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Analysis and Translation of the *Reglamento de buenas prácticas de farmacovigilancia* from Spanish into English and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline* from English into Spanish for Bioplus Care S.A.

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Dedication

I dedicate this project to my parents and older brother, who have always supported me through good times and bad. They are the people I treasure the most in this world.

Abstract

This research paper determines the most suitable translation methods for translating pharmacovigilance texts through the translation of two pharmacovigilance documents from English into Spanish and vice versa, which require a proper understanding of technical and specialized terminology. The approach used for this study was a combination of both qualitative and quantitative methods. The study integrates the researcher's linguistic skills, cultural knowledge, and interpretation of the translation process, aligning with the qualitative focus on understanding and interpreting textual data. Additionally, the study incorporates a quantitative aspect by counting the frequency of specific translation methods, techniques, or procedures used in selected paragraphs. The results revealed that transposition, modulation, literal translation, amplification, semantic translation, and communicative translation are the most suitable methods for translating pharmacovigilance documentation. The results highlight a balance between maintaining fidelity to the source text and adjusting to the particular requirements of the target language, ensuring that the final translation is both accurate and natural. The implications of this research could be used to promote formal training in medical translation and collaboration with experts in the field.

Resumen

Este trabajo de investigación determina los métodos de traducción más adecuados para traducir textos de farmacovigilancia a través de la traducción de dos documentos de farmacovigilancia del inglés al español y viceversa, que requieren una comprensión adecuada de la terminología técnica y especializada. El enfoque utilizado para este estudio fue una combinación de métodos tanto cualitativos como cuantitativos. El estudio integra las habilidades lingüísticas de la investigadora, el conocimiento cultural y la interpretación del proceso de traducción, alineándose con el enfoque cualitativo en la comprensión e interpretación de datos textuales. Además, el estudio incorpora un aspecto cuantitativo al contar la frecuencia de métodos, técnicas o procedimientos de traducción específicos utilizados en párrafos seleccionados. Los resultados revelaron que la transposición, la modulación, la traducción literal, la amplificación, la traducción semántica y la traducción comunicativa son los métodos más adecuados para traducir documentación de farmacovigilancia. Los resultados destacan un equilibrio entre mantener la fidelidad al texto fuente y ajustarse a las particularidades del idioma de destino, asegurando que la traducción final sea precisa y natural. Las implicaciones de esta investigación podrían usarse para promover la capacitación formal en traducción médica y la colaboración con expertos en el campo.

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Chapter I

Introductory Framework

"Sense-for-sense and not-word-word." This was written in 395 A.D. in a letter to Pammachius by St. Jerome, known as the Patron Saint of Translations, when he was writing about the best translation method after translating the Bible from Greek into Latin at the commission of Pope Damasus. This phrase means that a translator should translate sensibly and not literally. In other words, a translator must think of each sentence as one unit to preserve the original's meaning and avoid translating word by word by its literal meaning. This approach started a debate in the translators' community and, nowadays, translators still deal with this dilemma even though new translation theories have been developed, and new translation methods have been employed. Regardless of which method is the best for translating, it is a fact that translation has shaped the society and culture of many places worldwide. Burrow-Goldhahn (2018) explains that translation is indispensable in spreading information, knowledge, and ideas across cultures, ensuring effective and empathetic communication. Therefore, it is crucial for fostering social harmony and peace. Furthermore, translation enables individuals to access a variety of works that expand their understanding and perspective (para. 8). Simply put, translation plays a crucial role in disseminating information. Thanks to it, individuals have access to information from different fields such as education, science, technology, business, engineering, and healthcare, the latter being of great importance. Translating healthcare information makes it more accessible and understandable and promotes medical understanding and safety. Thus, the researcher of this paper aims to make accurate and faithful translations of pharmacovigilance documentation from English into Spanish and vice versa for Bioplus Care S.A. in San José, Costa Rica, specifically the *Reglamento de buenas prácticas de*

farmacovigilancia, which is not available in English, and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline*, which is not available in Spanish.

1.1 Problem Statement

Bioplus Care S.A. is a pharmaceutical company located in San José, Costa Rica. It started operations back in 2009 with the mission to bring access to better therapeutic options to patients in Central America and the Caribbean. The company works along with the pharmaceutical industry, healthcare providers, and patients, wanting to improve therapeutic guidelines and protocols that meet the needs of both patients and healthcare providers. In addition, the company performs tasks ranging from market mapping, selection of highly specialized medicinal products for marketing according to therapeutic area with reliable sources, product registration according to legal requirements, commercialization, promotion, and positioning of products, to monitoring pharmacovigilance protocols. Bioplus Care S.A. asked the researcher to please translate two documents regarding pharmacovigilance guidelines: the *Reglamento de buenas prácticas de farmacovigilancia* from Spanish into English, and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline* from English into Spanish. Before explaining the problem of the research, it is important to understand the content of both documents.

The World Health Organization (n.d.) defines pharmacovigilance as the field and practices concerning the detection, assessment, comprehension, and prevention of adverse effects or any other issues associated with medicines and vaccines (para. 1). Before being authorized for use, all medicinal products go through extensive testing in clinical trials to guarantee their safety and effectiveness. To achieve this, good pharmacovigilance practices are followed. Good Pharmacovigilance Practices (GVPs) serve as a quality standard for monitoring the safety of medicinal products and implementing measures to reduce their risks and increase their benefits if

needed. Moreover, Periodic Benefit-Risk Evaluation Reports (PBRERs) are documents created and submitted by marketing authorization holders. They are made at specific times after a medicinal product has been approved. The main goal of these reports is to carefully assess the balance between the risks and benefits of a medicinal product, considering any new or essential information that has come up since its approval, along with all the previous information about its risks and benefits. In short, pharmacovigilance protocols and guidelines guarantee the safety and effectiveness of medicinal products worldwide; therefore, it is necessary to translate these documents. If not, it is a problem that directly affects Bioplus Care S.A., which is a pharmaceutical company that needs these documents to be translated.

It is also relevant to mention that this documentation belongs to a specific area of study which is pharmacology; therefore, technical terminology is expected to be present. The purpose of this research is to translate accurately and faithfully the *Reglamento de buenas prácticas de farmacovigilancia* into English and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline* into Spanish considering translation theories and methods.

The question that the researcher aims to answer at the end of this research is: Which are the most suitable methods for translating pharmacovigilance documentation according to translation theory?

1.2 Objectives

The main purpose of an investigation is to achieve results; thus, the following are the objectives that will conduct this research.

1.2.1 General Objective

- To translate the *Reglamento de buenas prácticas de farmacovigilancia* into English and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline* into Spanish

1.2.2 Specific Objectives

- To evaluate which methods are the most suitable for translating pharmacovigilance documentation according to translation theory
- To determine the specific skills a translator needs to translate pharmacovigilance documentation
- To investigate how translators can specialize in pharmacovigilance translation

1.3 Justification of the Study

The objective of this research is not to just simply translate the *Reglamento de buenas prácticas de farmacovigilancia* into English and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline* into Spanish for Bioplus Care S.A. but to evaluate which methods are the most suitable for translating the content of both texts. This means the researcher will study, apply, and analyze the different translation theories and methods and consult reliable dictionaries and glossaries. Since specialized language is expected to be used in the texts, the researcher must always consider this. Specialized translation requires translators to possess in-depth knowledge of specific subjects. It encompasses various fields such as legal, technical, financial, medical, scientific, and other highly specialized areas. This type of translation demands a thorough understanding and proficiency in the respective field to accurately convey the

intended meaning across different languages (Angelone, n.d.). Therefore, the researcher will consider all these aspects and translate the documents as accurately as possible.

Additionally, this research is convenient and relevant, for translation is a field that is constantly growing and needs investigation to improve. Hence, the researcher expects the present study to work as a useful source for students majoring in translation, professional translators, and other individuals interested in the field.

1.4 Antecedents

For organizational purposes, the first section of this overview briefly examines the history of translation, and the second the different investigations carried out about this paper's topics.

1.4.1 The History of Translation

Translation gives individuals access to diverse works that broaden their understanding. It plays a crucial role in disseminating information, knowledge, and ideas. Therefore, it is relevant to briefly understand how this field has evolved over time.

Going back to the Ancient Era, the first indications of translation started in the 3rd century B.C. when 70 Jewish translators worked individually on a translation called Septuagint, the Bible translation from Hebrew to Greek, at the request of King Ptolemy II. Despite being separated, each of the translators produced identical translations. Furthermore, when Napoleon Bonaparte invaded Egypt in the 18th century, one soldier found the now-called Rosetta Stone, a black basalt stone inscribed with ancient writing. The stone contained fragments written in three different scripts: ancient Greek, Egyptian hieroglyphics, and Egyptian demotic. Through the examination of the scripts, archeologists discovered that the ancient Greek script indicated that the three scripts had the exact same meaning.

In the Medieval Era, specifically during the 12th and 13th centuries, several European translators used to meet at the Toledo School of Translators in Spain to translate extensive scientific, medical, philosophical, and religious texts. The translators at the time were principally Arabic speakers, who focused on translating from Arabic into Latin because of the Christian occupation, as Latin was the official language of the church. After some time, the language target was no longer Latin. Instead, the translators were now assigned to translate into Castilian which, in fact, led to the beginnings of the modern Spanish language. The impact of the Toledo School of Translators was so big that other European kingdoms invested in translating the already translated texts by the Toledo translators into other European languages.

Now in the Modern Era, the demand for translation has rapidly increased, and translators have needed to learn how to use software applications to speed up the process of translating. Several companies around the world had to produce resourceful inventions, for instance, CAT tools (Computer-Assisted Translation), because with the advancement of technology, the propagation of the internet, and the beginning of globalization, the need for translating material to multiple languages have increased. These tools use translation memory, termbases, dictionaries, and machine translation engines that can support the translation process and make it faster.

1.4.2 Investigations

Another consequence of the demand for translation has been the need to research the different approaches that translators adopt when doing their work.

For example, in the thesis *Analysis of the Effect of the Procedures and Methods Used to Translate some Documents from Spanish into English and Vice versa for ILANUD* conducted in by Giarlene Marie Jiménez Montes de Oca from the Universidad Internacional de las Américas,

the importance of doing a proper and exhaustive reading and analysis of the texts to be translated is stated. Jimenéz (2024) argues that if translators do so, they:

> would be able to appropriately use translation methods and procedures, and understand when to use certain expressions or alternatives for words to achieve a more natural and cohesive translation while ensuring that the original message or intention does not get lost or altered on the way. (p. 10)

Jiménez came to this conclusion by carefully analyzing the documentation that she translated while keeping in mind the theory of the translation theories, methods, and procedures that she studied in her research. The documents translated by Jiménez were three: the first one being a regional annual report of ILANUD (information such as the organization's goals, tasks, and projects was included), the second one being a copy of the Kyoto Declaration (information about crime prevention and criminal justice was included), and the third one being a few pages of the WHO Framework Convention on Tobacco Control. Jimenéz translated the documents by using the semantic method and six translation procedures.

Similarly, in the thesis *Translation and Analysis of some Documents from English into Spanish and Vice versa for a Public University Library* conducted by Mi Shan Song Chen from the Universidad Internacional de las Américas, it is also stated that translators should thoroughly read and analyze the texts to be translated to convey their meaning correctly. Nevertheless, Song (2024) emphasizes the importance of the readership. Song translated five documents (two from English into Spanish and three from Spanish into English) for a public university library; therefore, she expects the readership to be all kinds of readers, from professors, and students, to outsiders. The contents of the documents were about language and learning in a digital age, COVID-19, future pandemics, illegal wildlife trade, climate change, and the global economic

crisis. By just looking at the topics, it is expected that specialized terms would be used, so Song explains that while analyzing the texts, she looked for specific terms related to the areas of language, technology, science, and economics.

By the end of the research, Song used two methods, which were semantic translation and communicative translation, and nine procedures. Song explains that since the texts had several technical terms, she used semantic translation because she wanted to convey the meaning as close as possible to the original. Nonetheless, she kept in mind her readership, so she also used communicative translation, for she wanted the readers to grasp the meaning of the texts as easily as possible. Song (2024) concludes her research by stating that "it is possible to preserve semantically all components of a technical text yet making it communicative to all readers by using accurately and precisely all methods and techniques while following proper translations theories" (p. 10). Song's research highlights the importance of balancing accuracy and readability in translation. Her conclusions show that technical texts can stay accurate and still be easy to read when the right methods are used.

Since the researcher of this investigation is a Spanish-native speaker who will translate pharmacovigilance information into a foreign language (English), it is relevant to consider what some authors have to say about this.

In the article *Translating Medical Texts into a Foreign Language: some Methodological Considerations*, Plested et al. (1982) argue that "the correct establishment of text analysis features as well as linguistic characteristics in both languages make it possible to translate medical texts into English as a foreign language" (p. 49). The authors explain that although Newmark notes that his *Textbook of Translation* is written only for translators translating into their mother tongue, he recognizes the significance of translating into a foreign language in

promoting international cooperation. While he acknowledges the practice of translating into a foreign language, he does not elaborate on its methodology. In addition, Newmark observes that this type of translation is practiced in social, corporate, and professional settings; however, it is not appreciated by theorists. The authors argue that translation is more than just a linguistic process; it also involves cultural, social, and conceptual elements within specialized fields. Thus, aspects such as effectiveness, naturalness, and precision mostly rely on the translator's abilities rather than solely on the text's type or language.

Considering the points of view from several other authors, Plested et al., states that translation methodologies developed for translating into one's native language can also be effectively applied to translating into a foreign language without compromising quality. The authors also argue that translation into a foreign language is highly marked by a geopolitical factor. In a multilingual region like Europe, it is easier to find translators because countries like England, France, Spain, and Germany, for instance, are close enough geographically despite their linguistic diversity. In a region like Latin America, it is the contrary, for Spanish predominates as the official language. So, translation into a foreign language is often done by Spanish native speakers, many of whom lack academic training in translation. This situation has led the authors to call for bidirectional translation methods. They believe that with interdisciplinary cooperation and proper methodology, high standards can be achieved. Especially in fields like medical translation where specific training is required to ensure accurate translations.

Plested et al., conclude their research stating that they have tested this approach by translating articles about tropical diseases such as Malaria and Leishmaniasis which have been

published. Therefore, implementing controlled processes and employing linguistically and professionally competent translators enhances scientific translations.

Likewise, Drăcșineanu Cătălin presents in his article *Challenges in Medical Translation* how medical texts give translators difficult challenges due to the complexity of their terminology. Cătălin (2019) proposes a methodology focusing on two main aspects: decoding the translation accurately and transcoding it appropriately for the intended audience and context. In the decoding stage, he explains the significance of meticulous preparation before translating. A key aspect is the documentation phase, where translators familiarize themselves not only with the terminology but also the underlying concepts and contexts. Translators should also pay close attention to false friends, which are words that can lead to misunderstandings between languages. In the transcoding stage, Cătălin notes that key considerations include the target audience and the appropriate discourse type for the intended purpose. Adapting the structure and style of the translation to suit the target audience is crucial, whether it is for patients, medical professionals, or specialists. As for the choice of the discourse type, whether it is informative, persuasive, or mass-oriented, affects the readers' response and engagement with the text. Cătălin (2019) concludes his article by stating that:

> Errors in this field can lead to dramatic outcomes, either in a patient's life or a doctor's reputation and they show unmistakably that there is still room for improvement in this area, especially in the process of documentation and verification by third parties, ideally knowledgeable medical professionals. (p. 28)

Careful preparation and adapting translations for the audience in medical texts is crucial. The author stresses that mistakes in medical translation can have serious consequences; hence, thorough checks and expert reviews are essential.

Lastly, the study *Difficulties resulting from language diversity in teaching medical translation and methods to overcome them when teaching medical English to future translators* conducted by Anna Kuzio revealed that university students encounter significant challenges and obstacles when translating medical terms from English into Polish. This study analyzes an optional course called “The English language in medicine” offered to undergraduate students majoring in English philology. The course focuses on teaching medical translation, and about 20% of students take it. The study looks at work from students who took the course from 2017 to 2019, analyzing their translations of medical texts from English into Polish. Kuzio (2019) made sure that the texts they used were from reliable medical sources. The results showed that about 51.7% of the translations were considered acceptable, showing coherence and appropriate style and vocabulary. However, unacceptable translations made up 43.7%, demonstrating the difficulty in translating into Polish. And 8.8% did not answer. Kuzio concludes her study by emphasizing that translating medical terms is challenging for inexperienced translators and university students. Therefore, she highlights the need for regularly updated and high-quality medical dictionaries and suggests that teaching medical translation should be mandatory for translation majors.

1.5 Scope

The following are the exact goals that the researcher of this study will pursue:

- Study, apply, and analyze the different translation theories and methods
- Produce high-quality, accurate, and faithful translations
- Determine what is necessary to translate pharmacovigilance documentation and similar texts

- Assist students majoring in translation, professional translators, and other individuals interested in the filed
- Make available texts about pharmacovigilance in Spanish and English
- Note how translators can specialize themselves in pharmacovigilance translation and similar texts

Chapter II

Theoretical Framework

A theoretical framework is necessary in research, for it acts as the foundational structure for the entire study. Researchers must familiarize themselves with existing theories and models developed by others before embarking on their research. A theoretical framework offers a structured perspective through which researchers can examine their topic, shaping how they develop research questions and hypotheses, and choose methods. By grounding their study in established theories, researchers not only place their findings within a broader context of existing knowledge but also enrich the ongoing evolution of their field. In addition, a well-defined theoretical framework enhances the clarity and coherence of research outcomes, helping researchers interpret data, recognize patterns, and draw meaningful conclusions.

This chapter explores existing theories developed by several authors within the translation field. Since the main objective of this research is to translate documentation from English into Spanish and vice versa, it is essential to review translation methods, techniques, and procedures to render the meaning of the original texts accurately and faithfully. Therefore, this theoretical framework encompasses aspects such as text analysis, text styles, stylistic scales, text functions, translation methods and procedures, and the importance of glossaries for the translation process.

2.1 Text Analysis

Text analysis is a pivotal step in the translation process, for it allows translators to deeply understand the nuances, cultural aspects, and linguistic complexities of the source text. By carefully analyzing the text, translators can ensure they accurately convey the intended meaning, tone, and style of the original material into the target language. Robinson (2003) argues that

translators should never assume that they understand the text perfectly. They should always analyze the text type, genre, register, and purpose. Understand the syntax, semantics, and implied meanings. Consider the capabilities and limitations of both source and target languages. And adapt the translation based on the commission details and target audience needs (p. 208). Within their profession, translators encounter an extensive range of texts that require meticulous reading and analysis. Thus, they must engage in two essential steps of text analysis: general reading and close reading. General reading occurs when translators only want to get the big picture of the source text and generally understand its content. In the close reading step, translators search for specific words and phrases (acronyms, measures, quantities, idioms, false friends, neologisms, etc.) and understand their meaning in and out of context. These steps help identify potential challenges such as ambiguities, idiomatic expressions, and contextual factors that require careful consideration for effective translation. Furthermore, text analysis facilitates the adaptation of content to suit the cultural context of the target audience, ensuring that the translated work remains faithful to the original while resonating appropriately with readers.

It is also relevant to mention that since this research deals with the translation of specialized documents, text analysis is critically important because it allows the researcher to delve deeply into the specialized content of a subject area. Examining the text enables the researcher to accurately understand and interpret technical terminology and industry-specific concepts and identify any ambiguities or gaps in the source text, allowing her to research and clarify technical details.

2.1.1 Text Styles

As mentioned before, translators encounter diverse types of texts with diverse purposes, and it is important to identify them to convey their meaning accurately. According to Newmark

(1988), there are four types of text: narrative, description, discussion, and dialogue (p. 13). Understanding these categories helps ensure the meaning and purpose of the text are accurately conveyed, as each type may require different translation approaches and techniques.

2.1.1.1 Narrative Texts

Narrative texts describe the sequence of events and emphasize the use of verbs. They are organized with a clear beginning, middle, and end. They contain various episodes that include characters, settings, conflicts, objectives, actions, and solutions.

According to Susanto (n.d.), grammatical features in narrative texts are the following:

- They predominantly employ the simple past tense.
- They use specific nouns to refer to characters, animals, and objects within the story.
- Descriptive noun groups are formed using adjectives to characterize animals, people, or things.
- Events are sequenced over time using conjunctions and time connectors.
- Adverbial phrases are employed to specify the location or timing of particular events
- Verbs related to speech and thought are used to convey characters' emotions, thoughts, and dialogue.

Narrative texts can take various forms and genres, including novels, short stories, folktales and fairy tales, biographies and memoirs, historical fiction, epics, and myths and legends.

2.1.1.2 Descriptive Texts

Noprianto (2017) explains that descriptive text is used by writers to vividly portray a particular thing, person, animal, place, or event to their audience. This involves systematically detailing their characteristics, beginning with identification, and classification, and then exploring attributes, behaviors, and functions. The aim is for readers to visualize the subject as if

observing it directly. Structurally, descriptive texts include two main stages: identification, which introduces and identifies the subject (such as a person, thing, place, animal, or event), and description, which elaborates on its characteristics, appearances, personality, and qualities.

Grammatical features in descriptive texts are the following:

- They predominantly use the present tense.
- Linking verbs (e.g., “is,” “are,” “has,” “have,” and “belongs to”) are common for classifying and describing appearances, qualities, parts, or functions of subjects.
- Action verbs describe the actions and behaviors of subjects.
- Mental verbs describe feelings.
- Adjectives and adverbs add detailed information to nouns and verbs.
- Adverbial phrases provide additional details about manner, place, or time.

2.1.1.3 Discussion Texts

Discussion texts handle ideas and logical arguments using abstract nouns and verbs of thought. IELC (n.d.) explains that discussion texts serve multiple purposes: firstly, they inform readers about a specific topic by presenting different perspectives, opinions, or arguments. Secondly, they promote critical thinking by encouraging readers to analyze different viewpoints and form their own opinions. Lastly, they stimulate debate by presenting contrasting ideas, which fosters a deeper understanding of the issue discussed.

Grammatical characteristics in discussion texts include:

- Use of thinking verbs to express mental processes or opinions, such as “believing,” “considering,” or “assuming.”
- Modal verbs like “should,” “must,” and “may.”

- Adverbs of manner, such as “rapidly” or “carefully,” emphasize how actions or arguments are presented.
- Linking words (e.g., “however,” “moreover”) connect ideas and show relationships between arguments.
- Passive voice can provide a neutral tone or emphasize actions.
- Reported speech is used to convey opinions or arguments from sources without direct quotation.

2.1.1.4 Dialogue Texts

Lastly, dialogue texts are about casual communication and conversations using colloquialisms. According to Kramer (2022) dialogue plays an essential role in creative writing, including short stories, novels, plays, and personal essays, where characters express themselves verbally. It serves multiple functions beyond speech, including character development, where readers obtain insights into the characters’ mindsets, backgrounds, emotions, and relationships based on how they communicate. In addition, Kramer describes formatting guidelines common in dialogue writing, for instance:

- In American English, dialogue is enclosed within double quotation marks (“dialogue”), while in British English, it is enclosed within single quotation marks (‘dialogue’).
- All punctuation should be placed inside the quotation marks.
- A new paragraph is initiated and indented each time a new character speaks, regardless of the length of their speech.
- Em dashes indicate interruptions in dialogue (e.g., “Thank you for— Is that a giant spider?!”).

2.1.2 Stylistic Scales

Following the text analysis process, another aspect that translators must consider is the style used by the author of the source text. Stylistic scales in translation refer to the different language styles adopted depending on a text's context, purpose, and audience. These scales include various levels of formality, register, tone, and linguistic elements that translators consider to accurately convey the style of the source text into the target language. It is relevant to emphasize that formality refers to the vocabulary, syntax, and sentence structures used by the author to match the appropriate level of formality required by the context and audience. Register refers to the level of language appropriate for a particular context, such as technical, academic, colloquial, or literary registers. The tone indicates whether a text is serious, emotional, humorous, formal, or conversational.

