most precise way and thus avoid ambiguities and confusion. Nevertheless, the explicitation procedure was rarely utilized as compared to amplification. It should be noted that amplification was used to input small particles that would allow for greater naturalness in the target language. This procedure was mostly applied in translating the text from English to Spanish to add connectors, articles, prepositions, and some adverbs, thus allowing for greater coherence between sentences. The explicitation procedure was applied to those parts of the text that lacked meaning and required greater precision by introducing extra details in the translation.

Based on the information provided by the color-coding chart, it was observed that the adaptation, compensation, and sentence inversion procedures were used less frequently compared to the previously mentioned procedures. Notwithstanding, they were used in some cases. In the case of the sentence inversion procedure, it was observed that it was commonly applied in cases where the original sentence structure did not maintain its meaning and consistency in the target language; therefore, this procedure was used to maintain a harmonious construction in the sentences of the target language. Compensation was applied in those cases that required filling gaps in the target language to give complete meaning to the original message and compensate for the lost meaning. As for the adaptation procedure, it was determined that it was the least utilized procedure in both texts.

In summary, the implementation of all text translation techniques yielded an accurate translation that fully conveyed the idea of the original text, where the meaning of the source language texts was maintained in its entirety. Hence, it was determined that good results were obtained in the target language, and this objective was satisfactorily met.

6.2.3 To evaluate the effect of the translation techniques applied to the documents.

After analyzing and evaluating the techniques applied in translating the documents, it was deduced that the effects of applying these techniques were a natural and accurate translation. In order to reach these conclusions, it was necessary to assess all the techniques deployed in the translation process. To this purpose, each of these techniques was analyzed in detail, and it was identified in which situations it was pertinent to apply each one and their respective differences.

Consequently, one of the effects that could be observed is that their use made it possible to adjust the different parameters of the texts and to correctly convey the author's original message through the use of modulations and equivalences in the texts, thus making it possible to obtain the permanence of the meaning in the original language. In addition, it was observed that the translation techniques made it possible to identify, classify and name the equivalences chosen by the translator for micro textual units and obtain concrete data.

Its use also aided in resolving the complexities within the documents, as well as the structure of the phrases, sentences, or the form in which they were written, which mostly gave way to the development of problems arising from long sentences formed by subordinate clauses, where it was necessary to make use of more concrete terms such as equivalences synthesizing linguistic elements.

One of the effects that could be observed was that through the use of techniques and procedures, the application of some mechanisms contributed to achieving a better outcome in the target language. Another effect that could be seen was that after using the different techniques, the same message was transmitted from one language to the other. This resulted in the execution of a trustworthy translation and transmitting a coherent and precise message in the Target Text.

6.2.4 To create a glossary with the most relevant terminology in both texts.

Based on the results obtained, it is concluded that the use of a glossary in both languages was satisfactorily concluded. Creating a glossary in both languages was of utmost importance in the entire line of research since it clarified those concepts that were difficult to understand at first glance in the texts. The purpose of its application in this research was to generate concrete definitions of the terms found in the texts; due to the large scale of difficulty of the texts, a large amount of unknown vocabulary could be found. This allowed the creation and maintenance of a list of definitions, similar to a dictionary, and made it possible to compile and organize the information in an enriched way.

The results showed that the terminology included in the English into Spanish glossary was mainly vocabulary related to pharmacology, such as abbreviations and names of chemical compounds and procedures. This was very assistive to have a detailed understanding and interpretation of these concepts. The Spanish into English glossary reflected all the legal vocabulary and names of chemical compounds, among others.

In synthesis, the creation of this instrument was of pivotal importance in the translation process and its application in the research framework since they used a set of terms and concepts that were fundamental and permanent in the texts, being proper to their specificity. Developing a

glossary can be a good departure point to continue building knowledge and aid in reducing terminological confusion, thus allowing to generate a better understanding of the lexicon of the texts and be able to choose a correct equivalence in the target language, helping to use the correct terms in each context and to structure the message correctly in the Target Language.

6.3 Restatement of the Research Question

What is the effect of using procedures and methods in translating and analyzing some documents from English into Spanish and from Spanish into English for CALOX of Costa Rica S.A.? Based on the information gathered from the three instruments of this research, an in-depth analysis was obtained, which led to the answers of this research. Establishing the research question persists since the purpose stipulated in the objectives of this research was achieved, which were as follows.

First, to translate some documents from Spanish into English and for English into Spanish for CALOX of Costa Rica, S.A., which was achieved successfully in Chapter IV. Second, to apply various translation techniques to the documents in order to achieve accurate target texts, which was perfectly accomplished in Chapter V of this research; third, to evaluate the effect of the translation techniques applied to the documents and to create a glossary with the most relevant terminology found in both texts, as observed in chapter IV satisfactorily culminated. Concluding all the proposed objectives achieved their main purpose in this research line.

6.4 Recommendations

In this translation thesis, the effect of translation procedures and methods has been analyzed, in which it is deemed that a complete and comprehensive study has been provided.

Nevertheless, this work suggests the use of certain measures to assist future research of this kind to envisage good results, considering at least four lines of investigation.

Firstly, it is recommended to carry out a second reading, in which a specific reading of the documents is outlined to understand better the subject to be translated. Once a clear and complete and solid understanding of the content, it is suggested to determine all the Stylistics Scales put forward in the text analysis chart in order to have a better understanding of the kind of text to be translated and take into account the formality scales to start translating taking these aspects in consideration.

Likewise, it is vital to make a summary of all the translation procedures to have a broad knowledge of how each one of them works and thus be able to determine precisely how they are reflected in the translation, thus allowing a faster identification in the coding process. All this facilitates the color-coding process and avoids making mistakes when identifying them or generating confusion between one procedure and another.

Consequently, at the time of the first reading of the documents, it is recommended to apply a highlighting technique to all unknown terminology or to write down all the terms that may enrich the vocabulary to be used in the glossaries. The purpose of this is to enable the construction of the third instrument. In this way, it will be possible to get satisfactory results and simplify the process and carry it out in the best way, avoid omitting important terminology, and create a glossary with terminology that may be of interest to the readers. Furthermore, employing notes in the translation, both as a translation strategy and a translation procedure, is indispensable so that foreign language readers can benefit from the text as much as the Source Text readers.

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