Newmark (1988) categorizes the stylistic scales into three: the scale of formality, the scale of generality or difficulty, and the scale of emotional tone (p. 14). By considering these scales, the text's intended impact and clarity is maintained.

2.1.2.1 Scale of Formality

Newmark suggests eight categories for the scale of formality. The following are its respective examples:

1. *Officialese:* "The consumption of any nutriments whatsoever is categorically prohibited in this establishment."
2. *Official:* "The consumption of nutriments is prohibited."
3. *Formal:* "You are requested not to consume food in this establishment."
4. *Neutral:* "Eating is not allowed here."
5. *Informal:* "Please don't eat here."

6. *Colloquial:* “You can’t feed your face here.”
7. *Slang:* “Lay off the nosh.”
8. *Taboo:* “Lay off the fucking nosh.”

Firstly, one can notice how the *officialese* example is extremely formal and supervisory. It uses complex language (“categorically prohibited”) and formal terminology (“nutriments”).

The *official* example is more direct and concise but retains formal language (“prohibited”).

The *formal* example maintains formality but is slightly more polite and indirect compared to the previous examples.

The *neutral* example is straightforward. It conveys the prohibition clearly without using overly formal or informal language.

The *informal* example is informal but still polite due to the use of “please.” It is suitable for casual settings or personal requests.

The *colloquial* example uses slang (“feed your face”) and a casual tone (“can’t”), suitable for informal conversations but not appropriate in formal contexts.

The *slang* example is highly informal because of the use of slang (“nosh” instead of “food”). It is appropriate for casual and familiar communication but would be considered inappropriate in formal or professional settings.

Lastly, the *taboo* example is extremely informal because of the use of a taboo word (“fucking”), making it completely inappropriate for any formal or professional context. It is casual and colloquial, suitable only for informal settings where such language is acceptable.

Regardless of the level of formality or informality of the previous examples, they still carry the same message. Thus, the scale of formality helps translators identify which vocabulary, sentence structures, register, and tone were used by the author. Translators must consider this, for

formality is an aspect that highly influences how a message is perceived and received by its intended audience.

2.1.2.2 Scale of Generality or Difficulty

The six categories of the scale of generality and difficulty suggested by Newmark are the following:

1. *Simple:* "The floor of the sea is covered with rows of big mountains and deep pits."
2. *Popular:* "The floor of the oceans is covered with great mountain chains and deep trenches."
3. *Neutral:* "A graveyard of animal and plant remains lies buried in the earth's crust."
4. *Educated:* "The latest step in vertebrate evolution was the tool-making man."
5. *Technical:* "Critical path analysis is an operational research technique used in management."
6. *Opaquely technical:* "Neuraminic acid in the form of its alkali-stable methoxy derivative was first isolated by Klenk from gangliosides."

The *simple* example is quite general and straightforward. It uses basic vocabulary and describes a physical feature of the ocean floor clearly. Therefore, its difficulty level is low, and it is understandable by most readers.

The *popular* example is similar to the previous sentence but with more vivid language ("great mountain chains and deep trenches"). It is easily understandable.

The *neutral* example uses a metaphorical description of fossils ("graveyard of animal and plant remains"). Its difficulty level is low to moderate because while still using basic vocabulary, the metaphor might require additional interpretation for full understanding.

The *educated* example has a moderate difficulty level. It requires an understanding of evolutionary concepts and human development.

The *technical* example has a moderate to high difficulty level. Understanding this sentence requires familiarity with the terms “critical path analysis” and “operational research,” which are specialized concepts.

Lastly, the *opaquely technical* example has an extremely high difficulty level because of its scientific and technical language. It is likely comprehensible only to the experts in the scientific fields.

These sentences vary widely in generality and difficulty, ranging from simple and widely understandable to highly technical and specialized. Translators must be able to identify all these aspects of a text and proceed to employ adequate translation methods and techniques to convey its meaning accurately.

2.1.2.3 Scale of Emotional Tone

For the scale of emotional tone, Newmark suggests four categories:

1. *Intense:* “Absolutely wonderful… ideally dark bass… enormously successful… superbly controlled…”
2. *Warm:* “Gentle, soft, heart-warming melodies.”
3. *Factual:* “Significant, exceptionally well judged, personable, presentable, considerable…”
4. *Understatement:* “Not… undignified.”

As its name suggests, in the *intense* example the use of intensifiers predominates, which results in a highly enthusiastic and positive tone. Words like “absolutely wonderful” and “enormously successful” indicate strong admiration and excitement.

The *warm* example results in an affectionate tone. Words like “gentle,” “soft,” and “heart-warming” evoke feelings of tenderness and comfort.

The tone in the *factual* example is cool and objective. The words used are positive but are used neutrally and matter-of-factly.

In the *understatement* example, the tone is restrained. The sentence implies that something is quite dignified, but the tone suggests it with minimal emotional display.

Determining the emotional tone of a text helps translators understand what emotional response the author expects from the readers.

2.1.3 Text Function

The readers’ response to a text depends significantly on how the language is used. The psychologist Karl Bühler identified three main macro-functions of language: the informative (Darstellung), the expressive (Ausdruck), and the vocative (Appel). The informative function focuses on the language’s capacity to convey information about the external world. The expressive function involves the expression of attitudes, emotions, and subjective experiences by the speaker. And the vocative function pertains to the language’s role in influencing or directing the listener or recipient of the message (Palumbo, 2009, p. 68). The semanticist Ulrich Stiehler associated these three language functions with three types of human cognition: thinking (or perceiving), feeling, and willing (Hatim & Munday, 2004, p. 183). In the text analysis process, translators must be able to find the language function that the author used in the source text to reformulate it in the target text.

2.1.3.1 Informative Texts

Informative texts convey factual and objective information. These texts aim to inform, explain, or educate readers, often presenting facts, data, explanations, or instructions clearly and

objectively. Valdeon (2009) explains that informative texts often feature detailed information on specific topics, subjects, objects, or places. This information is specialized, focusing on particular subjects and using specific vocabulary. This characteristic is shared with genres like academic papers, legal language, and medical research, which also require precise and specialized terminology (p. 77). Therefore, examples of informative texts include scientific articles, technical manuals, informational brochures, news reports, and educational textbooks.

2.1.3.2 Expressive Texts

Expressive texts aim to communicate the feelings and thoughts of the author, focusing on the author's creativity and artistry to form his/her ideas (Aliurridha, 2019, p. 4). These texts are characterized by their subjective and emotional nature and use of vivid language, imagery, and sensory details. Translating expressive texts not only requires linguistic proficiency but also a deep understanding of literary techniques, cultural contexts, and the ability to convey emotions effectively. Examples of expressive texts are poems, novels, short stories, autobiographies, reflective essays, diaries, plays, and lyrics.

2.1.3.3 Vocative Texts

Vocative texts use the appellative function to persuade the reader or recipient to take specific actions. For instance, in advertisements, the goal is to encourage purchasing, while in political speeches or legal arguments, it aims to sway agreement or decision-making (Cheng & Zhang, 2020, p. 1). Moreover, vocative texts are characterized by five key elements: concreteness, evocation, intensification, tone, and epiphany. Concreteness involves using specific descriptions that place phenomena directly within the reader's lived experiences. Evocation brings phenomena to life through vivid language, encouraging readers to reflect deeply. Intensification enhances texts by using rich sensory descriptions and effective word

choices. Tone addresses readers directly with emotion and engagement. Finally, epiphany aims to provoke a life-changing experience, leaving readers profoundly affected by the text's insights. These elements create texts that provoke meaningful responses (Nicol, 2008, p. 5). Examples of vocative texts include political speeches and propaganda, prayers and religious texts, and advertisements.

2.1.4 Translation Methods

Translation methods encompass the different approaches translators employ to transfer meaning from a source language to a target language while maintaining the original text's essence, style, and purpose. Deciding which approaches to use when translating depends on factors such as the type of the source text, the intended readership, the cultural aspects, and the desired level of faithfulness to the original. In the context of pharmacovigilance documents, these considerations become particularly significant due to the specialized, technical nature of the content and the critical need for clarity and precision in the communication of medical information. Hence, choosing appropriate translation methods is key to ensuring that the translated text not only preserves the accuracy of the original but also ensures the comprehensibility of the information for its intended readership. The two methods pertinent for this research are semantic translation and communicative translation.

2.1.4.1 Semantic Translation

Semantic translation strives to faithfully replicate the original text's form within the target language's norms. It emphasizes conveying the author's original thought processes in the target text rather than interpreting the source text to fit the translator's perception of what is suitable for the target audience. Therefore, this method treats the original words as sacred, even if this means reproducing inconsistencies and ambiguities (Shuttleworth & Cowie, 2014, p. 151). This method

often leans toward excessive translation to capture nuanced meanings. It is subjective and unique, aligning closely with the author's thought patterns. Semantic translation is usually employed when translating expressive texts (Newmark, 1988, p. 47).

In pharmacovigilance documents, semantic translation is necessary because these texts contain specialized medical, scientific, and legal language related to drug safety, clinical trials, and adverse reactions. Accurately translating these terms is crucial, as even small mistakes or changes could lead to serious consequences, such as misunderstanding a drug's side effects or misrepresenting safety guidelines. Using semantic translation ensures that this information is conveyed as accurately as possible, helping healthcare professionals, regulators, and patients make informed decisions. While this approach may lead to a more formal or detailed translation, it is necessary to preserve the message of the original text.

2.1.4.2 Communicative Translation

Communicative translation focuses on meeting the linguistic and stylistic expectations of the readership, aiming to evoke a similar response in them as experienced by native readers of the original text (Laver & Mason, 2018, p. 19). Communicative translation prioritizes conveying the core message of the text and tends to simplify rather than elaborate, aiming for clarity and brevity. This method is used when translating informative and vocative texts (Newmark, 1988, p. 48).

In pharmacovigilance, communicative translation is essential when the audience includes non-experts, such as patients or the general public. Its goal is to make complex technical information clear and understandable. This approach helps prevent misuse or adverse reactions by focusing on clarity and simplicity. While semantic translation maintains technical precision,

communicative translation adapts the message to the audience's needs, making vital health information comprehensible and practical.

2.1.4.3 Semantic Translation vs Communicative Translation

The following table summarizes both the aspects of semantic and communicative translation for a better understanding of their use.

Table 1. Semantic Translation vs Communicative Translation

Semantic Translation	Communicative Translation
Written at author's linguistic level	Written at readers' linguistic level
Used for expressive texts	Used for informative and vocative texts
Expressive components rendered closely/literally	Normalized or toned down, neutral terms
Personal and individual	Social
Tends to over-translate	Tends to under-translate
Pursues nuances of meaning	Pursues message
Inferior to its original	Better than its original
Must interpret	Must explain
Less freedom	More freedom

Table 1. It represents the aspects of semantic translation and communicative translation. Source: ssuser2ff7292 (2020).

2.2 Translation Procedures

Translation procedures are specific methods or techniques translators use to produce accurate and effective translations from one language to another. They help ensure that the meaning, style, and nuances of the source text are conveyed appropriately in the target text. This

overview explores six translation procedures: transposition, modulation, omission, amplification, explicitation, literal translation, and punctuation changes. Examining these procedures is highly pertinent for this research, for the researcher must engage in the translation of documents from English to Spanish and vice versa.

2.2.1 Transposition

Transposition is a type of free translation. As the name suggests, free translation is a method where the translator has the freedom to make adjustments. This creates a new version in the target language that is more natural or more suitable for its intended purpose. According to Vinay & Darbelnet (1995), transposition replaces one grammatical category of words with another while maintaining the original meaning of the message. For instance, rendering a French noun with an English verb (p. 36).

Talaván (2016) explains that grammatical structures are rarely the same in different languages and provides an example of transposition from English into Spanish. The translation of "Governing Body" (adjective + noun) translates into Spanish as "Órgano de Gobierno" (noun + prepositional phrase). In addition, English frequently employs the passive voice, whereas in Spanish, it is preferred to use the active voice (p. 44). Another example is "He will soon be back" translated into Spanish as "Él no tardará en venir," changing the adverb *soon* for the verb *tardar*.

Furthermore, Transatlantic Translations Group (n.d.), describes three types of transposition: linguistic, structural, and stylistic.

Linguistic transposition focuses on adjusting language elements such as vocabulary, syntax, and grammatical structures. Nevertheless, it involves more than just substituting words; it requires rephrasing and restructuring sentences to accurately convey the original purpose. For

example, translating idiomatic expressions or colloquialisms often demands careful adaptation to fit the linguistic norms of the target language while preserving the original message.

Structural transposition aims to maintain the essence of the text by reorganizing its structure to align with the patterns of the target language. This is crucial when translating between languages with different structures (e.g., Subject-Object-Verb vs. Subject-Verb-Object), ensuring the translated text remains coherent and readable.

Finally, stylistic transposition focuses on adapting the text's tone, style, and rhetorical techniques to resonate with the target readers. It involves capturing the author's unique voice, nuances, and literary tone. Achieving this requires a deep understanding of both the source and target languages' cultural and linguistic aspects to accurately convey the message while maintaining the original's stylistic elements.

2.2.2 Modulation

Modulation is another type of free translation. It is a change in the point of view of the source language. This procedure is used when a translation is grammatically correct but lacks naturalness in the target language (Vinay & Darbelnet, 1995, p. 36).

Munday (2016) explains that modulation can be obligatory (e.g. *the time when* translated as *le moment où* [lit. 'the moment where']) or optional (linked to the preferred structures of the two languages, e.g. the reversal point of view in *it is not difficult to show > il est facile de démontrer* [lit. 'it is easy to show']) (p. 90). Munday also notes how modulation operates at the message level:

1. Abstract to concrete or general to particular: e.g., "She can do no other" to "She cannot act differently".

2. Explicative modulation (effect to cause): e.g., “You’re quite a stranger” to “We don’t see you anymore.”
3. Whole to part: e.g., “He shut the door in my face” to “He shut the door in my nose.”
4. Part to another part: e.g., “He cleared his throat” to “He cleared his voice.”
5. Reversal of terms: e.g., “You can have it” to “I’ll give it to you.”
6. Negation of opposite: e.g., “It does not seem unusual” to “It is very normal.”
7. Active to passive: e.g., “We are not allowed to access the internet” to “They don’t allow us to access the internet.”
8. Rethinking of intervals and limits in space and time: e.g., “No parking between signs” to “Limit of parking.”
9. Change of symbol (metaphorical translation): e.g., from French “La moutarde lui monta au nez” (literally “The mustard rose up to his nose”) to English “He saw red” (meaning “He became very angry”).

2.2.3 Omission

According to Jiménez (2018), omission is a method that translators adopt when elements or information from the source text cannot be translated into the target text. When this occurs, it is advisable to analyze the most prominent aspects of the text and categorize them by order of importance, considering the translation requirements and the intended function of the target text. From this analysis, one will focus on preserving the most essential aspects, even if it means sacrificing less important ones (p. 122-123). Moreover, Jiménez determines three main techniques of omission: reduction, condensation, and generalization.

2.2.3.1 Reduction

Jiménez explains that reduction refers to using fewer words in the target text compared to the original to convey the same meaning. This reduction can be either obligatory or strategic. Obligatory reduction occurs when grammatical and structural features of the target language require it. For instance, the Spanish phrase “alquiler de máquina para la limpieza a vapor de alfombras” (10 words) can be translated into English as “carpet steam cleaner rental” (4 words). This reduction is necessary because a more literal translation (“rental of machine for the steam cleaning of carpets”) would not sound as natural. In Spanish, prepositions are often needed to establish semantic relationships between words, whereas English relies on word order. Strategic reduction, on the other hand, is commonly used in translation tasks where space constraints are present (e.g., in comics, forms, and subtitles).

The following are more examples of reduction:

1. Spanish>English

   Consumir preferentemente antes de: (4 words)

   Best by: (2 words)

2. Spanish>English

   Servicio de atención al cliente (5 words)

   Customer service (2 words)

3. English>Spanish

   She is a cop. (4 words)

   Es policía. (2 words)

4. English>Spanish

   The dog was able to follow his master’s trail. (9 words)

El perro pudo rastrear a su dueño. (7 words)

In each case, the translation achieves conciseness while preserving the original meaning, demonstrating the application of obligatory and strategic reduction techniques.

2.2.3.2 Condensation

According to Jiménez, condensation involves omitting ideas or content from the original text. This method is often used for practical reasons, allowing the translator to maintain the main message while adapting the content for different contexts or limitations. For instance, subtitles usually have a strict time limit, meaning the translator needs to condense the dialogue without losing the meaning. A translator must fit the text within a few seconds of screen time, which requires shortening the sentences while ensuring the audience can follow the plot. The following are additional reasons to use condensation as a translation technique:

2.2.3.2.1 Space Constraints

Like reduction, condensation is often used when translating content with limited space, such as brochures, flyers, subtitles, comics, and advertisements. In these cases, the translator must condense the original text to fit the available space while maintaining the core message. This ensures the text remains clear, concise, and effective, even within strict space limits.

For example, comics typically have limited space in their speech bubbles or text boxes, so the dialogue needs to be concise. For instance, in an English comic, a character might say: “I can’t believe we’ve been on this mission for so long. Every plan we make seems to fall apart, but I’m not giving up. We’ll find a way to succeed, no matter the odds!” The condensed version in the Spanish version of the comic might be: “Llevamos mucho tiempo en esta misión, pero no me rendiré. ¡Lo lograremos!” This keeps the character’s determination but omits unnecessary elaborations; it makes the dialogue shorter and fits within the limited space of the speech bubble.

2.2.3.2.2 Client Requirements

Sometimes, clients only need a general understanding of the text rather than a complete translation. In such cases, translators summarize and translate the most relevant points. Condensation is particularly useful in situations where clients do not need a word-for-word translation but instead a quick, easy-to-read version that conveys the original message. For example, a company may need a translation of an internal business report that includes financial data and projections. However, the client may not require all the specific numbers or detailed financial analysis but rather just an overall summary of the report's conclusions. Condensation helps meet the specific needs of the client and ensures that the client receives a translation that is more functional and efficient for its intended purpose.

2.2.3.2.3 Cultural or Linguistic Norms

To respect the norms or expectations of the target culture or language, translators must consider excluding terms, concepts, expressions, or ideas from the original text that may not be appropriate. This decision depends on the translation requirements and the target audience. For instance, translating obscene terms, vulgar expressions, or taboo subjects requires careful analysis to determine their appropriateness in the translation context. In the context of translating and adapting a novel for children, it would be advisable to remove any offensive language present in the original text.

2.2.3.2.4 Avoiding Redundancy

Translators sometimes imply what was explicitly stated in the original text to avoid repeating information already known to the target audience. This approach is used when maintaining the same level of detail would be redundant for the target audience. For example, the Spanish headline "La reina Isabel II de Inglaterra se convierte en la monarca con más años en el trono en

el Reino Unido" (21 words) would be translated as "Queen Elizabeth II becomes the longest-reigning monarch" (7 words) when published in the United Kingdom. Several words are omitted because British readers would already be familiar with this information.

These examples illustrate when omitting information can be appropriate or advisable. The decision to condense should prioritize clarity and effectiveness, ensuring that the omitted information does not compromise the overall understanding of the translated text.

2.2.3.3 Generalization

As per Jiménez, generalization is applied when maintaining the exact details of the original text is impossible. Therefore, a broader term or phrase is used to convey a more general meaning. This approach is suitable when a more specific alternative is unavailable, and when the omitted detail remains clear or insignificant within the context. It is important to understand that generalization does not necessarily reduce the word count in the target text; instead, it often involves simplifying or omitting specific details, making the translation less specific than the original. For instance, "She was having a Moscow mule when I first laid eyes on her" is translated to "Se estaba tomando un cóctel cuando me fije en ella por primera vez". In this sentence, the specific drink "Moscow mule" is generalized to "cóctel" because the literal translation "mula de Moscú" might be unfamiliar to most Spanish-speaking readers.

Additionally, Jiménez explains that the concept of generalization has a close connection with "hypernym" and "hyponym." A hypernym is a general term that includes a more specific term within its meaning. For example, "fruit" is a hypernym of "apple," and vice versa.

In translation, opting for a hypernym often helps clarify meaning when a specific term is impossible to render. In the following example, the original sentence mentions a traditional Spanish wind instrument, but for clarity, a more general term has been chosen.

Example:

Spanish>English

Mi abuelo me enseñó a tocar el albogue cuando era niño.

My grandfather taught me how to play the flute when I was a child.

2.2.4 Amplification

Amplification is a procedure that involves elaborating on implicit details from the source text when translating into the target language (Kembaren, 2016, p. 71). Translators should provide annotations that clarify the context of specific words, ensuring readers understand their meaning in the target text. These explanations are typically placed as footnotes or endnotes (e.g., *Bulan depan adalah bulan Ramadhan* translates as *Next month is Ramadhan [The Muslim month of fasting]*) (Kembaren, 2018, p. 29).

Jiménez (2018) elaborates on the meaning of amplification by noting that this method is useful for explaining historical, social, or cultural references from the original text in the translated version. The author provides the following examples:

1. English>Spanish

   A teacher tells her students: “For tomorrow’s activity, you are going to bring something for *show and tell*.”

   Una maestra les dice a sus estudiantes: “Para la actividad de mañana, van a traer algún objeto y explicar la importancia que tiene para ustedes”.

2. Spanish>English

   El mes que viene el museo inaugurará una exposición temporal de Botero.

   Next month the museum will open a temporary exhibition on Botero, the famous Colombian painter and sculptor.

3. Spanish>English

   Los rebozos mexicanos suelen ser muy coloridos.

   Mexican rebozos, or shawls, are usually very colorful.

4. English>Spanish

   The day after Thanksgiving, North Americans celebrate Black Friday.

   El día después de Acción de Gracias, los norteamericanos celebran Black Friday, que es el día cuando las tiendas ofrecen muchos descuentos.

2.2.5 Explicitation

As its name suggests, explicitation is a technique that involves explicitly stating information in the target text that was implied in the source text (Baker & Saldanha, 2009, p. 104).

Munday (2016) explains that explicitation occurs in numerous ways, depending on the linguistic context of the source text and the requirements of the target text. For instance, at a grammatical level, if the source text uses a neutral term like “the doctor” without specifying gender, the translator may need to choose a feminine or masculine equivalent in the target language where that specification is necessary. This decision introduces additional information not present in the source text to maintain linguistic coherence in the target language.

On a semantic level, explicitation involves elaborating on cultural references or events mentioned in the source text to ensure they are fully understood by the readers. For example, when translating about U.S. Thanksgiving, the translator might provide explanations of its significance if it is not explicitly stated in the source text (p. 92).

The goal of explicitation is to make the target text more understandable or informative for the target audience, and it may result in a longer text compared to the source text.

2.2.6 Literal Translation

According to Vinay & Darbelnet (1995), literal translation involves directly converting a source-language text into a grammatically and idiomatically appropriate target-language text (p. 33). Literal translation is also known as word-for-word translation. This approach aims to maintain a close correspondence between the words of the source text and their equivalents in the target text, often resulting in a translation that mirrors the structure and order of the source language.

Aranda (2007) explains that this technique is more effective in straightforward sentences, especially when the languages involved share similarities. For example, translating “The movie is long” into Spanish as “La película es larga” or rendering “Háblame en inglés” as “Talk to me in English” illustrates how direct word-for-word translation can accurately convey basic statements. However, this technique’s usefulness diminishes when dealing with sentences that contain words with multiple meanings or complex structures. The phrase “Háblame en cristiano", translates literally to “Talk to me in Christian,” but idiomatically means “Talk to me in a language I understand” (p. 14). This example demonstrates the challenges of relying solely on literal translation to capture idiomatic expressions present in the source text. Therefore, translators must identify when this technique is appropriate to use or not.

2.2.7 Punctuation Changes

Punctuation is crucial for understanding the connection between sentences and clauses within texts, thereby revealing their meaning. Newmark (1998) notes that punctuation varies between languages and despite its significance, it is frequently ignored. However, translators should always meticulously check the punctuation of their translations (p. 58). Poor punctuation presents challenges for readers who expect standard spelling, grammar, and punctuation. While

speaking allows for clarification through stress, intonation, pauses, or repetition, writing relies heavily on punctuation for clarity. If one's punctuation is confusing or unconventional, readers might struggle to understand the text, possibly not understanding it at all (Trask, 1997, p. 2).

For instance, question and exclamation marks are only placed at the end of a sentence or phrase in English. In Spanish, however, they are used both at the beginning and the end of a sentence (Orellana, 1990, p. 199).

Amigueti (2024) explains that the use of the comma also varies between languages. Sometimes, when translating into Spanish, a sentence fragment needs to be enclosed in commas because it functions as an explanatory adjunct. For example, "occasionally pausing to look fabulous" (no commas) should be translated as "y se detiene, de vez en cuando, para verse fabuloso" (2 commas added).

It is worth mentioning that translators should adhere strictly to the punctuation rules of the languages they are proficient in, avoiding any mixing when translating from one language to another.

2.3 Glossaries

Glossaries are alphabetical lists of terms relating to a specific field, subject, or text, and provide definitions and explanations of those terms. They serve as reference tools and are typically found at the end of a book, document, or website, where readers can quickly locate and understand the meaning of unfamiliar terms found in the main content.

It is important to note that glossaries and dictionaries have distinct purposes. A glossary provides explanations for specialized terminology. For example, a glossary in a medical textbook would define medical terms within the book. Conversely, a dictionary covers a broader range of words and terms across the entire language. It includes definitions, pronunciations, etymologies,

and examples. The terms included in a glossary may not necessarily be found in a standard dictionary. Glossaries are indispensable tools for translators. Therefore, the following overview outlines their importance in the translation process.

2.3.1 Relevance for the Translator

Translators can enhance their efficiency and ensure accuracy by developing and maintaining glossaries tailored to each project and client. This practice guarantees consistency and precision throughout the entire translation process. Glossaries can be effectively managed using word processing tools, spreadsheets, translation memory software, or specialized terminology management programs.

Before accepting a translation project, translators should ask their clients if they manage internal glossaries with specialized terms that outsiders may not understand. This proactive approach helps translators familiarize themselves with specific terminology and guarantees that translations align closely with the client's expectations and industry standards (McKay, 2006).

2.3.2 Relevance for the Translation Process

Glossaries are crucial tools that compile significant terminology obtained from the source language alongside approved translations for that terminology in the target language. In addition to providing translations, glossaries include comprehensive details such as definitions, contexts, and parts of speech. As a result, glossaries assist translators in ensuring that each term is translated consistently and accurately and speeds up the translation process, reducing costs eventually (Lionbridge, n.d., p. 3).

2.3.3 How to Create a Glossary

The content of a glossary will always depend on the type of the source text, and it is always essential to create a list of important words and phrases. Argos (n.d.) advises searching

for key industry terms, acronyms, and initialisms and their full form, phrases that should not be translated, product names, words that require a special mark or annotation, and other pieces of text that are relevant.

When translators encounter unfamiliar terms that require clarification, it is necessary to promptly add them to the glossary for future reference, which ultimately saves time and ensures consistency. Gebhardt (2014) suggests using Excel as a tool to manage glossaries since it offers distinct advantages in terms of organization and efficiency. Excel allows for the systematic input of information and facilitates easy sorting of data alphabetically, enabling translators to maintain a structured and accessible repository of specialized terms whenever necessary.

2.4 How Translators Can Specialize in Pharmacovigilance Translation

As translating pharmacovigilance documents involves understanding specialized and technical terminology, it is important to investigate the pathways translators develop to specialize in this area. Specializing in this area requires a combination of specialized education, practical experience, and familiarity with the industry's specific documentation standards. According to Mao & Thakkar (2023), "medical documents are often complex and contain technical jargon, making them difficult for nonmedical professionals to understand. Therefore, a medical or life sciences background will greatly help a medical translator to accurately translate technical documents" (p. 5). This highlights the importance of specialized knowledge for translating pharmacovigilance documents. Translators could benefit from studying pharmacovigilance or enrolling in specialized courses to gain a deeper understanding of the main aspects of the pharmacovigilance field. Moreover, Collada & Milani (2019) argue that it is necessary to read about the subject one is translating in the target language (p. 2). Therefore, in addition to formal pharmacovigilance courses, translators can also gain more knowledge by

reading books, articles, guidelines, and reports related to the field. This will help them better understand and accurately translate pharmacovigilance texts.

Chapter III

Methodological Framework

Research is the pursuit of knowledge and involves systematically studying a problem using a deliberate strategy; therefore, developing a comprehensive methodological framework is pivotal. A methodological framework has manifold benefits for research. Firstly, it improves organization. A structured approach ensures that all the necessary steps for an investigation are followed in a logical order. This helps maintain clarity and prevents the omission of important aspects. Secondly, a robust methodological framework ensures that data collection, analysis, and interpretation are achieved rigorously. This enhances the validity and reliability of the findings, reducing bias and errors. Thirdly, a methodological framework guides decision-making. It offers direction on the collection, analysis, and interpretation of data, enabling researchers to make informed decisions based on solid methodologies. An additional benefit is that a methodological framework helps manage time effectively. It minimizes unnecessary effort and resources by focusing on what is essential for achieving the research objectives. Lastly, a clear methodological framework allows readers to understand how the investigation was conducted and assessed. This provides credibility to the research.

Accordingly, this third chapter outlines the methodological framework employed for this investigation. It covers the research approach, design, sources of information, analysis categories, instruments for data collection, and the processes involved in gathering and analyzing data.

The research approach refers to the method adopted by the researcher to collect, analyze, and interpret data. There are three primary research approaches: quantitative, qualitative, and mixed methods. The research design is the systematic strategy planned to conduct the

investigation. It involves designing the data collection and analysis methodologies. This structure aims to address the objectives. The sources of information are the foundational texts the researcher used to conduct the study. They are categorized as primary, secondary, and tertiary. The analysis categories refer to the specific aspects that the researcher analyzed to conduct the research. The instruments for data collection are the tools used by the researcher to gather information during the research process. Finally, the procedures involved in gathering and analyzing data are the methods employed for data collection and its respective analysis.

3.1 Research Approach

The research approach is the exhaustive plan that guides how a researcher investigates and explores a specific topic or issue. It details the strategies for addressing the research question and objectives, specifies the methods for gathering, analyzing, and interpreting data, and outlines the process for concluding. There are three primary research approaches: qualitative, quantitative, and mixed methods.

Firstly, the qualitative method focuses on understanding the complexity of concepts or experiences through in-depth exploration and interpretation of non-numerical data. A researcher who employs qualitative research commonly conducts interviews, observations, textual analysis, focus groups, and case studies as methods for data collection. For this reason, qualitative research is perceived as subjective. Bumbuc (2016) explains that qualitative research significantly relies on the researcher himself/herself as the primary instrument, unlike quantitative research, which uses tools like questionnaires. In a qualitative investigation, the researcher responsible for data collection also assumes the role of data interpreter. In addition, qualitative research is centered on the “how” and “why” of a problem; thus, this approach aims to answer open-ended questions. Open-ended questions are a research method that permits

respondents to provide diverse answers by encouraging them to give comprehensive and individualized responses. Weller et al. (2018) state that “open-ended questions are used alone or in combination with other interviewing techniques to explore topics in depth, to understand processes, and to identify potential causes of observed correlations”.

Secondly, the quantitative method focuses on quantifying phenomena through collecting and analyzing numerical data, aiming to generalize findings and validate hypotheses. Quantitative research explores the “when” and “where” of a problem. It uses tools such as surveys, questionnaires, experiments, or observational studies to gather and analyze data to produce statistics, which results in a more objective approach. Cint (2020) remarks on the reliability of quantitative research emphasizing that “quantitative research is objective, meaning the variables and data you collect are reliable and accurate. When you ask someone how many cups of coffee they drink every day, you get a direct, objective answer”.

Lastly, the mixed-methods approach integrates qualitative and quantitative research techniques to offer a thorough exploration of a research issue. Researchers employ this approach to gather and analyze both non-numerical and numerical data to enrich their findings.

The approach adopted for this research was a mix of both qualitative and quantitative methods. It is predominantly qualitative because the researcher as a translator engaged in analyzing, understanding, and interpreting the content of the *Reglamento de buenas prácticas de farmacovigilancia* and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline*, which mirrors textual analysis as one of the qualitative methods for data collection. In this investigation, the researcher also brought her understanding, cultural knowledge, and linguistic skills into the translation process and analyzed and interpreted the quality of each translation method, technique, or procedure used. These aspects parallel qualitative research’s

focus on interpreting and understanding textual information and subjectivity. Additionally, the research question of this study is an open-ended question, which is another characteristic of the qualitative approach.

Nonetheless, this research is also quantitative because the researcher quantified the number of times a method, technique, or procedure was used during the translation process. This reflects quantitative research's focus on collecting numerical data.

3.2 Research Design

The research design is the systematic strategy planned by the researcher to conduct this investigation and fulfill its objectives.

The general objective of this research was to translate two documents; therefore, the design appropriate for this goal was the descriptive research design. According to Singh (2023):

> Descriptive research is a methodological approach that seeks to depict the characteristics of a phenomenon or subject under investigation. In scientific inquiry, it serves as a foundational tool for researchers aiming to observe, record, and analyze the intricate details of a particular topic. This method provides a rich and detailed account that aids in understanding, categorizing, and interpreting the subject matter.

Correspondingly, the researcher collected the *Reglamento de buenas prácticas de farmacovigilancia* and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline* to translate them into Spanish and English, respectively. The researcher also understood and observed the complexities of the texts through the text analysis process. Lastly, she maintained records of the translation process, including any challenges faced, decisions made, and translation methods and techniques applied.

Furthermore, since the first specific objective is to evaluate which methods are the most suitable for translating pharmacovigilance documentation according to translation theory, the emphasis is on describing and analyzing various translation methods and techniques following their implementation in the translation of the *Reglamento de buenas prácticas de farmacovigilancia* and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline*.

The second specific objective is to determine the specific skills a translator needs to translate pharmacovigilance documentation. This was achieved through the examination of the texts to identify linguistic and technical challenges and the presentation of descriptive findings that outline unique skills essential for translating pharmacovigilance documentation.

Lastly, the third specific objective is to investigate how translators can specialize in pharmacovigilance translation. The researcher conducted a review of existing literature related to specialized translation and presented findings that describe the pathways, skills, and strategies translators use to specialize in this area.

3.3 Information Sources

Information sources in research refer to the various sources from which researchers gather data and knowledge relevant to their study, and they are categorized as primary, secondary, and tertiary sources.

Primary sources are provided by individuals directly involved. They present information for the first time and serve as the original material for further research. Primary sources are commonly found in libraries, archives, museums, or online databases if they are digitized. These sources encompass original documents such as laws, newspaper reports written by reporters who witnessed an event, speeches, autobiographies, personal letters and diaries, initial research,

surveys, interviews, and photographs, videos, or audio that serve as first-hand documentation of an event. The primary sources of this research were the *Reglamento de buenas prácticas de farmacovigilancia* and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline* provided by Bioplus Care S.A. and their respective translations into English and Spanish.

Secondary sources analyze or restate information found in primary sources, offering descriptions, explanations, or interpretations that help researchers understand the primary data and add context or insight to the original material, contributing to the theoretical framework or discussion of a research topic. Secondary sources include books that explore a specific subject, analyses of data, scholarly articles written by researchers not directly involved, dissertations, criticism of literature, artworks, or music, and documentaries that incorporate primary source elements such as photos, videos, or audio. The secondary sources used in this research were the various books and articles that explored translation methods, techniques, and procedures and added insight to the translation of the *Reglamento de buenas prácticas de farmacovigilancia* into English and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline* into Spanish.

Tertiary sources help researchers quickly understand a topic or locate primary and secondary sources for further explanation. These sources compile information from other sources, summarizing and indexing primary sources (which offer original data) and secondary sources (which interpret or describe data). Examples of tertiary sources are dictionaries, encyclopedias, manuals, and bibliographies. Since this research deals with the translation of two documents, one of the tertiary sources used was dictionaries to accurately convey the meaning of words that required clarification.

3.4 Analysis Categories

The categories analysis are the specific aspects the researcher examined for this research. This research focuses on the analysis of textual information, which is one of the methods of the qualitative approach. Analysis of textual information allows researchers to explore themes, patterns, and meanings within a text. Hence, categories essential for analysis are translation strategies. Translation strategies encompass text analysis techniques, translation methods, and translation procedures. As explained in the theoretical framework, these three elements are crucial in the translation process, for translators maintain accuracy and faithfulness in their work by comprehending translation strategies. Moreover, translation strategies help translators make numerous decisions regarding vocabulary choice, sentence structure, and cultural references. These strategies were carefully considered in this research for collecting and analyzing the data of the texts.

3.5 Data Collection Instruments

Data collection instruments are fundamental tools for gathering information in research; thus, they must be carefully designed. Examples of data collection instruments are surveys, questionnaires, interviews, focus groups, and observations, among other methods. To create an effective data collection instrument, researchers must first define their data's needs. They should begin by clarifying the goals and determining the data type required (quantitative or qualitative) and how it will be analyzed. Another aspect that researchers must consider is selecting a data collection tool based on factors such as feasibility, cost, time constraints, and participant accessibility. Lastly, researchers need to ensure that their instruments are easy to understand and free from ambiguity. The data collection instruments developed for this research are the following:

3.5.1 Text Analysis Chart

The first data collection instrument in this research was the text analysis chart. It was used to categorize the various elements within the source texts. The first column encompasses the text analysis criteria, with text style referring to whether the texts are narrative, descriptive, discussion, or dialogue. The text function refers to whether the texts are informative, expressive, or vocative. The scale of formality indicates the level of formality present in the language of the documents, ranging from highly formal to extremely informal. The scale of generality or difficulty refers to the comprehensibility or complexity of the context within each document, ranging from basic vocabulary to detailed, technical language. The scale of emotional tone assesses the emotional tone present in the text, ranging from intense to restrained. The translation method refers to whether a semantic or communicative approach is used. The other two columns are the names of the documents translated. The complete version of this chart appears in Chapter V.

Table 1. Text Analysis Chart

Text Analysis	***Reglamento de buenas prácticas de farmacovigilancia***	***Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline***
Text Style		
Text Function		
Scale of Formality		
Scale of Generality or Difficulty		
Scale of Emotional Tone		
Translation Method		

Table 1. It represents the different elements of the source texts. Source: Researcher's own creation

3.5.2 Color-Coded Text Chart

The second data collection instrument in this research was the text color-coded text chart. In the translated texts analysis, the researcher employed color coding to distinguish each translation procedure: purple for transposition (grammatical changes), blue for modulation (point of view changes), green for omission (leaving out text details), orange for amplification (addition of extra information for clarity), red for explicitation (converting implicit details into explicit), and pink for literal translation (word-for-word translation).

The complete version of this chart appears in Chapter V.

Table 2. Color-Coded Text Chart

Color	Meaning (Translation Procedure)
	Transposition
	Modulation
	Omission
	Amplification
	Explicitation
	Literal Translation

Table 2. The colors represent each translation procedure employed. Source: Researcher's own creation

3.6 Collection Data Process and Data Analysis

For the collection and analysis of data, the researcher as a translator followed several steps. Firstly, she carefully read the *Reglamento de buenas prácticas de farmacovigilancia* and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline*. In this step, the researcher engaged in two crucial steps of text analysis: general reading and close reading. While doing general reading, the researcher obtained the overall context of the texts and generally understood their content. In the close reading step, the researcher searched for specific words and phrases and understood their meaning in and out of context. The researcher also identified unfamiliar and specialized terms that required clarification using dictionaries and glossaries and added them to her glossary for future reference. These steps helped the researcher discover potential challenges such as ambiguities, idiomatic expressions, and contextual factors that require careful consideration for effective translation. Subsequently, the researcher used the first data collection instrument: the text analysis chart. In this step, the researcher determined the text style, function, and the scales of formality, generality, difficulty, and emotional tone. Eventually,

the researcher engaged in the translation of the texts. Here, the researcher applied her linguistic skills and cultural knowledge and implemented the previously reviewed translation strategies to the translation process. The researcher exhaustively analyzed every sentence to decide whether to use transposition, modulation, omission, amplification, explicitation, or literal translation to preserve accuracy, naturalness, and faithfulness. After meticulously revising the translation, the researcher employed the second data collection instrument: the color-coded text chart. Here, the researcher repeats the analysis of sentences to highlight each translation procedure with its respective color to facilitate their location within the texts. Finally, the researcher continued with the data analysis and interpretation of the results.

Chapter IV

Translation of Documents

The following chapter includes the translation of the documents *Reglamento de buenas prácticas de farmacovigilancia* and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline.*

4.1 Translation of the document *Reglamento de buenas prácticas de farmacovigilancia* from Spanish into English

Regulation of Good Pharmacovigilance Practices

CHAPTER I

General Provisions

1. GENERAL OBJECTIVE

To define the foundation for establishing a quality assurance system in the activities of the National Pharmacovigilance System. This involves establishing the obligations and responsibilities of the different agents involved, aiming to ensure consistent criteria for evaluating reports, generating alerts, and promoting the understanding and teaching of Pharmacovigilance.

2. SCOPE

The provisions of this regulation apply to all agents that make up the National Pharmacovigilance System and to all human medicines imported, manufactured, marketed, and used in the country.

3. REFERENCES

For proper interpretation and application of this regulation, the following documents should be consulted:

3.1 Reglamento del Sistema Nacional de Farmacovigilancia. Executive Decree No. 35244-S, dated April 13, 2009, published in La Gaceta No. 98 on May 22, 2009.

3.2 Reglamento Técnico Centroamericano RTCA 11.03.59:11 Productos Farmacéuticos. Medicamentos para Uso Humano. Requisitos de Registro Sanitario. Appendix 1 of Resolution No. 333-2013 (COMIECO-LXVI), published in Alcance Digital No. 20 of La Gaceta No. 103 on May 30, 2014.

3.3 Reglamento para la autorización para la importación y adquisición de medicamentos no registrados. Executive Decree No. 36358-S, dated October 4, 2010, published in La Gaceta No. 25 on February 4, 2011.

4. ABBREVIATIONS

4.1 GVPs: Good Pharmacovigilance Practices

4.2 CIOMS: Council for International Organizations of Medical Sciences

4.3 CNFV: Centro Nacional de Farmacovigilancia

4.4 DRPIS: Dirección de Regulación de Productos de Interés Sanitario

4.5 ESAVI: Event Supposedly Attributable to Vaccination or Immunization

4.6 PhV: Pharmacovigilance

4.7 IBD: International Birth Date

4.8 ICH: International Conference on Harmonization

4.9 PSUR: Periodic Safety Update Report

4.10 WHO: World Health Organization

4.11 PAHO: Pan American Health Organization

4.12 SOPs: Standard Operating Procedures

4.13 ADR: Adverse Drug Reaction

4.14 SNFV: Sistema Nacional de Farmacovigilancia

4.15 WHO-ART: The WHO Adverse Reaction Terminology

5. DEFINITIONS

To interpret this regulation, the following definitions are used in addition to those established in Executive Decree No. 35244-S, Regulation of the Sistema Nacional de Farmacovigilancia:

5.1 Alert: Information provided about a potential causal relationship between an adverse event and a medication when this relationship was previously unknown or incompletely documented.

5.2 Audit: The review of specific activities conducted to verify compliance with Good Pharmacovigilance Practices.

5.3 Pharmacovigilance Database: A computer system where suspected adverse reaction reports are recorded after they have been evaluated and coded.

5.4 Good Pharmacovigilance Practices: A set of rules designed to ensure the authenticity and quality of the data collected in pharmacovigilance. These practices facilitate the ongoing assessment of medication risks, maintain the confidentiality of information reported about adverse reactions, and ensure consistent criteria in evaluating and generating alerts.

5.5 Causality: The relationship between the occurrence of the reported adverse event and the use of a specific medication.

5.6 Confidentiality: The protection of the identity of the person who suffered a suspected adverse reaction, including all personal or clinical information. Similarly, the personal information of the reporting professionals is also confidential.

5.7 Crisis: A crisis occurs when new information about the safety or efficacy of a product that could significantly impact public health is revealed and thus requires immediate action. It can also happen when the media disseminates information expressing concern about the use of a particular product.

5.8 Efficacy: The ability of a medication to produce the intended effects.

5.9 Post-marketing Study: Any clinical or epidemiological study conducted during the marketing of a medication under the conditions authorized in the health registration, or under normal use conditions, where the medication(s) of interest are the primary factor investigated.

5.10 Therapeutic Failure: Any situation where the expected therapeutic effect is not achieved in a patient, despite administering the medication at appropriate dosages according to the prescription used for prophylactic, diagnostic, and therapeutic purposes or to modify a physiological function.

5.11 Pharmacovigilance: A public health activity focused on identifying, quantifying, assessing, and preventing risks associated with the use of human medications once they are on the market.

5.12 Intensive Pharmacovigilance: A pharmacovigilance method involving the systematic, high-quality, and comprehensive collection of information on suspected adverse drug reactions. This approach is characterized by its high sensitivity and reliability, especially when determining the frequency of adverse reactions and identifying predisposing factors and patterns of medication use, among other aspects.

5.13 Modified CIOMS Form: This is the form created by the CIOMS that has been modified by the CNFV for use by the pharmaceutical industry to report suspected adverse reactions.

5.14 Hospital: A healthcare facility with at least five inpatient beds that provides basic diagnostic and treatment services. It has an organized medical staff and provides ongoing care with documented admissions and continuous physician-led assistance.

5.15 Parallel Importation: The importation of patented and registered pharmaceutical products into Costa Rica by any pharmacy without the consent of the patent holder, and marketed per the health regulations of the exporting country.

5.16 Indication: The intended uses of a medication, once it has been scientifically proven its efficacy and safety for a specific purpose.

5.17 Pharmaceutical Industry, Product Holder, or Registration Holder: The natural or juridical person who owns the medication.

5.18 Periodic Safety Update Report: A document prepared by the product holder to update the medication's safety information. It includes, among other things, details of suspected adverse reactions that have been reported during the reference period and a scientific evaluation of the medication’s benefit-risk balance.

5.19 Monograph: A medication’s scientific and technical description that must include the information specified in section 7.6 of the Reglamento Técnico Centroamericano RTCA 11.03.59:11 Productos Farmacéuticos. Medicamentos para Uso Humano. Requisitos de Registro Sanitario:

a) The medication’s concentration and international nonproprietary or generic name

b) Dosage form

c) Structure and chemical name of the active substance, or if unavailable, the technical data sheet that provides this information

d) Clinical pharmacology

e) Indications

f) Contraindications

g) Precautions and warnings

h) Interactions

i) Adverse effects

j) Dosage and routes of administration

k) Overdose recommendations according to the toxicological profile.

l) Abuse and addiction

m) Date of monograph review

n) Complete bibliographic references

o) Therapeutic class according to the Anatomical Therapeutic Chemical (ATC) Classification

p) Preparation method

5.20 Notification: Reporting a medication's suspected adverse reaction to the CNFV using the adverse reaction notification forms (Yellow Card or Modified CIOMS Form) established by the Ministry of Health.

5.21 Risk Minimization Plan: A document in which the product holder specifies the risks associated with the medication, whether identified or potential, and provides safety information not yet covered in scientific literature. It is a strategic safety program designed to achieve specific goals and objectives to minimize the known risks of the medication while preserving its benefits.

5.22 Standard Operating Procedures: Written and detailed instructions to ensure uniformity in the performance of a specific activity. They are fundamental for internal or external audits.

5.23 Traceability: The ability to track and trace the production, storage, distribution, and marketing of a medication.

5.24 Risk: The likelihood of a medication causing harm or damage to health, associated with the extent of such harm.

5.25 Benefit-Risk Evaluation: It reflects the correlation between the benefit and the risk associated with the use of a medication. It is used to assess the medication's role in medical practice based on data regarding its efficacy and safety, as well as considerations of potential misuse, the severity and prognosis of the disease, etc. This concept can be applied to a single medication or in comparisons between two or more medications used for the same indication.

5.26 Signal: A potential causal relationship between an adverse event and a medication when this relationship was previously unknown or incompletely documented. Typically, more than one report is required to generate a signal, depending on the severity of the adverse event and the quality of the information.

5.27 Spontaneous Notification System: A pharmacovigilance method based on the communication, reporting, collection, and evaluation of reports on suspected adverse drug reactions made by healthcare professionals using established forms.

5.28 WHO-ART: It is the World Health Organization's dictionary of adverse reactions, which contains the terminology used to code clinical information related to medications.

6. SISTEMA NACIONAL DE FARMACOVIGILANCIA

The SNFV is regulated by Executive Decree No. 35244-S "Reglamento del Sistema Nacional de Farmacovigilancia," which applies to the pharmacovigilance of all human-use medications imported, manufactured, marketed, and used in the country.

7. OPERATION OF THE SISTEMA NACIONAL DE FARMACOVIGILANCIA

7.1 Healthcare professionals must submit reports to the CNFV using the designated forms for data collection.

7.2 The CNFV must periodically evaluate safety information according to the established SOPs to identify potential safety issues from medication use early and generate signals.

7.3 The signals will be discussed and analyzed by the Comisión Nacional de Farmacovigilancia, following the established SOPs.

7.4 The Comisión Nacional de Farmacovigilancia must guide the DRPIS for decision-making.

7.5 The DRPIS must take necessary actions to maintain a favorable benefit-risk ratio for medications.

7.6 The DRPIS must inform healthcare professionals and the public about the safety measures taken to maintain the favorable benefit-risk ratio.

CHAPTER II

About the Information of the Sistema Nacional de Farmacovigilancia

8. DOCUMENTATION

The agents of the SNFV must maintain complete and up-to-date documentation under this regulation.

8.1 Reporting Forms

8.1.1 All healthcare professionals must report suspected adverse reactions using the Yellow Card (Appendix A) and ensure that the information provided is complete.

8.1.2 The pharmaceutical industry must report suspected adverse reactions using the Modified CIOMS Form (Appendix B) and ensure that the information provided is complete.

8.1.3 Both the pharmaceutical industry and healthcare professionals must report suspected therapeutic failures using the forms mentioned in sections 8.1.1 and 8.1.2 (see Appendixes A and B).

8.1.4 To analyze a report, the following information is required (written legibly and in permanent ink):

a) Identifiable patient: the patient's name or initials, identification number, or gender.

b) Suspected medication: generic name or brand name.

c) Exact or approximate date of when the medication was started.

d) Adverse reaction, including anatomical position and severity (mild, moderate, severe, or fatal), if available.

e) Exact or approximate date of the reaction's onset.

f) Identifiable reporter: name, signature, professional code, phone number, and email address.

8.1.5 If additional information is available, notifiers must document, send, and retain it to expand on the details provided in the adverse reaction report form. If the information is confidential, a summary of the information obtained must be included in the form.

8.1.6 The report must be submitted in a physical form to the CNFV through the Customer Service Department. The information can be sent by fax, email, or communicated by phone to the CNFV, with the physical documentation delivered subsequently according to the Reglamento del Sistema Nacional de Farmacovigilancia.

8.2 Standard Operating Procedures

8.2.1 The CNFV must have established SOPs for each of its activities.

8.2.2 Healthcare providers and the pharmaceutical industry must have SOPs for each pharmacovigilance activity they perform. These SOPs must be reviewed and approved by the pharmacovigilance staff in charge, implemented, and known to all involved staff.

CHAPTER III

Obligations and Responsibilities of SNFV Agents

9. CENTRO NACIONAL DE FARMACOVIGILANCIA

The CNFV must fulfill the following obligations and responsibilities:

9.1 Receive, evaluate, analyze, and code reports of suspected ADRs.

9.2 Monitor medication safety through the analysis of signals.

9.3 Communicate all safety information related to human-use medications detected during analyses to the DRPIS.

9.4 Disseminate pharmacovigilance information to patients and healthcare professionals.

9.5 Coordinate the pharmacovigilance activities of the SNFV agents to collect necessary and timely information on suspected ADRs.

9.6 Participate in training activities on pharmacovigilance, mainly aimed at healthcare professionals and university students in health-related fields.

9.7 Conduct inspections of the work performed by the pharmacovigilance staff in charge and the pharmaceutical industry to ensure compliance with GVPs and assess their effectiveness in achieving specific objectives. To facilitate pharmacovigilance inspections, the Ministry of Health will provide the Guía de Verificación de BPFV on its website.

9.8 Identify and analyze generated signals and conduct investigations to determine whether the medication is the cause of the event. These signals may primarily be detected through the following pharmacovigilance methods:

a) Individual patient descriptions

b) Publication of cases in scientific literature

c) Spontaneous reporting to the Sistema de Farmacovigilancia

d) Observational studies in populations: cohort or case-control studies.

e) Experimental studies: biomedical research.

A single, well-documented reported case may be considered a signal, especially if it describes a positive re-exposure or if the event is unknown without the use of the medication.

9.9 Periodically evaluate the information contained in the CNFV's pharmacovigilance database to detect signals, which will then be assessed and analyzed. If a detected signal is considered an imminent public health issue, an investigation and report must be conducted to implement appropriate health measures.

9.10 Quantify the strength of the association between the adverse reaction and the medication, once a risk has been identified and its impact on public health assessed.

9.11 Evaluate the potential benefits and risks of medications for which a risk has been quantified and ensure that the benefit-risk ratio remains favorable.

9.12 Develop strategies to prevent and minimize the risks associated with medications, including:

a) Implement intensive pharmacovigilance programs or monitoring for specific medications or risk groups.

b) Establish processes to integrate health surveillance activities related to promotion and advertising, in connection with information on adverse reactions, warnings and precautions, and contraindications.

c) Systematically and periodically perform risk prevention. Healthcare professionals, users, the pharmaceutical industry, healthcare providers, the CNFV, and the DRPIS all share responsibilities.

For unavoidable adverse reactions, the goal should be early detection as the primary preventive measure to reduce the extent of harm.

9.13 Collaborate with public health programs, including the immunization program, so that reports of events and suspected ADRs detected through these programs are reported to the CNFV for evaluation. The ESAVIs, even if referred to other public health authorities, must be reported to the CNFV using the Yellow Card, following the guidelines established for managing ESAVIs.

10. HEALTHCARE PROVIDERS

All healthcare providers, including public and private hospitals and the healthcare facilities of the CCSS, must have a designated pharmacovigilance officer.

10.1 The medical director of the healthcare facility must appoint a pharmacovigilance officer and notify the CNFV in writing, including their contact details. Additionally, the director must provide the necessary resources to enable the pharmacovigilance officer to fulfill their responsibilities effectively.

10.2 The pharmacovigilance officer must meet the following requirements, obligations, and responsibilities:

a) Serve as the contact with the CNFV.

b) Have access to a telephone, fax, computer with internet, email, and photocopier.

c) Promote the Spontaneous Reporting System for Adverse Drug Reactions and other programs following GVPs within their healthcare facility.

d) Distribute the adverse reaction reporting form (Yellow Card) to healthcare professionals within their facility.

e) Receive reports of suspected ADRs generated within the healthcare facility with the sole purpose of forwarding them to the CNFV.

f) Maintain a record of the reports received.

g) Verify that the forms (Yellow Cards) are complete; otherwise, take the necessary steps to complete the information.

h) Ensure the confidentiality of reports made by healthcare professionals.

i)Forward any inquiries or requests for information related to suspected ADRs from healthcare professionals within the facility to the CNFV.

j) Respond to information requests from the CNFV.

k) Coordinate with the CNFV to organize training activities for healthcare professionals.

l)Participate in meetings, training sessions, and other activities organized by the CNFV.

m) Establish the necessary SOPs to guarantee GVPs at the healthcare facility.

11. PROFESSIONALS IN HEALTH SCIENCES

11.1. Professionals in the health sciences must meet the following requirements, obligations, and responsibilities:

a) Actively participate in the Sistema Nacional de Farmacovigilancia to effectively and promptly gather all information related to suspected ADRs, which have a direct impact on the safety of medications used in the country.

b) Comply with the obligations stated in Executive Decree No. 35244-S "Reglamento del Sistema Nacional de Farmacovigilancia" in Article 11.

c) Complete the Yellow Card fully when a suspected adverse reaction is identified.

d) Submit suspected ADRs to the CNFV using official forms and within the deadlines specified in Executive Decree No. 35244-S. This submission can be done through the Health Directorates of the Ministry of Health.

e) Ensure the confidentiality of the reports made to the CNFV.

f) Respond to information requests from the CNFV.

g) Participate in meetings, training sessions, and other activities organized by the CNFV.

h) Stay informed about safety data related to medications they commonly prescribe, dispense, or administer.

i) If needed, provide expert assistance to the CNFV in evaluating medication safety issues.

11.2. The managers of pharmacies that import medications through parallel importation and under Article 117 of the Ley General de Salud, specifically Article 3 of Executive Decree No. 36358-S, must fulfill, in addition to the requirements mentioned in the previous section, the following requirements, obligations, and responsibilities:

a) Ensure that SOPs are established and followed to guarantee pharmacovigilance for products imported through the specified modality.

b) Ensure that all staff working in the pharmacy are aware of the SOPs.

c) Either manage the Pharmacovigilance Program personally or delegate this responsibility to a trained healthcare professional, who will be the contact person with the CNFV.

d) Establish agreements on pharmacovigilance if there is any transfer of obligations and functions. These agreements must be documented in a written and notarized agreement signed by the legal representatives of both companies and must be notified to the CNFV. Functions not transferred through this agreement remain the responsibility of the importer.

e) Implement any health measures requested by the DRPIS regarding medication safety.

f) Maintain a detailed record of suspected ADRs detected, including all information contained in the Suspected ADR Reporting Form. This record must be kept in a filing system, either physical or digital, that ensures proper storage of all documentation related to pharmacovigilance responsibilities and activities for a period of 5 years.

g) Respond to any information request from the DRPIS regarding medication safety within a maximum of 10 business days.

h) Continuously evaluate the benefit-risk ratio of medications and report any new safety information to the DRPIS within a maximum of 10 business days.

i) Identify signals, assess their severity, and report them to the CNFV.

j) Conduct intensive pharmacovigilance on medications when the CNFV requires it. To facilitate compliance with intensive pharmacovigilance requirements, the Ministry of Health will provide the Guía para realizar FV Intensiva on its website.

12. PHARMACEUTICAL INDUSTRY

All drug registration holders must have a Pharmacovigilance Program. This program should outline the roles and responsibilities related to the safety of the medications they market and ensure appropriate measures are taken when necessary.

12.1 Obligations and Responsibilities of the Registration Holder:

a) Ensure that all company staff are knowledgeable about Pharmacovigilance.

b) Appoint a healthcare professional to manage the Pharmacovigilance Program, who will be the contact person with the CNFV.

c) Provide the professional in charge of the Pharmacovigilance Program with access to updated monographs and basic safety information for each medication.

d) Establish agreements on pharmacovigilance. If there is any transfer of obligations and functions, it must be documented in a written and notarized agreement signed by the legal representatives of both companies. These agreements must be notified to the CNFV and should also be included in the health registration file. Functions not transferred through this agreement remain the responsibility of the registration holder.

e) Ensure that SOPs are established and followed to guarantee pharmacovigilance.

f) Maintain a filing system, whether physical or digital, that properly preserves all documentation related to pharmacovigilance responsibilities and activities for 5 years. The responsibilities for managing the file system must be defined in writing.

g) Implement an internal audit program to ensure that the Pharmacovigilance Program complies with the provisions of this regulation.

h) The registration holder should provide the CNFV with any information related to the safety of their medications.

i) The registration holder should submit to the CNFV (before distribution) any statement related to the safety of their medications that they wish to share with healthcare professionals or the public. The CNFV may request additional information or modifications to the statement.

j)All safety-related statements about their medications must include the following caption: "Any suspicion of adverse reaction must be reported to the CNFV using the forms and within the deadlines established by current regulations."

12.2 Obligations and Responsibilities of the Pharmacovigilance Officer:

a) Report any suspected ADRs, recalls, or other safety-related issues concerning medications marketed nationally or internationally to the CNFV.

b) Implement any health measures requested by the DRPIS related to medication safety.

c) Maintain a detailed record that includes all information in the Suspected Adverse Reaction Reporting Form.

d) Submit the PSUR to the CNFV. To help meet IPS requirements in terms of content, the Ministry of Health will provide the Guía de presentación de IPS para la Industria Farmacéutica on its website.

e) Respond to any information request from the DRPIS regarding medication safety within a maximum of 10 business days.

f) Continuously evaluate the benefit-risk ratio of medications marketed in the country and report any new safety information to the DRPIS within a maximum of 10 business days.

g)Identify signals, assess their severity, and report them to the CNFV.

h) Conduct intensive pharmacovigilance on medications when the CNFV requires it. To facilitate compliance with intensive pharmacovigilance requirements, the Ministry of Health will provide the Guía para realizar FV intensiva on its website.

i)Participate in meetings, training sessions, and other activities organized by the CNFV.

j) If needed, provide expert assistance to the CNFV in evaluating medication safety issues.

k) If you are aware of a suspected adverse reaction related to medications not produced by your company, you must report it to the holder of that product.

12.3 Organization and Staff:

The Pharmaceutical Industry must maintain an updated organizational chart that reflects the hierarchical relationship between the Pharmacovigilance Officer, the Medical Director, and other departments. It must adhere to the following requirements:

a) There must be a designated Pharmacovigilance Officer and a substitute, both with training and experience in pharmacovigilance.

b) The pharmacovigilance staff must be aware of their assigned roles and responsibilities, which should be written in job descriptions approved by management.

c) The registration holder must keep the résumé, job description, and training records of staff involved in pharmacovigilance tasks up to date.

d) The registration holder must provide the Pharmacovigilance Officer with the necessary human resources and materials to carry out their responsibilities effectively.

12.4 Pharmacovigilance Training for the Registration Holder's Staff:

12.4.1 An initial and ongoing pharmacovigilance training program must be established and approved by the Pharmacovigilance Officer.

12.4.2 All company staff that receive reports of suspected adverse reactions must receive initial and continuous training in pharmacovigilance.

12.4.3 Records that validate the staff's training must be kept.

12.5 Standard Operating Procedures (SOPs):

The registration holder must have SOPs approved by the Pharmacovigilance Officer and the Medical Director, detailing the functions and activities related to pharmacovigilance. These SOPs must:

a) Be updated according to the latest scientific information and current legislation. A historical archive of SOP updates must be maintained.

b) Ensure that the Pharmacovigilance Officer and all staff involved in the Pharmacovigilance Program perform their tasks according to the established SOPs.

c) Be accessible to staff responsible for carrying out the tasks described in their job descriptions, as well as to relevant guidelines and regulations on pharmacovigilance.

12.6 Management of Suspected Adverse Drug Reaction Reports:

12.6.1 The information recorded in reports of suspected adverse drug reactions will be treated as a sworn declaration; the Ministry of Health may verify the veracity of the information.

12.6.2 When a staff member of the registration holder receives initial or follow-up information about an ADR, they must report it to the Pharmacovigilance Officer no later than one business day after receiving the information. The date the registration holder became aware of the ADR must be documented.

12.6.3 The Pharmacovigilance Officer must ensure that each received ADR report is recorded, dated, and assigned a unique and unequivocal correlative identification number.

12.6.4 For any suspected ADR, the Pharmacovigilance Officer must ensure that all necessary information is collected and must evaluate the following criteria: severity, whether it is referenced according to the product's basic safety information, whether it is expected or unexpected according to the monograph, and compliance with reporting deadlines as specified in Executive Decree No. 35244-S "Reglamento del Sistema Nacional de Farmacovigilancia." This information should be recorded in the CIOMS-modified form in the section for describing ADRs.

12.6.5 The Pharmacovigilance Officer must ensure that the evolution and outcome of each individual case are monitored after making at least three attempts to contact the reporter, which must be documented. Any additional follow-up information received must be recorded and dated in the same way as the initial information and sent to the CNFV using the CIOMS-modified form in the section for describing ADRs.

12.6.6 All documents and records related to the same ADR must be kept together or in a way that allows for easy retrieval and tracking of all activities related to detection, evaluation, and reporting.

12.6.7 When information is received directly from a patient suggesting an ADR, the registration holder must seek the patient's consent to contact the healthcare professional responsible for clinical follow-up to obtain additional information.

12.6.8 Information regarding overdose, exposure during pregnancy or breastfeeding, misuse, dependence, drug abuse, or medication errors must be collected and sent to the CNFV using the CIOMS-modified form within the deadlines established by Executive Decree No. 35244-S "Reglamento del Sistema Nacional de Farmacovigilancia."

4.2 Translation of the document *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline* from English into Spanish

INFORME PERIÓDICO DE EVALUACIÓN BENEFICIO-RIESGO (PBRER)

1. INTRODUCCIÓN

El Informe Periódico de Evaluación Beneficio-Riesgo (PBRER, por sus siglas en inglés), descrito en esta guía, está destinado a ser un estándar común para los informes periódicos de evaluación beneficio-riesgo de los productos comercializados entre las regiones de la ICH (incluidos los medicamentos aprobados que están bajo investigación).

En la presente guía se define el formato y el contenido recomendados para un PBRER, y se proporciona un esquema de los puntos que se deben tener en cuenta en su preparación y presentación.

Las definiciones de muchos términos técnicos utilizados en la guía se incluyen en un glosario (Anexo A); la primera mención de un término en la guía está marcada con un asterisco (*).

1.1 Antecedentes

Cuando se aprueba la comercialización de un nuevo medicamento, la demostración de su seguridad y eficacia generalmente se basa en datos de un número limitado de pacientes, muchos de ellos estudiados en condiciones controladas de ensayos aleatorizados. A menudo se excluyen de los ensayos clínicos a los subgrupos de mayor riesgo y a los pacientes con enfermedades concomitantes que requieren el uso de otros medicamentos, y los datos sobre tratamientos a largo plazo son limitados. Además, los pacientes que participan en los ensayos son monitoreados de cerca para detectar evidencia de eventos adversos. En la práctica clínica, el monitoreo es menos intensivo, se trata a una gama más amplia de pacientes (edad, comorbilidad, medicamentos, anomalías genéticas), y pueden observarse eventos demasiado raros para ocurrir en ensayos clínicos (por ejemplo, una lesión hepática grave). Estos factores subrayan la necesidad de un análisis continuo de la información pertinente sobre seguridad, eficacia y efectividad[1] a lo largo del ciclo de vida de un medicamento: de manera inmediata, cuando se producen hallazgos importantes, y periódicamente, para permitir una evaluación general de los datos acumulados. Aunque la mayoría de la información nueva estará relacionada con la seguridad, la nueva información sobre la efectividad, las limitaciones de uso, los tratamientos alternativos y muchos otros aspectos del rol del medicamento en la terapia, pueden ser pertinentes para su evaluación de beneficio-riesgo.

La guía E2C de la ICH, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, alcanzó el *Paso 4* en 1996, y tenía como objetivo armonizar los requisitos de informes periódicos a las autoridades reguladoras y proporcionar, en un formato común, la experiencia mundial de seguridad en intervalos de un medicamento en momentos definidos después de su aprobación. En ese momento, el Informe Periódico de Seguridad (PSUR, por sus siglas en inglés), se centraba en la nueva información de seguridad pertinente en el contexto de la exposición del paciente para determinar si era necesario realizar cambios en la Información de Referencia de Seguridad* (RSI, por sus siglas en inglés), con el fin de optimizar el uso seguro y continuo del producto. La guía se revisó en 2003 para proporcionar la aclaración, la orientación y la flexibilidad necesarias.

[1] Los términos eficacia y efectividad no están estandarizados y tienen significados diferentes en algunas regiones. Véase la sección 2.6

Desde entonces, el entorno de la farmacovigilancia ha evolucionado, lo que ha motivado una reevaluación del rol del PSUR dentro del conjunto de documentos de seguridad presentados a las autoridades reguladoras. Esta reevaluación destacó varios factores que llevaron a un consenso sobre la revisión y el reenfoque de la guía, a fin de mejorar su utilidad a la luz de los avances en el campo:

- Un avance significativo en la tecnología y la ciencia de la farmacovigilancia, incluida la presentación electrónica de Informes de Seguridad de Casos Individuales (ICSRs, por sus siglas en inglés), a las autoridades reguladoras, técnicas automatizadas de minería de datos y una mayor atención a la evaluación de la relación beneficio-riesgo.
- Un mayor énfasis en la planificación proactiva y documentada de la gestión de riesgos.
- Un mayor reconocimiento de que la evaluación significativa de la nueva información importante sobre riesgos debe realizarse en el contexto de los beneficios de un medicamento.
- Coincidencia en el contenido de las guías de la ICH relacionadas con la documentación de farmacovigilancia.

Como se mencionó anteriormente, el objetivo principal del PSUR era proporcionar un panorama completo de la seguridad de los medicamentos aprobados. Teniendo en cuenta que la evaluación del riesgo de un medicamento es más significativa cuando se considera a la luz de sus beneficios, el informe propuesto pondría un mayor énfasis en el beneficio que el PSUR, especialmente cuando las estimaciones de riesgo cambien significativamente. En tales casos, será necesario que haya una evaluación general explícita del beneficio-riesgo. En consecuencia, el nombre del informe propuesto es “Informe periódico de evaluación beneficio-riesgo” (PBRER). El PBRER también pondría un mayor énfasis en el conocimiento acumulativo sobre un medicamento, al tiempo que mantendría un enfoque en la información nueva.

Una nueva característica del PBRER es la evaluación formal del beneficio, sin embargo, se reconoce que un análisis conciso del beneficio suele ser suficiente, a menos que el perfil de seguridad o de beneficio-riesgo haya cambiado significativamente durante el intervalo de informe. Por lo tanto, el nivel de detalle proporcionado en ciertas secciones del PBRER (por ejemplo, evaluación de los datos de seguridad y eficacia, evaluación de las señales de seguridad* y evaluación de beneficio-riesgo), debe ser proporcional a los riesgos importantes conocidos o emergentes del medicamento y a la evidencia de beneficios importantes emergentes.

Dado que el alcance del PBRER se ha ampliado para incluir tanto el beneficio como la seguridad, la información de referencia para el informe también debe tener en cuenta este nuevo factor. En general, no resulta práctico para los titulares de autorizaciones de comercialización (TAC) tener una fuente de información de referencia que:

- Abarque todos los parámetros que contribuyen a la evaluación beneficio-riesgo (es decir, información sobre el beneficio, la eficacia/efectividad, las indicaciones y la seguridad).
- Sea común a todas las regiones de la ICH.
- Aborde todas las circunstancias (por ejemplo, genéricos, productos autorizados solo en un país).

Por lo tanto, esta guía propone opciones más prácticas que los TAC pueden considerar al seleccionar la información de referencia del producto más adecuada para el PBRER. Estas propuestas incorporan el concepto original de la E2C de la ICH de información de referencia de seguridad (por ejemplo, Company Core Safety Information* [CCSI]), con la adición de las indicaciones aprobadas para el producto. Esta información de referencia del producto puede ser la Company Core Data Sheet* (CCDS) u otro documento propuesto por el TAC (véase la sección 2.4).

La información importante de referencia sobre eficacia y efectividad resumida en la sección 17.1 del PBRER formará la base (o “referencia”) para la evaluación del beneficio, independientemente de la información de referencia del producto utilizada por el TAC.

La frecuencia de presentación de informes a las autoridades reguladoras está sujeta a requisitos reguladores nacionales o regionales y puede variar según diversos factores. La guía incluye recomendaciones sobre cómo gestionar diferentes frecuencias de presentación de PBRER en las distintas regiones.

Uno de los factores que motivaron la revisión de la guía E2C(R1) de la ICH fue el deseo de mejorar la eficiencia al disminuir la duplicación de esfuerzos necesaria para la preparación de diversos documentos reguladores. Por lo tanto, esta guía se ha desarrollado de manera que las secciones correspondientes del PBRER, el Development Safety Update Report (DSUR, ICH E2F) y la especificación de seguridad de un plan de gestión de riesgos (ICH E2E) puedan ser idénticas en contenido. (Véase también la sección 1.4, Relación del PBRER con otros documentos de la ICH).

1.2 Objetivos

El objetivo principal de un PBRER es presentar un análisis completo, conciso y crítico de la información nueva o emergente sobre los riesgos del medicamento y sobre su beneficio en las indicaciones aprobadas para permitir una evaluación del perfil beneficio-riesgo general del producto. El PBRER debe contener una evaluación de la nueva información pertinente para el medicamento que se puso a disposición del TAC durante el intervalo de informe en el contexto de la información acumulativa mediante:

- El resumen de la nueva información pertinente sobre seguridad que podría afectar el perfil beneficio-riesgo del medicamento.
- El resumen de cualquier nueva información importante sobre eficacia/efectividad que haya estado disponible durante el intervalo de informe.
- El examen de si la información obtenida por el TAC durante el intervalo de informe concuerda con el conocimiento previo del perfil de beneficio y riesgo del medicamento.
- La realización de una evaluación integrada de beneficio-riesgo para las indicaciones aprobadas en caso de que haya surgido nueva información importante sobre seguridad.

Cuando corresponda, el PBRER debe incluir las acciones propuestas para optimizar el perfil beneficio-riesgo.

La información de seguridad urgente debe notificarse a través del proceso adecuado; el PBRER no está destinado a ser utilizado para proporcionar una notificación inicial de nueva información de seguridad significativa, ni para proporcionar los medios por los cuales se detectan nuevos problemas de seguridad*.

1.3 Alcance del PBRER

El enfoque principal de cada PBRER es la evaluación de nueva información de seguridad pertinente a partir de las fuentes de datos disponibles[2], situada en el contexto de cualquier información pertinente de eficacia/efectividad que pueda estar disponible desde la Fecha Internacional de Nacimiento* (IBD, por sus siglas en inglés), la fecha de la primera aprobación de comercialización en cualquier país del mundo, o la Fecha Internacional de Nacimiento de Desarrollo (DIBD, por sus siglas en inglés), la fecha de la primera autorización para la realización de un ensayo clínico de intervención en cualquier país[3]. Toda nueva información pertinente de seguridad y eficacia/efectividad descubierta durante el intervalo de informe debe analizarse en las secciones correspondientes del PBRER.

A efectos de la presente guía, las fuentes de información disponibles se refieren a los datos sobre el principio o los principios activos incluidos en el medicamento o el medicamento al que se puede esperar

[2] A efectos de este documento, los términos “autorización” y “autorizado” se refieren a ensayos clínicos, y los términos “aprobación” y “aprobado” se refieren a solicitudes de comercialización.

[3] Esta guía no debe servir para limitar el alcance de la información que debe proporcionarse en la evaluación de la relación beneficio-riesgo de un medicamento. Consulte las leyes y las regulaciones aplicables en los países y las regiones donde se debe presentar el PBRER.

razonablemente que el TAC tenga acceso, y que sean pertinentes para la evaluación del perfil de seguridad o beneficio-riesgo (véase también el Anexo E, Ejemplos de posibles fuentes de información que pueden utilizarse en la preparación del PBRER). Por ejemplo, puede haber menos información disponible para el TAC en relación con un producto genérico en comparación con un producto para el cual el TAC es el innovador, y solo un informe publicado puede ser accesible para un ensayo clínico no patrocinado por el TAC. Por otro lado, para un ensayo clínico patrocinado por el TAC, este tendrá acceso a datos de pacientes para evaluar la relación beneficio-riesgo del producto. Cuando el TAC lo desee, se puede proporcionar una lista de las fuentes de información utilizadas para preparar el PBRER como un anexo del informe.

El PBRER debe incluir el conocimiento acumulativo del producto sin dejar de centrarse en la información nueva, es decir, la evaluación general de seguridad y la evaluación integrada del beneficio-riesgo tendrán en cuenta la información acumulativa. Dado que el desarrollo clínico de un medicamento continúa con frecuencia después de la aprobación para su comercialización, la información pertinente proveniente de estudios poscomercialización o de ensayos clínicos en indicaciones o poblaciones no aprobadas también debe incluirse en el PBRER. Del mismo modo, como el conocimiento de la seguridad de un medicamento puede derivarse de la evaluación de datos asociados con usos distintos de las indicaciones aprobadas, dicho conocimiento se reflejaría en la evaluación del riesgo, cuando sea pertinente y apropiado.

1.4 Relación del PBRER con otros documentos de la ICH

Actualmente, algunos países y regiones de la ICH aceptan la presentación de distintos tipos de informes periódicos para cumplir con los requisitos nacionales y regionales dentro del período posterior a la aprobación: el PSUR (Guía E2C[R1] de la ICH), para informes periódicos sobre la seguridad de los medicamentos aprobados; el DSUR (Guía E2F de la ICH), para informes periódicos sobre la seguridad de los medicamentos que siguen en fase de desarrollo clínico, y el componente de especificación de seguridad de la Guía E2E de la ICH que podría presentarse en el momento de la solicitud de comercialización y la presentación del PSUR para ayudar en la planificación de las actividades de farmacovigilancia. Como estos documentos tienen diferentes propósitos reguladores, diferentes periodicidades y pueden ser revisados por distintos departamentos dentro de una sola autoridad reguladora, cada documento debe ser completo por sí mismo y ser un documento integral que pueda funcionar por sí solo.

Sin embargo, la coincidencia y las inconsistencias entre el contenido del DSUR, el PSUR y la especificación de seguridad, pueden generar ineficiencias en la producción de los documentos por parte del TAC.

Enfoque modular

Esta guía tiene como objetivo facilitar la flexibilidad al fomentar el uso de secciones individuales que sean comunes a más de un informe, es decir, “módulos” que puedan ser utilizados para diferentes autoridades reguladoras y fines. Por lo tanto, el PBRER se ha desarrollado de tal manera que el contenido de varias secciones se pueda utilizar en secciones de otros documentos como base para un enfoque modular. Por ejemplo, si la DIBD de un DSUR para un medicamento está alineada con la IBD del PBRER para el mismo producto, tal como se sugiere en la E2F de la ICH, el contenido de varias secciones del DSUR también se puede utilizar en el PBRER cuando las fechas de cierre de datos (DLPs, por sus siglas en inglés) sean las mismas, es decir, cuando cada informe cubre un intervalo de un año basado en la IBD.

En el Anexo D de esta guía se enumeran las secciones del PBRER que pueden compartirse con el DSUR (E2F de la ICH) o con la especificación de seguridad de un plan de gestión de riesgos (E2E de la ICH), si corresponde.

El uso de secciones comunes en el PBRER, el DSUR y la especificación de seguridad como un enfoque modular tiene varias ventajas:

- Maximiza la utilidad de los módulos en múltiples documentos reguladores.
- Promueve la coherencia entre el PBRER, el DSUR y la especificación de seguridad.

- Evita la duplicación innecesaria de esfuerzos.
- Se espera que mejore la eficiencia para los TAC en la preparación de estos documentos.
- Facilita la utilización flexible de las secciones existentes (módulos) cuando, por ejemplo, el PBRER cubre diferentes intervalos de tiempo o debe presentarse en distintos momentos a múltiples autoridades. En estas circunstancias, solo los módulos que incluyan nueva información o nueva evaluación necesitarían actualizarse al presentar el PBRER.

Aunque actualmente no está contemplado en la E2C(R2) de la ICH, se prevé que el enfoque modular propuesto, basado en secciones comunes en varios documentos, facilitará en última instancia el desarrollo de módulos electrónicos para su uso en futuras presentaciones reglamentarias.

2. PRINCIPIOS GENERALES

2.1 PBRER único para un principio activo

El PBRER debe proporcionar información sobre todas las indicaciones, las formas farmacéuticas y los regímenes aprobados para el principio activo, con una única DLP. En algunas circunstancias, será adecuado presentar datos por indicación, forma farmacéutica, régimen de dosificación o población (por ejemplo, niños frente a adultos), dentro de la sección o secciones pertinentes del PBRER. En casos excepcionales, podría ser apropiado presentar PBRERs separados, por ejemplo, para un principio activo utilizado en dos formulaciones para administración sistémica y tópica en indicaciones completamente diferentes. En estos casos, se debe notificar a las autoridades reguladoras y obtener su consentimiento, preferiblemente en el momento de la aprobación.

2.2 PBRERs para productos de combinación de dosis fija

Para las combinaciones de sustancias que también se comercializan por separado, la información sobre la combinación fija puede ser reportada ya sea en un PBRER separado o incluida como secciones independientes en el informe de una de las sustancias individuales, según las circunstancias. Es importante enumerar los PBRERs relacionados.

2.3 Productos fabricados o comercializados por más de una empresa

Cada TAC es responsable de presentar los PBRERs para sus propios productos.

Cuando las empresas están involucradas en relaciones contractuales (por ejemplo, otorgante de la licencia-beneficiario de la licencia), las responsabilidades respectivas para la preparación y presentación del PBRER ante las autoridades reguladoras, deben estar claramente especificadas en el acuerdo escrito.

Cuando los datos recibidos de una o más empresas asociadas puedan contribuir significativamente a los análisis de seguridad, beneficio o relación beneficio-riesgo e influir en la información del producto de la empresa declarante, estos datos deben incluirse y analizarse en el PBRER.

2.4 Información de referencia

Un objetivo del PBRER es evaluar si la información obtenida durante el intervalo de informe concuerda con el conocimiento previo sobre el perfil de beneficios y riesgos del producto, e indicar si se deben realizar cambios en la información de referencia del producto. Contar con una fuente de información de referencia que pueda aplicarse en las tres regiones de la ICH facilitaría un enfoque práctico, eficiente y coherente para la evaluación de la relación beneficio-riesgo, y convertiría al PBRER en un informe único aceptado en todos los países y regiones.

La información de referencia del producto para el PBRER incluiría componentes de “seguridad básica” e “indicaciones aprobadas”. Para facilitar la evaluación del beneficio y el beneficio-riesgo por indicación en las secciones de evaluación del PBRER, el documento de información de referencia del producto debería

enumerar todas las indicaciones aprobadas en los países o regiones de la ICH. Es probable que estas indicaciones también se apliquen en otros países o regiones. Sin embargo, cuando el PBRER también se va a presentar en otros países donde hay indicaciones adicionales aprobadas localmente, estas indicaciones pueden añadirse a la información de referencia del producto o manejarse como un anexo/anexos regionales, según lo considere más adecuado el TAC. La base para la evaluación del beneficio debe ser la información estándar importante de eficacia/efectividad resumida en la sección 17.1 del PBRER.

Los TAC pueden tener en cuenta las siguientes opciones posibles a la hora de seleccionar la información de referencia del producto más adecuada para un PBRER:

- Company Core Data Sheet

De acuerdo con las recomendaciones de la E2C(R1) de la ICH, es una práctica habitual que los TAC preparen su propia CCDS, que incluye secciones relacionadas con la seguridad, las indicaciones, la dosificación, la farmacología y cualquier otra información sobre el medicamento. La información básica de seguridad contenida en la CCDS se conoce como CCSI. Una opción práctica es que los TAC utilicen la CCDS más actual al final del intervalo de informe como la información de referencia del producto, tanto para las secciones de riesgo del PBRER como para las principales indicaciones aprobadas para las cuales se evalúa el beneficio.

Cuando la CCDS de un medicamento no contiene información sobre las indicaciones aprobadas, el TAC debe especificar claramente qué documento se utiliza como información de referencia para las indicaciones aprobadas en el PBRER.

- Otras opciones para la información de referencia del producto

Cuando no exista una CCDS o CCSI para un producto, por ejemplo, cuando el producto está aprobado solo en un país o región, o para productos establecidos/genéricos en el mercado durante muchos años, el TAC debe especificar claramente la información de referencia que se está utilizando. Esto puede incluir información nacional o regional del producto, como el Prospecto de Estados Unidos (USPI, por sus siglas en inglés), o el Resumen de las Características del Producto de Europa (SmPC, por sus siglas en inglés), o el prospecto japonés, según corresponda. La base para la evaluación del beneficio debe ser la información de referencia importante sobre eficacia/efectividad resumida en la sección 17.1 del PBRER.

Cuando la información de referencia para las indicaciones aprobadas sea un documento separado de la RSI, la versión vigente en la DLP del PBRER debe incluirse en el Anexo 1.

El TAC debe evaluar continuamente si es necesario revisar la información de referencia del producto/RSI cada vez que se obtenga nueva información de seguridad durante el intervalo de informe. Los cambios significativos en la información de referencia del producto/RSI realizados durante el intervalo deben describirse en la sección 4 del PBRER (“Cambios en la información de referencia de seguridad”) e incluir:

- Cambios en las secciones de contraindicaciones, advertencias/precauciones de la RSI.
- Adición de reacciones adversas al medicamento (RAM) e interacciones.
- Adición de nueva información importante sobre el uso en caso de sobredosis.
- Eliminación de una indicación u otras restricciones por razones de seguridad o falta de eficacia.

Si es posible, los cambios significativos en la RSI realizados después de la DLP pero antes de la presentación del PBRER deben incluirse en la sección 14 del informe (Información de última hora).

Si así lo estipulan los requisitos regionales aplicables, el TAC debe proporcionar, en un anexo regional, información sobre cualquier cambio final, en curso o propuesto en la información del producto autorizado a escala nacional o local.

2.5 Grado de detalle en el PBRER

El grado de detalle que se proporciona en determinadas secciones del PBRER, debe depender de los beneficios y riesgos importantes conocidos o emergentes del medicamento. Este enfoque es aplicable a aquellas secciones del PBRER en las que se evalúan datos de seguridad, datos de eficacia/efectividad, señales de seguridad y la relación beneficio-riesgo. Por lo tanto, la extensión de la información proporcionada en dichas secciones de PBRER variará entre los distintos PBRERs.

Por ejemplo, cuando hay nueva información importante sobre seguridad, se debe incluir una presentación detallada de esa información, además de la información pertinente sobre los beneficios, a fin de facilitar un análisis sólido de la relación beneficio-riesgo. Por el contrario, cuando se dispone de poca información nueva e importante sobre seguridad durante el intervalo de informe, basta con un resumen conciso de la información básica sobre los beneficios, y la evaluación de la relación beneficio-riesgo consistiría principalmente en una evaluación de los datos de seguridad actualizados del intervalo.

2.6 Eficacia/efectividad

Para los fines de esta guía, se debe informar sobre la evidencia de los beneficios en los ensayos clínicos y en la práctica médica diaria. Debido a que los términos no están armonizados en todas las regiones, en esta guía se utilizan los términos "eficacia/efectividad" para aclarar que la información, tanto de ensayos clínicos como de la práctica médica diaria, está dentro del alcance de la información sobre los beneficios que se debe incluir en el PBRER. En algunas regiones, "eficacia" se refiere a la evidencia de beneficios proveniente de ensayos clínicos controlados, mientras que "efectividad" implica el uso en la práctica médica cotidiana. Por el contrario, en otras regiones, no se hace esta distinción.

2.7 Evaluación de la relación beneficio-riesgo

Cuando se aprueba la comercialización de un medicamento, se llega a la conclusión de que, si se utiliza de acuerdo con la información aprobada del producto, sus beneficios superan sus riesgos. A medida que surge nueva información sobre el medicamento durante la comercialización, se debe realizar una evaluación de la relación beneficio-riesgo para determinar si los beneficios siguen siendo mayores que los riesgos y considerar si es necesario tomar medidas para mejorar el equilibrio beneficio-riesgo mediante actividades de minimización de riesgos, por ejemplo, cambios en el etiquetado, comunicaciones con los prescriptores u otras acciones.

2.8 Periodicidad y fecha de cierre de datos del PBRER

2.8.1 Fecha internacional de nacimiento y fecha de cierre de datos

Cada medicamento debe tener una IBD. La IBD es la fecha de la primera aprobación de comercialización para cualquier producto que contenga el principio activo otorgada a cualquier compañía en cualquier país del mundo. Cuando un informe contiene información sobre diferentes formas farmacéuticas, formulaciones o usos (indicaciones, vías o poblaciones), la fecha de la primera aprobación de comercialización para cualquiera de las distintas autorizaciones debe considerarse como la IBD y, por lo tanto, determinar la DLP a efectos del PBRER. La DLP es la fecha designada como el límite para incluir datos en un PBRER. A través de los PBRERs preparados con DLPs armonizadas basadas en una IBD común, la misma información actualizada sobre seguridad y beneficio-riesgo puede ser revisada globalmente por diferentes autoridades reguladoras.

Cuando se prepara un PBRER separado para un producto de combinación de dosis fija (véase la sección 2.2), la DLP para ese PBRER puede basarse en la IBD más temprana de uno de los principios activos componentes, o en la IBD de la primera aprobación de comercialización en cualquier parte del mundo para la combinación de dosis fija.

Cuando el desarrollo clínico de un medicamento continúa después de la aprobación de comercialización, si lo desea el patrocinador/TAC, el inicio del intervalo de informe de DSUR puede sincronizarse con el ciclo

basado en la IBD, de modo que tanto el DSUR como el PBRER puedan prepararse al mismo tiempo, utilizando la misma DLP. Este enfoque facilitará el uso de las secciones/módulos comunes propuestos tanto para el PBRER y el DSUR cuando ambos se presenten anualmente (véase el Anexo D).

2.8.2 Gestión de distintas frecuencias de presentación de informes PBRER

La necesidad de presentar un PBRER y la frecuencia de presentación de informes a las autoridades reguladoras están sujetas a requisitos reguladores nacionales o regionales y, por lo general, dependen de factores como fechas de aprobación, el tiempo que el producto lleva en el mercado y el grado de conocimiento del perfil beneficio-riesgo del producto. El formato y el contenido del PBRER están destinados a aplicarse a informes periódicos que abarcan períodos de informe de 6 meses o más. Una vez que un medicamento ha estado en el mercado durante varios años, la normativa nacional o regional puede permitir que la frecuencia de presentación se extienda a intervalos de tiempo más largos, por ejemplo, más de un año para productos que se considera que tienen un perfil establecido y aceptable o de bajo riesgo. Sin embargo, es posible que se sigan exigiendo PBRERs más frecuentes en otras regiones. Como resultado, los TACs pueden encontrarse con los siguientes escenarios:

- Es posible que se requieran PBRERs con una frecuencia semestral, anual o menor en diferentes regiones.
- También pueden aplicarse cambios en la frecuencia de informes después de que se aprueben adiciones o cambios importantes en el uso clínico (por ejemplo, nuevas indicaciones o nuevas poblaciones). En estas circunstancias, es posible que se acorte el intervalo de informes, incluso para productos más viejos con una frecuencia de presentación de PBRER previamente reducida.
- Una autoridad reguladora puede solicitar un PBRER *ad hoc* (véase la sección 2.8.2.1 de esta guía).

Independientemente de la duración del intervalo cubierto por el informe:

- Cada PBRER debe ser independiente y reflejar la información nueva y acumulativa actualmente disponible para el TAC.
- Los reguladores normalmente aceptarán el uso de la IBD para determinar la DLP para los PBRERs. Cuando los requisitos nacionales o regionales difieran de esto, el TAC puede desear consultarlo con la autoridad reguladora correspondiente. El uso de una única IBD y DLP armonizadas para cada producto, es importante para reducir la carga de trabajo que implica la preparación de los PBRERs, y respeta el propósito original del PBRER: preparar un resumen mundial único sobre un producto que pueda presentarse a diferentes autoridades reguladoras.
- Para productos recientemente aprobados, se aplica una periodicidad semestral en muchas regiones, al menos durante los primeros 2 años después de la aprobación.
- Para PBRERs presentados de manera rutinaria/regular, los informes deben basarse en datos acumulativos, con conjuntos de datos de intervalos de 6 meses o múltiplos de estos.
- Es probable que sea necesario actualizar en cada PBRER las secciones que proporcionan información sobre intervalos, y el contenido utilizado en el PBRER anterior puede revisarse y reutilizarse para las secciones en las que no ha surgido información nueva desde la preparación del último PBRER, si corresponde. Después de la revisión, puede determinarse que las secciones que proporcionan evaluación de datos acumulativos pueden no necesitar ser actualizadas si el contenido se mantiene actualizado con la información actual. Véase la figura 1.
- En situaciones en las que un TAC prepara PBRERs tanto de forma semestral como anual para diferentes autoridades reguladoras, la autoridad reguladora que requiera un PBRER en un ciclo de 6 meses puede aceptar PBRERs que contengan datos de intervalos de 12 meses. Véase la figura 2. Los TACs deben consultar la aceptabilidad de este enfoque con la(s) autoridad(es) reguladora(s) correspondiente(s).

2.8.2.1 PBRERs ad hoc (“por causa”)

Los PBRERs *ad hoc* son informes fuera de los requisitos de informes rutinarios y pueden ser solicitados por algunas autoridades reguladoras. Cuando se solicita un informe *ad hoc* y no se ha preparado un PBRER durante varios años, es probable que el TAC necesite preparar un informe completamente nuevo.

2.8.3 Intervalo de tiempo entre la Fecha de Cierre de Datos (DLP, por sus siglas en inglés) y la presentación

Como resultado del alcance ampliado del PBRER, el intervalo de tiempo entre la DLP y la presentación de los PBRERs debe ser el siguiente:

- PBRERs que cubren intervalos de 6 o 12 meses: dentro de 70 días naturales.
- PBRERs que cubren intervalos superiores a 12 meses: dentro de 90 días naturales.
- PBRERs *ad hoc*: 90 días naturales, a menos que se especifique lo contrario en la solicitud *ad hoc*.

El día de la DLP se considera el día 0 del intervalo de 70 o 90 días naturales entre la DLP y la presentación del informe. Cuando los requisitos nacionales o regionales difieran de lo anterior, el TAC debe consultar el plazo para la presentación con la autoridad reguladora correspondiente.

2.9 Formato y presentación del PBRER

2.9.1 Formato

A continuación, se describe el formato y el contenido recomendados del PBRER, incluyendo la tabla de contenidos, la numeración de las secciones y el contenido de cada sección.

Se debe utilizar el formato completo de la Guía E2C(R2) de la ICH para todos los PBRERs. Cuando no haya información pertinente disponible o una sección del PBRER no sea aplicable, se debe indicar. Algunas secciones particulares del PBRER pueden compartir contenido con otros informes reguladores, por ejemplo, los documentos descritos en las Guías E2E y E2F de la ICH. Es posible que los TACs aprovechen el enfoque modular del PBRER (es decir, secciones que se pueden separar y presentar de manera independiente o combinadas con otros documentos), para facilitar dichas necesidades reguladoras, maximizar la utilidad del contenido y reducir el trabajo duplicado.

2.9.2 Presentación

A continuación, se proporciona la tabla de contenidos recomendada, incluyendo la numeración de las secciones, para el PBRER:

Página de título

Resumen ejecutivo

Tabla de contenidos

1. Introducción
2. Estado de la aprobación de comercialización a escala mundial
3. Medidas adoptadas en el intervalo de presentación de informes por motivos de seguridad
4. Cambios en la información de referencia de seguridad
5. Exposición estimada y patrones de uso
   - 5.1 Exposición acumulativa de los sujetos en ensayos clínicos
   - 5.2 Exposición acumulativa y por intervalos de los pacientes en la experiencia de comercialización
6. Datos en tablas resumen
   - 6.1 Información de referencia
   - 6.2 Tablas resumen acumulativas de eventos adversos graves en ensayos clínicos
   - 6.3 Tablas resumen acumulativas y por intervalos de fuentes de datos poscomercialización
7. Resúmenes de hallazgos significativos de ensayos clínicos durante el período de informe

3. GUÍA SOBRE EL CONTENIDO DEL PBRER

Se deben completar todas las secciones y, cuando no haya información disponible, se debe indicar. Tenga en cuenta que la sección "3.N" de esta guía proporciona orientación sobre el contenido de la sección "N" del PBRER. Por ejemplo, "Información de referencia", descrita en la sección 3.6.1 de esta guía, corresponde a la sección 6.1 del PBRER.

Página de título

La página de título del PBRER debe incluir la siguiente información:

- Fecha del informe
- Medicamento(s)
- IBD
- Intervalo de informe
- Nombre(s) y dirección(es) del TAC
- Cualquier declaración sobre la confidencialidad de la información incluida en el PBRER

Resumen ejecutivo

Esta sección debe proporcionar un resumen conciso de la información más importante contenida en el informe.

El Resumen ejecutivo debe incluir la siguiente información:

- Introducción
- Intervalo de informe
- Medicamento(s): mecanismo(s) de acción, clase(s) terapéutica(s), indicación(es), dosis, vía(s) de administración, formulación(es)
- Exposición acumulativa estimada de los sujetos en ensayo clínicos; intervalo y exposición posaprobación acumulativa
- Número de países en los que el medicamento está aprobado
- Resumen de la evaluación general del beneficio-riesgo (basado en la sección 18.2 del PBRER)
- Medidas adoptadas o propuestas por razones de seguridad, por ejemplo, cambios significativos en la información de referencia del producto, otras actividades de minimización de riesgos
- Conclusiones

Tabla de contenidos

3.1 Introducción

La sección 1 del PBRER debe incluir:

- IBD
- Intervalo de informe
- Medicamento(s): mecanismo(s) de acción, clase(s) terapéutica(s), dosis, vía(s) de administración, formulación(es)
- Una breve descripción de la(s) indicación(es) y población(es) aprobada(s)
- Una breve descripción y explicación de cualquier información que no se haya incluido en el PBRER
- Si corresponde, la justificación para la presentación de múltiples PBRER para el medicamento

3.2 Estado de la aprobación de comercialización a escala mundial

Si corresponde, la sección 2 del PBRER debe proporcionar una breve descripción general narrativa que incluya la fecha de la primera aprobación, indicación(es), dosis aprobada(s) y dónde se aprobó.

3.3 Medidas adoptadas en el intervalo de informe por motivos de seguridad

La sección 3 del PBRER debe incluir una descripción de las medidas significativas relacionadas con la seguridad que se hayan adoptado durante el intervalo de informe, relacionadas ya sea con usos en investigación o con la experiencia de comercialización por parte del TAC, patrocinador de ensayos clínicos, autoridades reguladoras, comités de monitoreo de datos o comités de ética que hayan tenido:

- Una influencia significativa en el perfil beneficio-riesgo del medicamento aprobado.
- Un impacto en la realización de ensayos clínicos específicos o en el programa general de desarrollo clínico.

Si se conocen, se deben indicar las razones de cada medida, y se debe proporcionar información adicional pertinente cuando corresponda. En esta sección también se deben resumir las actualizaciones pertinentes de medidas anteriores. Entre los ejemplos de medidas significativas adoptadas por razones de seguridad se incluyen:

<u>Medidas relacionadas con medicamentos en investigación:*</u>

- Rechazo de la autorización de un ensayo clínico por motivos éticos o de seguridad.

- Suspensión parcial[4] o total del ensayo clínico, o terminación anticipada de un ensayo clínico en curso* debido a hallazgos de seguridad o falta de eficacia.
- Retiro del medicamento en investigación o del comparador.
- No obtener la aprobación de comercialización para una indicación probada, incluida la retirada voluntaria de una solicitud de comercialización.
- Actividades de gestión de riesgos, incluidas:
  - Modificaciones en el protocolo debido a preocupaciones de seguridad o eficacia (por ejemplo, cambios en la dosis, cambios en los criterios de inclusión/exclusión del estudio, intensificación del monitoreo de los sujetos, limitación en la duración del ensayo).
  - Restricciones en la población del estudio o indicaciones.
  - Cambios en el documento de consentimiento informado relacionados con preocupaciones de seguridad.
  - Cambios en la formulación.
  - Incorporación por parte de los reguladores de un requisito especial de informe relacionado con la seguridad.
  - Emisión de una comunicación a los investigadores o profesionales de la salud.
  - Planes para nuevos estudios para abordar preocupaciones de seguridad.

Medidas relacionadas con medicamentos comercializados:

- Falta de obtención o solicitud de renovación de la aprobación de comercialización.
- Retiro o suspensión de una aprobación de comercialización.
- Suspensión del suministro por parte del TAC.
- Actividades de gestión de riesgos, incluidas:
  - Restricciones significativas en la distribución o introducción de otras medidas de minimización de riesgos.
  - Cambios significativos relacionados con la seguridad en los documentos de etiquetado que podrían afectar el programa de desarrollo, incluidas restricciones sobre el uso o la población tratada.
  - Comunicaciones a profesionales de la salud.
  - Nuevos requisitos de estudios poscomercialización impuestos por el organismo regulador.

3.4 Cambios en la información de referencia de seguridad

La sección 4 del PBRER debe incluir cualquier cambio significativo en la información de referencia de seguridad hecho durante el intervalo de informe. Estos cambios pueden incluir información relacionada con contraindicaciones, advertencias, precauciones, reacciones adversas al medicamento, sobredosis e interacciones; hallazgos importantes de ensayos clínicos en curso y finalizados,* y hallazgos no clínicos significativos (por ejemplo, estudios de carcinogenicidad). La información específica pertinente para estos cambios debe proporcionarse en las secciones correspondientes del PBRER.

Se debe incluir una versión limpia del documento de referencia vigente en la DLP del PBRER en el Anexo 1. No se requiere una versión con seguimiento de cambios de la información de referencia.

3.5 Exposición estimada y patrones de uso

Las secciones 5.1 y 5.2 del PBRER deben proporcionar estimaciones del tamaño y la naturaleza de la población expuesta al medicamento. La sección 5.1 del PBRER debe proporcionar información sobre la exposición acumulativa en ensayos clínicos. La sección 5.2 debe proporcionar la exposición acumulativa y por intervalos en el entorno de comercialización. Se deben incluir descripciones breves de los métodos

[4] La "suspensión parcial" podría incluir varias medidas (por ejemplo, suspensión de estudios de dosis repetidas, pero continuación de estudios de dosis única; suspensión de ensayos en una indicación, pero continuación en otra, o suspensión de un régimen de dosificación específico en un ensayo, pero continuación con otras dosis).

utilizados para estimar la exposición sujeto/paciente, así como sus limitaciones. Se deben utilizar métodos consistentes para calcular la exposición paciente en todos los PBRERs para el mismo producto. Si es adecuado un cambio en el método, se deben incluir tanto los métodos como los cálculos en el PBRER que introduce el cambio.

3.5.1 Exposición acumulativa de los sujetos en ensayos clínicos

Si corresponde, la sección 5.1 del PBRER debe incluir la siguiente información presentada en formato de tablas (véase el Anexo B, Tablas 1-3 para ver ejemplos):

- Números acumulativos de los sujetos de ensayos clínicos en curso y finalizados expuestos al medicamento en investigación, placebo o comparador(es) activo(s) desde la DIBD. Se reconoce que, para productos más viejos, es posible que no se disponga de datos precisos.
- Se debe presentar la exposición acumulativa de los sujetos en ensayos clínicos de manera más detallada si está disponible, por ejemplo, desglosada por edad, sexo y grupo racial/étnico para todo el programa de desarrollo.
- Las diferencias importantes entre ensayos en cuanto a dosis, vías de administración o poblaciones de pacientes se pueden indicar en las tablas, si corresponde, o se pueden considerar tablas separadas.
- Si se han realizado o se están realizando ensayos clínicos en poblaciones especiales (por ejemplo, mujeres embarazadas, pacientes con insuficiencia renal, hepática o cardíaca, o pacientes con polimorfismos genéticos pertinentes), se deben proporcionar los datos de exposición, según corresponda.
- Cuando existen diferencias sustanciales en la duración de la exposición entre los sujetos aleatorizados al medicamento en investigación o comparador(es), o disparidades en la duración de la exposición entre ensayos clínicos, puede ser útil expresar la exposición en tiempo sujeto (días, meses o años sujeto).
- La exposición al medicamento en investigación en voluntarios sanos puede ser menos concerniente para el perfil general de seguridad, dependiendo del tipo de reacción adversa, en particular cuando los sujetos están expuestos a una sola dosis. Tales datos se pueden presentar por separado con una explicación, según corresponda.
- Si los eventos adversos graves de los ensayos clínicos se presentan por indicación en las tablas resumen, la exposición de los pacientes también se debe presentar por indicación, cuando esté disponible.
- Para ensayos individuales de particular importancia, las características demográficas se deben proporcionar por separado.

3.5.2 Exposición acumulativa y por intervalos de los pacientes en la experiencia de comercialización

Se deben proporcionar estimaciones separadas para la exposición por intervalos (desde la DLP del PBRER anterior) y, cuando sea posible, la exposición acumulativa (desde la IBD). Véase el Anexo B, Tablas 4 y 5 para ver ejemplos. Se debe proporcionar el número estimado de pacientes expuestos, cuando sea posible, junto con el método o los métodos utilizados para determinar la estimación. Si no se dispone de una estimación del número de pacientes, se deben presentar medidas alternativas estimadas de exposición junto con el método o los métodos utilizados para obtenerlas, si están disponibles. Ejemplos de medidas alternativas incluyen los días de exposición de los pacientes y el número de recetas. Solo si no se dispone de estas medidas, se pueden utilizar medidas de ventas de medicamentos, como tonelaje o unidades de dosificación. También se puede utilizar el concepto de una dosis diaria definida para estimar la exposición de los pacientes.

Los datos deben presentarse según las siguientes categorías:

1. *Exposición posaprobación (ensayo no clínico)*

Se debe proporcionar una estimación general de la exposición de los pacientes.

Además, los datos deben presentarse de manera rutinaria por indicación, sexo, edad, dosis, formulación y región, cuando corresponda.

Dependiendo del producto, pueden ser relevantes otras variables, como el número de ciclos de vacunación, la(s) vía(s) de administración y la duración del tratamiento.

Cuando existan patrones de informes que indiquen una señal de seguridad, se deben presentar los datos de exposición en los subgrupos concernientes, si es posible.

2. Uso posaprobación en poblaciones especiales

Cuando se haya producido un uso posterior a la aprobación en poblaciones especiales, se debe proporcionar la información disponible sobre el número acumulativo de pacientes expuestos y el método de cálculo. Las fuentes de dichos datos incluyen estudios no intervencionistas diseñados para obtener esta información, incluidos los registros. Las poblaciones que se deben considerar para el análisis incluyen, entre otras:

- Población pediátrica
- Población de edad avanzada
- Mujeres embarazadas o en período de lactancia
- Pacientes con insuficiencia hepática y/o renal
- Pacientes con otra comorbilidad pertinente
- Pacientes con una gravedad de la enfermedad diferente a la estudiada en los ensayos clínicos
- Subpoblaciones portadoras de polimorfismos genéticos pertinentes
- Pacientes de diferentes orígenes raciales o étnicos.

3. Otro uso posaprobación

Si el TAC tiene conocimiento de patrones de uso del medicamento que se consideren pertinentes para la interpretación de los datos de seguridad, debe proporcionar una breve descripción de estos. Ejemplos de estos patrones de uso pueden incluir sobredosis, abuso de fármacos, uso indebido y uso más allá de lo recomendado en la información de referencia del producto (por ejemplo, un medicamento antiepiléptico utilizado para el dolor neuropático o la profilaxis de migrañas). Dichos patrones pueden ser regionales. Si se conoce, el TAC puede comentar brevemente si el uso más allá de lo recomendado en la información de referencia del producto está respaldado por directrices clínicas, evidencia de ensayos clínicos o ausencia de tratamientos alternativos aprobados. Si está disponible, se debe proporcionar información cuantitativa sobre el uso. Para identificar patrones de uso fuera de los términos de la información de referencia del producto, el TAC debe utilizar las secciones correspondientes de la información de referencia del producto que estaba en vigor en la DLP del PBRER (por ejemplo, indicación aprobada, contraindicaciones).

3.6 Datos en tablas resumen

Las secciones 6.1 a 6.3 del PBRER deben presentar tablas resumen acumulativas de los eventos adversos graves, provenientes de ensayos clínicos y fuentes poscomercialización que se han reportado al TAC desde la DIBD. A criterio del TAC, se pueden utilizar representaciones gráficas para ilustrar aspectos específicos de los datos, cuando sea útil para mejorar la comprensión.

3.6.1 Información de referencia

La sección 6.1 del PBRER debe especificar la(s) versión(es) del diccionario de codificación utilizada(s) para los análisis de reacciones adversas.

3.6.2 Tablas resumen acumulativas de eventos adversos graves de ensayos clínicos

La sección 6.2 del PBRER debe proporcionar antecedentes para el anexo que proporciona una tabla resumen acumulativa de los eventos adversos graves reportados en los ensayos clínicos del TAC, desde la

DIBD hasta la DLP del PBRER actual. El TAC debe explicar cualquier omisión de datos (por ejemplo, los datos de ensayos clínicos podrían no estar disponibles para productos comercializados durante muchos años). Las tablas deben organizarse por Clasificación de Órganos y Sistemas (SOC, por sus siglas en inglés), tanto para el medicamento en investigación como para los grupos de control (comparadores activos, placebo), utilizados en el programa de desarrollo clínico. Los datos se pueden integrar en todo el programa. Alternativamente, cuando sea útil y factible, las tablas de eventos adversos graves se pueden presentar por ensayo, indicación, vía de administración u otras variables. Esta sección no debe usarse para proporcionar análisis o conclusiones basadas en los eventos adversos graves.

El Anexo B, Tabla 6 de esta guía ofrece un ejemplo de tablas resumen de eventos adversos graves provenientes de ensayos clínicos. Se deben considerar los siguientes puntos:

- En general, las tablas de eventos adversos graves de ensayos clínicos deben incluir solo aquellos términos que se usaron para definir el caso como grave; no deben incluir eventos no graves.
- Cuando se utiliza la terminología del Diccionario Médico para Actividades Regulatorias (MedDRA, por sus siglas en inglés), para codificar los términos de los eventos o reacciones adversas, se deben presentar el Término Preferido (TP) y la SOC en las tablas resumen.
- Las tablas deben incluir datos de ensayos clínicos ciegos y no ciegos. Los eventos adversos graves no ciegos pueden originarse de ensayos completos y casos individuales que se han desenmascarado por razones relacionadas con la seguridad (por ejemplo, informes acelerados), si corresponde. Los patrocinadores/TACs no deben desenmascarar los datos con el propósito específico de preparar el PBRER.
- Ciertos eventos adversos en ensayos clínicos pueden excluirse de las tablas resumen de ensayos clínicos, pero tales exclusiones deben explicarse en el informe. Por ejemplo, los eventos adversos que se han definido en el protocolo como "exentos" de la recopilación especial e ingreso en la base de datos de seguridad porque se anticipan en la población de pacientes, y aquellos que representan puntos finales del estudio, pueden excluirse (por ejemplo, muertes reportadas en un ensayo de un medicamento para insuficiencia cardíaca congestiva, donde la mortalidad por cualquier causa es el principal punto final de eficacia, progresión de la enfermedad en ensayos de cáncer).
- La evaluación de causalidad es generalmente útil para la evaluación de RAMs raras individuales. La evaluación de causalidad en casos individuales tiene menos valor en el análisis de datos totales, donde es posible realizar comparaciones grupales de tasas. Por lo tanto, las tablas resumen deben incluir todos los eventos adversos graves del medicamento en investigación, los controles activos y el placebo. Puede ser útil proporcionar tasas por dosis.

3.6.3 Tablas resumen acumulativas y por intervalos de las fuentes de datos poscomercialización

La sección 6.3 del PBRER debe proporcionar antecedentes para el anexo que aporta tablas resumen y por intervalos de las reacciones adversas, desde la IBD hasta la DLP del PBRER actual. Según lo descrito en la Guía E2D de la ICH, para los medicamentos comercializados, los eventos adversos reportados espontáneamente* generalmente implican al menos una sospecha de causalidad por parte de la persona que reporta y deben considerarse reacciones adversas para fines de reporte regulador. La tabla debe incluir:

- Reacciones adversas graves y no graves a medicamentos provenientes de ICSRs espontáneos, incluidos informes por parte de profesionales de la salud, consumidores, literatura científica y autoridades reguladoras;
- Reacciones adversas graves de estudios no intervencionistas; y
- Informes solicitados* de reacciones adversas graves.

La tabla debe incluir datos de intervalos y acumulativos presentados uno al lado del otro (ver Anexo B, Tabla 7), y debe estar organizada por SOC. En caso de problemas o inquietudes en específico, se pueden

presentar tablas adicionales de reacciones adversas por indicación, vía de administración u otras variables. Esta sección no debe usarse para proporcionar análisis o conclusiones basados en los datos presentados.

3.7 Resúmenes de los hallazgos de seguridad significativos de los ensayos clínicos durante el intervalo de informe

Esta sección del PBRER debe proporcionar un breve resumen de los hallazgos emergentes clínicamente importantes de eficacia/efectividad y seguridad obtenidos de los ensayos clínicos patrocinados por el TAC que surgieron durante el intervalo de informe del reporte. Las señales de seguridad provenientes de ensayos clínicos deben tabularse en la sección 15 del PBRER. La evaluación de las señales (categorizadas como señales refutadas o no, o como riesgos potenciales* o identificados*), que se cerraron durante el intervalo de informe se debe presentar en la sección 16.2 del PBRER. La nueva información relacionada con cualquier riesgo potencial o identificado previamente y no considerado una nueva señal identificada debe evaluarse y caracterizarse en las secciones 16.3 y 16.4, respectivamente. Los hallazgos de ensayos clínicos no patrocinados por el TAC deben describirse en las secciones pertinentes del PBRER.

Cuando sea conveniente para la evaluación del beneficio-riesgo, también se debe resumir en esta sección la información sobre la falta de eficacia proveniente de ensayos clínicos para el tratamiento de enfermedades que no ponen en peligro la vida en indicaciones aprobadas. La información sobre la falta de eficacia de ensayos clínicos con productos destinados a tratar o prevenir enfermedades graves o potencialmente mortales debe resumirse en la sección 13 del PBRER.

Cuando sea posible y pertinente, se deben presentar los datos categorizados por sexo y edad (en particular, niños frente a adultos), indicación, dosis y región.

Se debe incluir en un anexo una lista de los ensayos intervencionistas poscomercialización patrocinados por el TAC, cuyo objetivo principal sea identificar, caracterizar o cuantificar un riesgo de seguridad, o confirmar el perfil de seguridad del medicamento, y que hayan sido completados o estén en curso durante el intervalo de informe. La lista debe incluir la siguiente información para cada ensayo:

- Identificación del estudio (p. ej., número de protocolo u otro identificador).
- Título del estudio (título abreviado del estudio, si corresponde).
- Tipo de estudio (por ejemplo, ensayo clínico aleatorizado, estudio de cohorte, estudio de casos y controles).
- Población estudiada (incluido el país y otros descriptores pertinentes de la población (por ejemplo, población pediátrica o sujetos del ensayo con insuficiencia renal).
- Fecha de inicio del estudio (según lo definido por el TAC) y fechas proyectadas de finalización.
- Estado:
- En curso (el ensayo clínico ha comenzado)
- Completo (el informe del estudio clínico está finalizado)

3.7.1 Ensayos clínicos completos

La sección 7.1 del PBRER debe proporcionar un resumen breve de los hallazgos clínicamente importantes sobre eficacia y seguridad que hayan surgido de ensayos clínicos completos durante el intervalo de informe. Esta información puede presentarse en formato narrativo o como una sinopsis.[5] Puede incluir información que respalde o refute preocupaciones de seguridad identificadas previamente, así como evidencia de nuevas señales de seguridad.

3.7.2 Ensayos clínicos en curso

[5] Se proporcionan 5 ejemplos de sinopsis en la ICH E3 y en el CIOMS VII.

Si el TAC tiene conocimiento de información clínicamente importante que ha surgido de ensayos clínicos en curso (por ejemplo, obtenida a través de análisis interinos de seguridad o como resultado del desenmascaramiento de sujetos con eventos adversos), esta sección debe resumir brevemente la(s) preocupación(es). Puede incluir información que respalde o refute preocupaciones de seguridad identificadas previamente, así como evidencia de nuevas señales de seguridad.

3.7.3 Seguimiento a largo plazo

Cuando corresponda, esta sección debe proporcionar información del seguimiento a largo plazo de los sujetos de ensayos clínicos de medicamentos en investigación, en particular productos de terapia avanzada.

3.7.4 Otro uso terapéutico del medicamento

Esta sección del PBRER debe incluir información de seguridad clínicamente importante de otros programas realizados por el TAC que sigan un protocolo específico, con informes solicitados según la Guía E2D de la ICH (por ejemplo, programas de acceso ampliado, programas de uso compasivo, uso en pacientes particulares, solicitudes del programa Investigational New Drug [IND] para un solo paciente, solicitudes de tratamiento IND y otras recopilaciones de datos organizadas).

3.7.5 Nuevos datos de seguridad relacionados con terapias de combinación fija

A menos que se indique lo contrario por requisitos reguladores nacionales o regionales, se pueden utilizar las siguientes opciones para presentar datos de terapias combinadas:

- Si el producto que es objeto de un PBRER también está aprobado o en desarrollo como un componente de un producto de combinación fija o un régimen de múltiples fármacos, esta sección debe resumir los hallazgos de seguridad importantes derivados del uso de la terapia combinada.
- Si este PBRER es para un producto de combinación fija, esta sección debe resumir la información de seguridad importante que surja de los componentes individuales.

La información específica de la combinación se puede incorporar en una o más secciones separadas del PBRER, para uno o todos los componentes individuales de la combinación.

3.8 Hallazgos de estudios no intervencionistas

Esta sección debe resumir la información de seguridad pertinente o la información con un impacto potencial en las evaluaciones de beneficio o riesgo, proveniente de estudios no intervencionistas patrocinados por el TAC que estuvieron disponibles durante el intervalo de informe (por ejemplo, estudios observacionales, estudios epidemiológicos, registros y programas de vigilancia activa). Esto debe incluir información concerniente a estudios de utilización de medicamentos cuando sea aplicable a varias regiones.

Se debe incluir en un anexo una lista de los estudios no intervencionistas poscomercialización patrocinados por el TAC, cuyo objetivo principal sea identificar, caracterizar o cuantificar un riesgo de seguridad, confirmar el perfil de seguridad del medicamento o medir la efectividad de las medidas de gestión de riesgos, que hayan sido completados o estén en curso durante el intervalo de informe (véase la sección 3.7 de esta guía para ver la información que debe incluirse en la lista).

Los informes finales de estudios completados durante el intervalo de informe para los estudios mencionados en el párrafo anterior, también deben incluirse en el anexo regional del informe cuando así lo estipulen los requisitos regionales.

3.9 Información de otros ensayos clínicos y fuentes

3.9.1 Otros ensayos clínicos

Esta subsección debe resumir la información accesible para el TAC con un esfuerzo razonable y apropiado proveniente de cualquier otra fuente de ensayos clínicos/estudios, incluidos resultados de análisis combinado o metaanálisis de ensayos clínicos aleatorizados, y la información de seguridad proporcionada por socios de codesarrollo o de ensayos iniciados por investigadores.

3.9.2 Errores de medicación

Esta subsección debe resumir la información correspondiente a patrones de errores de medicación y posibles errores de medicación, incluso cuando no estén asociados con resultados adversos. Un posible error de medicación es el reconocimiento de circunstancias que podrían conducir a un error de medicación y puede involucrar a un paciente o no. Esta información puede ser pertinente para la interpretación de datos de seguridad o la evaluación general del beneficio-riesgo del medicamento. Un error de medicación puede surgir en cualquier etapa del proceso de uso del medicamento, y puede involucrar a pacientes, consumidores o profesionales de la salud.

Esta información puede ser recibida por el TAC a través de sistemas de reportes espontáneos, consultas de información médica, quejas de clientes, revisión de medios digitales, programas de apoyo al paciente u otras fuentes de información disponibles.

Las señales o riesgos identificados de cualquier fuente de información o categoría de informes deben presentarse y evaluarse en la sección correspondiente del PBRER.

3.10 Datos no clínicos

Esta sección debe resumir los hallazgos de seguridad más importantes de estudios no clínicos *in vivo* e *in vitro* (por ejemplo, estudios de carcinogenicidad, reproducción o inmunotoxicidad), que estén en curso o se hayan completado durante el intervalo de informe. Los resultados de estudios diseñados para abordar preocupaciones específicas de seguridad deben incluirse en el PBRER, independientemente del resultado. Las implicaciones de los hallazgos presentados en la sección 10 del PBRER deben analizarse en las secciones de evaluación pertinentes del informe.

3.11 Literatura

Esta sección debe resumir los hallazgos de seguridad nuevos y significativos, ya sea publicados en la literatura científica revisada por pares o disponibles, como manuscritos no publicados, que sean pertinentes para el medicamento aprobado del cual el TAC haya tenido conocimiento durante el intervalo de informe. Las búsquedas bibliográficas para los PBRERs deben ser más amplias que las de casos individuales de reacciones adversas, e incluir estudios que informen resultados de seguridad en grupos de sujetos. Si es pertinente, debe considerarse la información sobre principios activos de la misma clase.

3.12 Otros informes periódicos

A menos que los requisitos reguladores nacionales o regionales especifiquen lo contrario, el TAC debe preparar un único PBRER para un solo principio activo. Sin embargo, si un TAC elabora múltiples PBRERs para un mismo principio activo (por ejemplo, para diferentes indicaciones o formulaciones), esta sección debe resumir los hallazgos significativos de los otros informes periódicos, si no se presentan en otras partes de este informe.

Cuando estén disponibles, y en función de los acuerdos contractuales, el TAC debe resumir los hallazgos significativos de los informes periódicos proporcionados durante el intervalo de informe por otras partes (por ejemplo, patrocinadores, titulares de la autorización de comercialización, otros socios contractuales).

3.13 Falta de eficacia en ensayos clínicos controlados

Los datos de ensayos clínicos que indiquen falta de eficacia, o falta de eficacia en relación con terapias establecidas, para productos destinados a tratar o prevenir enfermedades graves o potencialmente mortales

(por ejemplo, exceso de eventos adversos cardiovasculares en un ensayo de un nuevo medicamento antiplaquetario para síndromes coronarios agudos), podrían reflejar un riesgo significativo para la población tratada y deberían resumirse en esta sección.

3.14 Información de última hora

Esta sección debe resumir la información sobre hallazgos potencialmente importantes de seguridad y eficacia/efectividad que surjan después de la DLP, pero mientras se está preparando el PBRER. Ejemplos incluyen nuevas publicaciones clínicamente significativas, datos de seguimiento importantes, hallazgos toxicológicos clínicamente relevantes y cualquier medida que haya tomado por razones de seguridad el TAC, un comité de monitoreo de datos o una autoridad reguladora. No se deben incluir nuevos informes de casos individuales, a menos que se consideren un caso índice importante (es decir, la primera instancia de un evento importante), una señal de seguridad importante, o que añadan información a la evaluación de preocupaciones de seguridad ya presentadas en el PBRER (por ejemplo, un informe de caso bien documentado y sin factores de confusión de anemia aplásica en un medicamento que se sabe que está asociado con efectos adversos en la médula ósea).

Cuando sea posible, cualquier cambio significativo propuesto a la información de referencia del producto que haya ocurrido después de la DLP del informe, pero antes de la presentación, también debe incluirse en esta sección. Dichos cambios podrían incluir una nueva contraindicación, advertencia/precaución o nueva reacción adversa al medicamento.

Los datos presentados en esta sección también deben tenerse en cuenta en la evaluación de riesgos e información nueva (véase la sección 3.16.3 de esta guía).

3.15 Resumen de señales: nuevas, en curso o cerradas

La ubicación general para la presentación de la información sobre señales y riesgos dentro del PBRER se muestra en el Anexo F de esta guía. El propósito de la sección 15 del PBRER es proporcionar una perspectiva general de alto nivel de las señales de seguridad que se cerraron (es decir, cuya evaluación se completó) durante el intervalo de informe, así como las señales en curso* que estaban en evaluación al final del intervalo. A efectos del PBRER, una señal debe ser incluida una vez que haya pasado por la etapa inicial de selección o aclaración, y se haya decidido realizar una evaluación adicional por parte del TAC. Cabe destacar que una señal de seguridad no es sinónimo de una estadística de informe desproporcionado para una combinación específica de medicamento/evento, ya que se requiere un paso de validación. Las señales pueden ser cualitativas (por ejemplo, un informe de caso de seguridad individual fundamental, una serie de casos) o cuantitativas (por ejemplo, una puntuación de desproporcionalidad, hallazgos de un ensayo clínico o estudio epidemiológico). Las señales pueden surgir en forma de una solicitud de información o consulta sobre un problema de seguridad por parte de una autoridad reguladora.

Las decisiones sobre la clasificación posterior de estas señales y las conclusiones de la evaluación implican criterio médico e interpretación científica de los datos disponibles, los cuales se presentan en la sección 16 del PBRER.

Una nueva señal es una señal de la que el TAC se percató durante el intervalo de informe. La nueva información clínicamente importante sobre una señal previamente cerrada* que surgió durante el período de informe del PBRER (es decir, un nuevo aspecto de una señal previamente refutada o un riesgo reconocido que probablemente justifique más acciones para su verificación), también constituiría una nueva señal. Las nuevas señales pueden clasificarse como cerradas o en curso, dependiendo del estado de la evaluación de la señal en la DLP del PBRER. Los ejemplos incluirían nueva información sobre una señal previamente:

- Cerrada y refutada, lo que resultaría en la reapertura de la señal.

- Riesgo identificado que es indicativo de una diferencia clínicamente significativa en la gravedad del riesgo, por ejemplo, si se identifican aumentos transitorios de las enzimas hepáticas como riesgos y se recibe nueva información que indica un resultado más grave, como insuficiencia hepática; la neutropenia es un riesgo identificado y se recibe un informe de caso bien documentado y sin factores de confusión de agranulocitosis.
- Riesgo identificado para el cual se encuentra recientemente una mayor frecuencia del riesgo, por ejemplo, en una subpoblación.
- Riesgo potencial* que, de confirmarse, justificaría una nueva advertencia, precaución, una nueva contraindicación o restricción en las indicaciones o poblaciones, u otras actividades de minimización de riesgos.

En esta sección, o como un anexo, incluya una lista tabular de todas las señales en curso o cerradas en la DLP del PBRER. Esta tabla debe incluir la siguiente información (véase el anexo C para ver un ejemplo).

- Una breve descripción de la señal
- Fecha en la que el TAC tuvo conocimiento de la señal
- Estado de la señal (cerrada o en curso en la DLP)
- Fecha en la que se cerró la señal, si corresponde
- Origen de la señal
- Un breve resumen de los datos clave
- Planes para una evaluación adicional
- Acciones tomadas o planeadas

Las evaluaciones detalladas para las señales cerradas no deben incluirse en esta sección, sino que deben presentarse en la sección 16.2 del PBRER (Evaluación de señales). La evaluación de información nueva en relación con riesgos identificados y potenciales previamente conocidos y que no se considera que constituyan una señal recientemente identificada*, debe proporcionarse en la sección 16.3 del PBRER (Evaluación de riesgos e información nueva).

Cuando una autoridad reguladora haya solicitado que se supervise y se informe sobre un tema específico (no considerado una señal) en un PBRER, el TAC debe resumir el resultado del análisis en la sección 15 del PBRER, si es negativo. Si el tema específico se convierte en una señal, inclúyalo en la tabulación de señales y analícelo en la sección 16.2 del PBRER.

3.16 Evaluación de señales y riesgos

El propósito de la sección 16 del PBRER es proporcionar:

- Un resumen conciso de lo que se sabe sobre los riesgos importantes identificados y potenciales y la información importante faltante* al inicio del intervalo de informe cubierto por el informe (16.1).
- Una evaluación de todas las señales cerradas durante el intervalo de informe (16.2).
- Una evaluación de la nueva información con respecto a los riesgos identificados y potenciales previamente reconocidos (16.3).
- Una caracterización actualizada de los riesgos importantes potenciales e identificados, cuando corresponda (16.4).
- Un resumen de la efectividad de las actividades de minimización de riesgos en cualquier país o región que pueda ser útil en otros países o regiones (16.5).

El anexo F de esta guía proporciona un diagrama de flujo para ilustrar la asignación de señales y riesgos a secciones específicas del PBRER.

Las subsecciones de evaluación no deben resumir ni repetir la información presentada en secciones anteriores del PBRER, sino que deben proporcionar una interpretación de la información, con el objetivo

de caracterizar el perfil de los riesgos evaluados como importantes. Como regla general, no es necesario incluir narrativas de casos individuales en las secciones de evaluación del PBRER; sin embargo, cuando sea fundamental para el análisis científico de una señal o riesgo, se debe proporcionar una evaluación clínica de casos clave o ilustrativos (por ejemplo, el primer caso de agranulocitosis sospechada con un principio activo que pertenece a una clase conocida por estar asociada con esta reacción adversa).

3.16.1 Resumen de preocupaciones de seguridad

El propósito de esta sección es proporcionar un resumen de las preocupaciones de seguridad al inicio del intervalo de informe, contra el cual se podrá comparar la nueva información y las evaluaciones. Estas incluyen:

- Riesgos importantes identificados*
- Riesgos potenciales importantes*
- Información importante faltante

Los siguientes factores deben considerarse a la hora de determinar si un riesgo es importante o no:

- La gravedad médica del riesgo, incluido el impacto en los pacientes individuales
- Su frecuencia, predictibilidad, prevenibilidad y reversibilidad
- El posible impacto en la salud pública (frecuencia; tamaño de la población tratada)
- El potencial para evitar un producto médico con un beneficio preventivo como resultado de la percepción pública del riesgo.

En el caso de los productos con una especificación de seguridad existente, esta sección puede ser igual a, o derivada del resumen de la especificación de seguridad (según la Guía E2E de la ICH), al inicio del intervalo de informe del PBRER actual. Para los productos sin una especificación de seguridad existente, esta sección debe proporcionar información sobre los riesgos importantes identificados y potenciales y la información importante faltante asociada con el uso del producto, según la experiencia previa y posterior a la aprobación. Los riesgos importantes identificados y potenciales pueden incluir, por ejemplo:

- Reacciones adversas importantes
- Interacciones con otros medicamentos
- Interacciones con alimentos y otras sustancias
- Errores de medicación
- Efectos de la exposición ocupacional
- Efectos de la clase farmacológica

El resumen sobre la información importante faltante debe tener en cuenta si existen lagunas críticas en el conocimiento sobre problemas de seguridad específicos o poblaciones que usan el medicamento.

3.16.2 Evaluación de señales

La sección 16.2 del PBRER debe resumir los resultados de las evaluaciones de todas las señales de seguridad (sean clasificadas como importantes o no), que se cerraron durante el intervalo de informe. Una señal de seguridad puede cerrarse ya sea porque se ha refutado o porque, tras la evaluación, se ha determinado que es un riesgo potencial o identificado. Por lo tanto, las dos categorías principales que deben incluirse en esta sección son:

1. Las señales que, después de la evaluación, han sido refutadas como señales "falsas" basándose en el criterio médico y en una evaluación científica de la información actualmente disponible.
2. Las señales que, después de la evaluación, se han clasificado como un riesgo potencial o identificado, incluida la falta de eficacia.

Para ambas categorías de señales cerradas, se debe incluir una descripción concisa de la evaluación de cada señal, para proporcionar a las autoridades reguladoras la base sobre la cual la señal fue refutada o considerada como un riesgo potencial o identificado por el TAC.

Se recomienda que el grado de detalle proporcionado en la descripción de la evaluación de la señal sea proporcional a la importancia médica de la señal, su importancia para la salud pública y el alcance de la evidencia disponible. Cuando se incluyan múltiples evaluaciones en ambas categorías de señales cerradas, se pueden presentar en el siguiente orden:

- Señales cerradas y refutadas
- Señales cerradas que se clasifican como riesgos potenciales importantes
- Señales cerradas que se clasifican como riesgos identificados importantes
- Señales cerradas que son riesgos potenciales no clasificados como importantes
- Señales cerradas que son riesgos identificados no clasificados como importantes

Cuando corresponda, las evaluaciones de señales cerradas se pueden presentar por indicación o población.

La(s) descripción(es) de las evaluaciones de señales se puede incluir en esta sección del PBRER o en un anexo. Cada evaluación de señal debe incluir la siguiente información, según corresponda:

- Origen de la señal
- Antecedentes pertinentes para la evaluación
- Método(s) de evaluación, incluidas las fuentes de datos, los criterios de búsqueda (cuando corresponda, los términos MedDRA específicos [por ejemplo, PTs, HLTs, SOCs, etc.] o consultas MedDRA estandarizadas [SMQ] que se revisaron), y los enfoques analíticos.
- Resultados: un resumen y análisis crítico de los datos considerados en la evaluación de la señal; cuando sea parte integral de la evaluación, esto puede incluir una descripción de una serie de casos o un ICSR, por ejemplo, un caso índice de agranulocitosis bien documentada o síndrome de Stevens-Johnson.
- Análisis
- Conclusión

3.16.3 Evaluación de riesgos e información nueva

Esta sección debe proporcionar una evaluación critica de la nueva información pertinente para los riesgos previamente reconocidos que no esté ya incluida en la sección 16.2 del PBRER (Evaluación de señales).

La nueva información que constituya una señal respecto a un riesgo previamente reconocido o una señal anteriormente refutada debe presentarse en el resumen tabulado del anexo C y evaluarse en la sección 16.2 del PBRER, si la señal también se cierra durante el intervalo del PBRER.

La información actualizada sobre un riesgo previamente reconocido que no constituya una señal debe incluirse en esta sección. Ejemplos de esto son la información que confirma un riesgo potencial como un riesgo identificado, o información que permita una mayor caracterización de un riesgo previamente reconocido.

La nueva información se puede organizar de la siguiente manera:

1. Nueva información sobre riesgos potenciales importantes
2. Nueva información sobre riesgos identificados importantes
3. Nueva información sobre otros riesgos potenciales no categorizados como importantes
4. Nueva información sobre otros riesgos identificados no categorizados como importantes
5. Actualización sobre información importante faltante

El enfoque de las evaluaciones está en la nueva información que ha surgido durante el intervalo de informe del PBRER. Esto debe ser conciso e interpretar el impacto, si lo hay, en la comprensión y caracterización del riesgo. Cuando corresponda, la evaluación servirá de base para una actualización de la caracterización de los riesgos potenciales e identificados importantes en la sección 16.4 del informe. Se recomienda que el grado de detalle de la evaluación incluida en esta sección sea proporcional a la evidencia disponible sobre el riesgo y su importancia médica y relevancia para la salud pública.

Las evaluaciones de nueva información y las actualizaciones de información faltante pueden incluirse en esta sección del PBRER o en un anexo. Cada evaluación debe incluir la siguiente información, según corresponda:

- Fuente de la nueva información
- Contexto pertinente para la evaluación
- Método(s) de evaluación, incluyendo fuentes de datos, criterios de búsqueda y enfoques analíticos
- Resultados: un resumen y análisis crítico de los datos considerados en la evaluación del riesgo
- Discusión
- Conclusión, que incluya si la evaluación respalda una actualización de la caracterización de alguno de los riesgos potenciales e identificados importantes en la sección 16.4 del PBRER o no.

Cualquier nueva información sobre poblaciones expuestas o datos generados para abordar información previamente faltante, debe ser evaluada críticamente en esta sección. Se deben reconocer las preocupaciones y las incertidumbres no resueltas.

Chapter V

Data Analysis

Data analysis is the process of examining raw data in order to draw meaningful conclusions. The primary objective of data analysis is to transform disorganized or complex data into a clear, easy-to-understand format that helps make informed decisions. The University of Pretoria (2024) explains that “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, relationships or trends.” Therefore, this chapter focuses on analyzing the data from the translations presented in the previous chapter.

The researcher used the data collection instruments described in Chapter III, which are the Text Analysis Chart and Color-Coded Text Chart, to guide the analysis.

5.1 Analysis and Interpretation of the Results

In the following sections of this chapter, the researcher analyzes the data related to the texts in Chapter IV, using Chapter III (Theoretical Framework) as a guide. The analysis includes a review of each text and an examination of translation procedures for selected paragraphs through color coding.

5.1.1 Text Analysis Chart

The first data collection instrument used in this research is the text analysis chart, which categorizes various elements within the source texts. The chart includes columns for text style (narrative, descriptive, etc.), text function (informative, expressive, or vocative), scale of formality (ranging from formal to informal), scale of generality or difficulty (ranging from basic to technical language), emotional tone (from intense to restrained), and translation method (semantic or communicative).

5.1.1.1 Text Analysis Chart of the Document Translated from Spanish into English

Table 4. Text Analysis: Document from Spanish into English

Text Analysis	***Reglamento de buenas prácticas de farmacovigilancia***
Text Style	Descriptive
Text Function	Informative
Scale of Formality	Official and Formal
Scale of Generality or Difficulty	Educated and Technical
Scale of Emotional Tone	Factual
Translation Method	Semantic and Communicative

Table 4. It represents the analysis of the text translated from Spanish into English. Source: Researcher's own creation

Firstly, the style of the first text is descriptive, as its purpose is to explain the regulation of good pharmacovigilance practices that healthcare professionals and regulatory authorities should follow. As a result, the researcher identified clear descriptions of instructions and procedures that healthcare professionals should follow.

The function of the text is informative, as it clearly and objectively conveys instructions, procedures, and concepts regarding the reporting of adverse drug reactions.

The formality of the text is official and formal, for it is direct and concise while using formal language appropriate for an official document issued by the Ministry of Health of Costa Rica.

The generality or difficulty of the text is educated and technical, as it focuses on the specialized subject of pharmacovigilance. It uses specific vocabulary and technical terms that

require familiarity with the field to fully understand, resulting in a text of moderate to high difficulty.

The emotional tone of the text is factual, as the language used is objective and neutral.

Lastly, the translation approach employed for this text combines both the semantic and communicative methods. Given that the source text includes specialized and technical terminology, the researcher aimed to retain as much fidelity to the original text as possible, while ensuring the translation remains accurate and clear in the target language.

5.1.1.2 Text Analysis Chart of the Document Translated from English into Spanish

Table 5. Text Analysis: Document from English into Spanish

Text Analysis	***Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline***
Text Style	Descriptive
Text Function	Informative
Scale of Formality	Official and Formal
Scale of Generality or Difficulty	Educated and Technical
Scale of Emotional Tone	Factual
Translation Method	Semantic and Communicative

Table 5. It represents the analysis of the text translated from English into Spanish. Source: Researcher's own creation

Firstly, this text is a guideline designed for healthcare professionals and Marketing Authorization Holders that emphasizes the importance of the Periodic Benefit-Risk Evaluation Report and outlines the steps for creating one. As a result, its style is descriptive, as it provides clear and detailed instructions and procedures to follow.

The function of the text is informative, as it clearly and objectively conveys instructions, procedures, and concepts regarding the creation of a Periodic Benefit-Risk Evaluation Report.

The formality of the text is official and formal, for it is direct while using formal language appropriate for an official document issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

The generality or difficulty of the text is educated and technical, as it focuses on the creation of a pharmacovigilance report. It uses specialized vocabulary and technical terms that require familiarity with the field to fully understand, resulting in a text of moderate to high difficulty.

The emotional tone of the text is factual, as the language used is objective and neutral.

Lastly, the translation approach employed for this text combines both the semantic and communicative methods. Given that the source text includes specialized and technical terminology, the researcher aimed to retain as much fidelity to the original text as possible while ensuring the translation remains accurate and clear in the target language. This approach allows for both fidelity to the source text and adaptability to the needs of the target language, ensuring that the translation is precise and natural.

5.1.2 Color-Coded Text Chart

The second data collection instrument used in this research is the text color-coded text chart. The researcher selected fifteen paragraphs from each translated text and applied color coding to identify translation procedures used within those paragraphs: purple for transposition (grammatical changes), blue for modulation (point of view changes), green for omission (leaving out text details), orange for amplification (addition of extra information for clarity), red for

explicitation (converting implicit details into explicit), and pink for literal translation (word-for-word translation).

Table 6. Color-Coded Text Chart

Color	Meaning (Translation Procedure)
	Transposition
	Modulation
	Omission
	Amplification
	Explicitation
	Literal Translation

Table 6. The colors represent each translation procedure employed. Source: Researcher's own creation

It is important to mention that the fifteen paragraphs selected from the Spanish-to-English translation range from 45 to 80 words, while those from the English-to-Spanish translation range from 118 to 190 words. This difference arises because Spanish generally prefers longer sentences than English, often incorporating multiple subordinate clauses within a single sentence. Spanish writers commonly connect these clauses using commas, colons, or conjunctions, rather than splitting them into separate sentences. Moreover, short sentences are usually avoided in Spanish, as they may be perceived as repetitive or monotonous. In contrast, English benefits from shorter, simpler sentences that enhance clarity (Lingard et al., 2021).

5.1.2.1 Color Coding of the Text *Reglamento de buenas prácticas de farmacovigilancia* Translated from Spanish into English

Paragraph 1

Definir las bases que contribuyan a establecer un sistema de garantía de calidad en las actividades del Sistema Nacional de Farmacovigilancia, mediante el establecimiento de las obligaciones y responsabilidades que deben cumplir los diferentes agentes que lo conforman, con el fin de garantizar criterios uniformes para realizar la evaluación de las notificaciones, la generación de alertas y fomentar la comprensión y la enseñanza de la Farmacovigilancia.

To define the bases for establishing a quality assurance system in the activities of the National Pharmacovigilance System. This involves establishing the obligations and responsibilities of the different agents involved, aiming to ensure consistent criteria for evaluating reports, generating alerts, and promoting the comprehension and teaching of Pharmacovigilance.

Paragraph 2

5.12 Farmacovigilancia intensiva: Método de la farmacovigilancia que consiste en obtener información de sospechas de reacciones adversas a los medicamentos de manera sistemática, de calidad y completa, caracterizada por su elevada sensibilidad y fiabilidad; especialmente cuando se necesita determinar la frecuencia de las reacciones adversas e identificar agentes predisponentes y patrones de uso de medicamentos, entre otros.

5.12 Intensive Pharmacovigilance: A pharmacovigilance method involving (gerund) the systematic, high-quality, and comprehensive collection of information on suspected adverse drug reactions. This approach is characterized by its high sensitivity and reliability, especially when

determining the frequency of adverse reactions and identifying predisposing agents and patterns of medication use, among other aspects.

Paragraph 3

5.21 Plan de minimización de riesgos: Documento en el que el titular del producto especifica los riesgos asociados al medicamento, identificados o potenciales y señala la información de seguridad no conocida en la literatura científica. Consiste en un programa estratégico de seguridad orientado a alcanzar metas y objetivos específicos para reducir al mínimo los riesgos conocidos de los medicamentos preservando sus beneficios.

5.21 Risk Minimization Plan: A document in which the product holder specifies the risks associated with the medication, whether identified or potential, and provides safety information not yet covered in scientific literature. It consists of a strategic safety program designed to achieve specific goals and objectives to minimize the known risks of the medication while preserving its benefits.

Paragraph 4

5.25 Relación Beneficio/riesgo: Refleja la correlación entre el beneficio y el riesgo que presenta el uso de un medicamento. Sirve para expresar un juicio sobre la función del medicamento en la práctica médica, basado en datos sobre su eficacia y seguridad y en consideraciones sobre su posible uso indebido, la gravedad y el pronóstico de la enfermedad, etcétera. El concepto puede aplicarse a un solo medicamento o a las comparaciones entre dos o más medicamentos empleados para una misma indicación.

5.25 Benefit-Risk Evaluation: It reflects the correlation between the benefits and risks associated with the use of a medication. It serves to assess the medication's role in medical practice based on data regarding its efficacy and safety, and on considerations on its potential

misuse, the severity and prognosis of the disease, etc. This concept can be applied to a single medication or to comparisons between two or more medications used for the same indication.

Paragraph 5

9.13 Trabajar en forma articulada con los programas de salud pública incluyendo el de inmunizaciones, de forma tal que las notificaciones de eventos y sospechas de RAM detectadas a través de esos programas sean notificadas al CNFV para su evaluación. Los ESAVIS, aunque se remitan a otras instancias de salud pública, deben ser comunicados al CNFV en la Tarjeta Amarilla según los lineamientos establecidos para el manejo de ESAVIS.

9.13 Collaborate with public health programs, including the immunization program, so that reports of events and suspected ADRs detected through those programs are reported to the CNFV for evaluation. ESAVIs, even if they are sent to other public health authorities, must be reported to the CNFV using the Yellow Card, following the guidelines established for managing ESAVIs.

Paragraph 6

d) Establecer acuerdos en materia de FV en caso de existir cualquier transferencia de obligaciones y funciones. Estos deben estar documentados mediante un acuerdo escrito firmado y legalizado entre los representantes legales de las dos empresas, los cuales deben ser notificados al CNFV. Las funciones no transferidas mediante este acuerdo siguen siendo asumidas por el responsable de la importación.

d) Establish agreements on pharmacovigilance if there is any transfer of obligations and functions. These agreements must be documented in a written and notarized agreement signed by the legal representatives of both companies, which must be notified to the CNFV. Functions not transferred through this agreement remain the responsibility of the importer.

Paragraph 7

f) Llevar un registro detallado de las sospechas de RAM detectadas que incluya toda la información contenida en el Formulario de Notificación de Sospechas de RAM. Tal registro debe mantenerse en un sistema de archivo ya sea físico o digital que permita conservar adecuadamente toda la documentación relacionada con las responsabilidades y actividades de FV por un periodo de 5 años.

f) Maintain a detailed record of suspected ADRs detected, including all information contained in the Suspected ADR Reporting Form. This record must be kept in a filing system, either physical or digital, that ensures proper storage of all documentation related to pharmacovigilance responsibilities and activities for a period of 5 years.

Paragraph 8

d) Establecer acuerdos en materia de FV. En caso de existir cualquier transferencia de obligaciones y funciones, debe estar documentada mediante un acuerdo escrito firmado y legalizado entre los representantes legales de las dos empresas. Estos acuerdos deben ser notificados al CNFV y además deben adjuntarse al expediente de registro sanitario. Las funciones no transferidas mediante este acuerdo siguen siendo asumidas por el titular del registro.

d) To establish agreements on pharmacovigilance. If there is any transfer of obligations and functions, it must be documented in a written and notarized agreement signed by the legal representatives of both companies. These agreements must be notified to the CNFV and should also be included in the health registration file. Functions not transferred through this agreement remain the responsibility of the registration holder.

Paragraph 9

12.6.4 Para cualquier sospecha de RAM el encargado de FV debe asegurarse que se recopile toda la información necesaria y debe evaluar los siguientes criterios: gravedad, si está referenciada o no de acuerdo con la información básica de seguridad del producto, si es esperada o inesperada de acuerdo con la monografía, cumpliendo con los plazos de reporte de acuerdo a lo establecido en el Decreto Ejecutivo N° 35244-S "Reglamento del Sistema Nacional de Farmacovigilancia". Esta información debe anotarse en el formulario adaptado CIOMS en la sección de descripción de la RAM.

12.6.4 For any suspected ADR, the Pharmacovigilance Officer must ensure that all necessary information is collected and must evaluate the following criteria: severity, whether it is referenced or not according to the product's basic safety information, and whether it is expected or unexpected according to the monograph. The Pharmacovigilance Officer must also comply with the reporting deadlines as specified in Executive Decree No. 35244-S "Reglamento del Sistema Nacional de Farmacovigilancia." This information should be recorded in the CIOMS-adapted form in the section for describing ADRs.

Paragraph 10

12.6.5 El encargado de Farmacovigilancia debe asegurar que se realice un seguimiento de la evolución y el desenlace de cada caso individual, luego de realizar al menos 3 intentos de contacto al notificador, los cuales deben quedar documentados. La información de seguimiento adicional que se reciba quedará registrada y fechada de igual forma que la información inicial y debe ser enviada al CNFV en el formulario adaptado CIOMS en la sección de descripción de la RAM.

12.6.5 The Pharmacovigilance Officer must ensure that the evolution and outcome of each individual case is monitored after making at least three attempts to contact the reporter, which must be documented. Additional follow-up information received will be recorded and dated in the same way as the initial information and must be sent to the CNFV using the CIOMS-adapted form in the section for describing ADRs.

Paragraph 11

9.7 Realizar inspecciones a la labor del profesional encargado de FV y a la industria farmacéutica con el fin de comprobar el cumplimiento de las BPFV y evaluar su eficacia para alcanzar los objetivos específicos. Para facilitar las inspecciones de FV, el Ministerio de Salud mantendrá a disposición de los administrados la Guía de Verificación de BPFV disponible en la página web del Ministerio.

9.7 Conduct inspections of the work done by the Pharmacovigilance Officer and the pharmaceutical industry to ensure compliance with GVPs and evaluate their effectiveness in achieving the specific objectives. To facilitate pharmacovigilance inspections, the Ministry of Health will provide the Guía de Verificación de BPFV on its website.

Paragraph 12

5.4 Buenas Prácticas de Farmacovigilancia: Conjunto de reglas destinadas a garantizar la autenticidad y la calidad de los datos recolectados en Farmacovigilancia, que permitan evaluar en cada momento los riesgos atribuibles al medicamento; la confidencialidad de la información que se ha notificado sobre las reacciones adversas y el uso de criterios uniformes en la evaluación de las notificaciones y en la generación de señales de alerta.

5.4 Good Pharmacovigilance Practices: A set of rules intended to guarantee the authenticity and quality of the data collected in pharmacovigilance, allowing for the continuous

evaluation of risks attributable to the medication. These practices also ensure the confidentiality of information that has been reported about adverse reactions and the use of consistent criteria in evaluating reports and generating alerts.

Paragraph 13

8.1.6 La notificación debe ser entregada en forma física al CNFV a través de la Dirección de Atención al Cliente. La información puede ser enviada por fax, correo electrónico o puede ser comunicada por vía telefónica al CNFV con posterior entrega de la documentación física de acuerdo al Reglamento del Sistema Nacional de Farmacovigilancia.

8.1.6 The report must be submitted in physical form to the CNFV through the Customer Service Department. The information can be sent by fax, email, or communicated by phone to the CNFV, with the physical documentation delivered subsequently according to the "Reglamento del Sistema Nacional de Farmacovigilancia."

Paragraph 14

5.7 Crisis: Una crisis se produce cuando se da a conocer información nueva sobre la seguridad o eficacia de un producto que puede tener un efecto importante en la salud pública y que, por tanto, requiere acciones inmediatas. También puede sobrevenir cuando los medios de comunicación difunden información en la que se expresa alguna preocupación acerca del consumo de determinado producto.

5.7 Crisis: A crisis occurs when new information about the safety or efficacy of a product that could significantly impact public health is revealed and thus requires immediate action. It can also happen when the media disseminates information expressing concern about the use of a particular product.

Paragraph 15

5.26 Señal: Posible relación causal entre un evento adverso y un medicamento cuando previamente se desconocía esta relación o estaba documentada en forma incompleta. Habitualmente se requiere más de una notificación para generar una señal, dependiendo de la gravedad del evento adverso y de la calidad de la información.

5.26 Signal: A potential causal relationship between an adverse event and a medication when this relationship was previously unknown or incompletely documented. Typically, more than one report is required to generate a signal, depending on the severity of the adverse event and the quality of the information.

5.1.2.2 Color Coding of the Text *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline* Translated from English into Spanish

Paragraph 1

The ICH Guideline E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, achieved Step 4 in 1996, and was intended to harmonise the periodic reporting requirements to regulatory authorities and to provide, in a common format, the worldwide interval safety experience of a medicinal product at defined times post-approval. At that time, the focus of the Periodic Safety Update Report (PSUR) was on relevant new safety information in the context of patient exposure, to determine if changes were needed to the Reference Safety Information* (RSI) in order to optimise the continued safe use of the product. The Guideline was revised in 2003, to provide needed clarification, guidance and flexibility.

La guía E2C de la ICH, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, alcanzó el *Paso 4* en 1996, y tenía como objetivo armonizar los requisitos de informes periódicos a las autoridades reguladoras y proporcionar, en un formato

común, la experiencia mundial de seguridad en intervalos de un medicamento en momentos definidos después de su aprobación. En ese momento, el Informe Periódico de Seguridad (PSUR, por sus siglas en inglés), se centraba en la nueva información de seguridad pertinente en el contexto de la exposición del paciente para determinar si era necesario realizar cambios en la Información de Referencia de Seguridad* (RSI, por sus siglas en inglés), con el fin de optimizar el uso seguro y continuo del producto. La guía se revisó en 2003 para proporcionar la aclaración, la orientación y la flexibilidad necesarias.

Paragraph 2

The PBRER should include cumulative knowledge of the product while retaining focus on new information, i.e., the overall safety evaluation and integrated benefit-risk evaluation will take into account cumulative information. Because clinical development of a drug frequently continues following marketing approval, relevant information from post-marketing studies or clinical trials in unapproved indications or populations should also be included in the PBRER. Similarly, as knowledge of the safety of a medicinal product may be derived from evaluation of data associated with uses other than the approved indication(s), such knowledge would be reflected in the risk evaluation, where relevant and appropriate.

El PBRER debe incluir el conocimiento acumulativo del producto sin dejar de centrarse en la información nueva, es decir, la evaluación general de seguridad y la evaluación integrada del beneficio-riesgo tendrán en cuenta la información acumulativa. Dado que el desarrollo clínico de un medicamento continúa con frecuencia después de la aprobación para su comercialización, la información pertinente proveniente de estudios poscomercialización o de ensayos clínicos en indicaciones o poblaciones no aprobadas también debe incluirse en el PBRER. Del mismo modo, como el conocimiento de la seguridad de un medicamento puede

derivarse de la evaluación de datos asociados con usos distintos de las indicaciones aprobadas, dicho conocimiento se reflejaría en la evaluación del riesgo, cuando sea pertinente y apropiado.

Paragraph 3

This Guideline aims to facilitate flexibility by encouraging the use of individual sections that are common to more than one report – "modules" that can be used for different regulatory authorities and for different purposes. Therefore, the PBRER has been developed in such a way that the content of several sections may be used for sections of other documents as a basis for a modular approach. For example, if the DIBD of a DSUR for a medicinal product is aligned to the IBD of the PBRER for the same product as suggested in ICH E2F, the content of a number of sections of the DSUR can also be used in the PBRER when the Data Lock Points (DLPs) are the same, i.e., when each report covers an interval of one year based on the IBD.

Esta guía tiene como objetivo facilitar la flexibilidad al fomentar el uso de secciones individuales que sean comunes a más de un informe, es decir, "módulos" que puedan ser utilizados para diferentes autoridades reguladoras y distintos fines. Por lo tanto, el PBRER se ha desarrollado de tal manera que el contenido de varias secciones se pueda utilizar en secciones de otros documentos como base para un enfoque modular. Por ejemplo, si la DIBD de un DSUR para un medicamento está alineada con la IBD del PBRER para el mismo producto, tal como se sugiere en la E2F de la ICH, el contenido de varias secciones del DSUR también se puede utilizar en el PBRER cuando las fechas de cierre de datos (DLPs, por sus siglas en inglés) sean las mismas, es decir, cuando cada informe cubre un intervalo de un año basado en la IBD.

Paragraph 4

The reference product information for the PBRER would include "core safety" and "approved indications" components. In order to facilitate the assessment of benefit and benefit-

risk by indication in the evaluation sections of the PBRER, the reference product information document should list all approved indications in ICH countries or regions. It is likely that these indications will also apply in other countries or regions. However, when the PBRER is also to be submitted to other countries in which there are additional locally approved indications, these indications may either be added to the reference product information or handled as a regional appendix/appendices as considered most appropriate by the MAH. The basis for the benefit evaluation should be the baseline important efficacy/effectiveness information summarised in Section 17.1 of the PBRER.

La información de referencia del producto para el PBRER incluiría componentes de "seguridad básica" e "indicaciones aprobadas". Para facilitar la evaluación del beneficio y el beneficio-riesgo por indicación en las secciones de evaluación del PBRER, el documento de información de referencia del producto debería enumerar todas las indicaciones aprobadas en los países o regiones de la ICH. Es probable que estas indicaciones también se apliquen en otros países o regiones. Sin embargo, cuando el PBRER también se va a presentar en otros países donde hay indicaciones adicionales aprobadas localmente, estas indicaciones pueden añadirse a la información de referencia del producto o manejarse como un anexo/anexos regionales, según lo considere más adecuado el TAC. La base para la evaluación del beneficio debe ser la información estándar importante de eficacia/efectividad resumida en la sección 17.1 del PBRER.

Paragraph 5

Each medicinal product should have an IBD: the IBD is the date of the first marketing approval for any product containing the active substance granted to any company in any country in the world. When a report contains information on different dosage forms, formulations, or uses (indications, routes and/or populations), the date of the first marketing approval for any of

the various authorisations should be regarded as the IBD and, therefore, determine the DLP for purposes of the PBRER. The DLP is the date designated as the cut-off for data to be included in a PBRER. Through PBRERs prepared with harmonised DLPs based on a common IBD, the same updated safety and benefit-risk information can be reviewed globally by different regulatory authorities.

Cada medicamento debe tener una IBD. La IBD es la fecha de la primera aprobación de comercialización para cualquier producto que contenga el principio activo otorgada a cualquier compañía en cualquier país del mundo. Cuando un informe contiene información sobre diferentes formas farmacéuticas, formulaciones o usos (indicaciones, vías o poblaciones), la fecha de la primera aprobación de comercialización para cualquiera de las distintas autorizaciones debe considerarse como la IBD y, por lo tanto, determinar la DLP a efectos del PBRER. La DLP es la fecha designada como el límite para incluir datos en un PBRER. A través de los PBRERs preparados con DLPs armonizadas basadas en una IBD común, la misma información actualizada sobre seguridad y beneficio-riesgo puede ser revisada globalmente por diferentes autoridades reguladoras.

Paragraph 6

This section of the PBRER should provide a brief summary of clinically important emerging efficacy/effectiveness and safety findings obtained from the MAH's sponsored clinical trials that became available during the reporting interval of the report. The safety signals arising from clinical trial sources should be tabulated in Section 15 of the PBRER. Evaluation of the signals (whether or not categorised as refuted signals or either potential* or identified risks*) that were closed during the reporting interval should be presented in Section 16.2 of the PBRER. New information in relation to any previously known potential or identified risks and not

considered to constitute a newly indentified signal should be evaluated and characterised in Sections 16.3 and 16.4, respectively. Findings from clinical trials not sponsored by the MAH should be described in the relevant sections of the PBRER.

Esta sección del PBRER debe proporcionar un breve resumen de los hallazgos emergentes clínicamente importantes de eficacia/efectividad y seguridad obtenidos de los ensayos clínicos patrocinados por el TAC que surgieron durante el intervalo de informe del reporte. Las señales de seguridad provenientes de ensayos clínicos deben tabularse en la sección 15 del PBRER. La evaluación de las señales (categorizadas como señales refutadas o no, o como riesgos potenciales* o identificados*) que se cerraron durante el intervalo de informe se debe presentar en la sección 16.2 del PBRER. La nueva información relacionada con cualquier riesgo potencial o identificado previamente y no considerado una nueva señal identificada debe evaluarse y caracterizarse en las secciones 16.3 y 16.4, respectivamente. Los hallazgos de ensayos clínicos no patrocinados por el TAC deben describirse en las secciones pertinentes del PBRER.

Paragraph 7

This section should summarise information on potentially important safety and efficacy/effectiveness findings that arise after the DLP but while the PBRER is in preparation. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the MAH, a data monitoring committee, or a regulatory authority has taken for safety reasons. New individual case reports should not be included unless they are considered to constitute an important index case (i.e., the first instance of an important event), an important safety signal, or where they may add information to the evaluation of safety concerns already presented in the PBRER (e.g., a well documented and

unconfounded case report of aplastic anaemia in a medicinal product known to be associated with adverse effects on the bone marrow).

Esta sección debe resumir la información sobre hallazgos potencialmente importantes de seguridad y eficacia/efectividad que surjan después de la DLP, pero mientras se está preparando el PBRER. Ejemplos incluyen nuevas publicaciones clínicamente significativas, datos de seguimiento importantes, hallazgos toxicológicos clínicamente relevantes y cualquier medida que el TAC, un comité de monitoreo de datos o una autoridad reguladora haya tomado por razones de seguridad. No se deben incluir nuevos informes de casos individuales, a menos que se consideren un caso índice importante (es decir, la primera instancia de un evento importante), una señal de seguridad importante, o que añadan información a la evaluación de preocupaciones de seguridad ya presentadas en el PBRER (por ejemplo, un informe de caso bien documentado y sin factores de confusión de anemia aplásica en un medicamento que se sabe que está asociado con efectos adversos en la médula ósea).

Paragraph 8

As noted above, the primary objective of the PSUR was to provide a comprehensive picture of the safety of approved medicinal products. With recognition that the assessment of the risk of a medicinal product is most meaningful when considered in light of its benefits, the proposed report would provide greater emphasis on benefit than the PSUR, particularly when risk estimates change importantly. In such cases there will need to be an overall explicit evaluation of benefit-risk. Consequently the name of the proposed report is the "Periodic Benefit-Risk Evaluation Report" (PBRER). The PBRER would also provide greater emphasis on the cumulative knowledge regarding a medicinal product, while retaining a focus on new information.

Como se mencionó anteriormente, el objetivo principal del PSUR era proporcionar un panorama completo de la seguridad de los medicamentos aprobados. Teniendo en cuenta que la evaluación del riesgo de un medicamento es más significativa cuando se considera a la luz de sus beneficios, el informe propuesto pondría un mayor énfasis en el beneficio que el PSUR, especialmente cuando las estimaciones de riesgo cambien significativamente. En tales casos, será necesario que haya una evaluación general explícita del beneficio-riesgo. En consecuencia, el nombre del informe propuesto es "Informe periódico de evaluación beneficio-riesgo" (PBRER). El PBRER también pondría un mayor énfasis en el conocimiento acumulativo sobre un medicamento, al tiempo que mantendría un enfoque en la información nueva.

Paragraph 9

At present, some ICH countries and regions accept submission of separate types of periodic reports to fulfil national and regional requirements within the post-approval period: the PSUR (ICH Guideline E2C(R1)) for periodic reporting of the safety of approved medicinal products, the DSUR (ICH Guideline E2F) for periodic reporting on the safety of medicinal products that remain in clinical development, and the safety specification component of ICH Guideline E2E that might be submitted at the time of marketing application and/or PSUR submission to aid in the planning of pharmacovigilance activities. As these documents have different regulatory purposes, different periodicities, and can be reviewed by different divisions within a single regulatory authority, each document needs to be complete in its own right – a comprehensive document that can stand alone.

Actualmente, algunos países y regiones de la ICH aceptan la presentación de distintos tipos de informes periódicos para cumplir con los requisitos nacionales y regionales dentro del período posterior a la aprobación: el PSUR (Guía E2C(R1) de la ICH), para informes periódicos

sobre la seguridad de los medicamentos aprobados; el DSUR (Guía E2F de la ICH) para informes periódicos sobre la seguridad de los medicamentos que siguen en fase de desarrollo clínico, y el componente de especificación de seguridad de la Guía E2E de la ICH que podría presentarse en el momento de la solicitud de comercialización y la presentación del PSUR para ayudar en la planificación de las actividades de farmacovigilancia. Como estos documentos tienen diferentes propósitos reguladores, diferentes periodicidades y pueden ser revisados por diferentes departamentos dentro de una sola autoridad reguladora, cada documento debe ser completo por sí mismo y ser un documento integral que pueda funcionar por sí solo.

Paragraph 10

The need for the submission of a PBRER and the frequency of report submission to regulatory authorities are subject to national or regional regulatory requirements, and usually depend on such factors as approval dates, the length of time the product has been on the market, and the extent of knowledge of the benefit-risk profile of the product. The PBRER format and content are intended to apply to periodic reports that cover reporting periods of 6 months or longer. Once a drug has been marketed for several years, national or regional regulation may allow the frequency of submission to be extended to longer time intervals, e.g., greater than one year for products considered to have an established and acceptable profile or considered to be low risk; however, more frequent PBRERs may continue to be required in other regions. As a result, the following scenarios may be encountered by MAHs:

La necesidad de presentar un PBRER y la frecuencia de presentación de informes a las autoridades reguladoras están sujetas a requisitos reguladores nacionales o regionales y, por lo general, dependen de factores como fechas de aprobación, el tiempo que el producto lleva en el mercado y el grado de conocimiento del perfil beneficio-riesgo del producto. El formato y

contenido del PBRER están destinados a aplicarse a informes periódicos que abarcan períodos de informe de 6 meses o más. Una vez que un medicamento ha estado en el mercado durante varios años, la normativa nacional o regional puede permitir que la frecuencia de presentación se extienda a intervalos de tiempo más largos, por ejemplo, más de un año para productos que se considera que tienen un perfil establecido y aceptable o de bajo riesgo. Sin embargo, es posible que se sigan exigiendo PBRERs más frecuentes en otras regiones. Como resultado, los TACs pueden encontrarse con los siguientes escenarios:

Paragraph 11

Separate estimations should be provided for interval exposure (since the DLP of the previous PBRER) and, when possible, cumulative exposure (since the IBD). See Appendix B, Tables 4 and 5 for examples. The estimated number of patients exposed should be provided when possible, along with the method(s) used to determine the estimate. If an estimate of the number of patients is not available, alternative estimated measures of exposure should be presented along with the method(s) used to derive them, if available. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a defined daily dose may also be used to estimate patient exposure.

Se deben proporcionar estimaciones separadas para la exposición por intervalos (desde la DLP del PBRER anterior) y, cuando sea posible, la exposición acumulativa (desde la IBD). Véase el Anexo B, Tablas 4 y 5 para ver ejemplos. Se debe proporcionar el número estimado de pacientes expuestos cuando sea posible, junto con el método o los métodos utilizados para determinar la estimación. Si no se dispone de una estimación del número de pacientes, se deben presentar medidas alternativas estimadas de exposición junto con el método o los métodos

utilizados para obtenerlas, si están disponibles. Ejemplos de medidas alternativas incluyen los días de exposición de los pacientes y el número de recetas. Solo si no se dispone de estas medidas, se pueden utilizar medidas de ventas de medicamentos, como tonelaje o unidades de dosificación. También se puede utilizar el concepto de una dosis diaria definida para estimar la exposición de los pacientes.

Paragraph 12

If the MAH becomes aware of patterns of use of the medicinal product considered relevant for the interpretation of safety data, provide a brief description thereof. Examples of such patterns of use may include overdose, drug abuse, misuse, and use beyond that recommended in the reference product information (e.g., an anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). Such patterns may be regional. If known, the MAH may briefly comment on whether use beyond that recommended in the reference product information is supported by clinical guidelines, clinical trial evidence, or an absence of approved alternative treatments. Quantitative use information should be provided, if available. For purposes of identifying patterns of use outside the terms of the reference product information, the MAH should use the appropriate sections of the reference product information that was in effect at the DLP of the PBRER (e.g., approved indication, contraindications).

Si el TAC tiene conocimiento de patrones de uso del medicamento que se consideren pertinentes para la interpretación de los datos de seguridad, debe proporcionar una breve descripción de estos. Ejemplos de estos patrones de uso pueden incluir sobredosis, abuso de fármacos, uso indebido y uso más allá de lo recomendado en la información de referencia del producto (por ejemplo, un medicamento antiepiléptico utilizado para el dolor neuropático o la profilaxis de migrañas). Dichos patrones pueden ser regionales. Si se conoce, el TAC puede

comentar brevemente si el uso más allá de lo recomendado en la información de referencia del producto está respaldado por directrices clínicas, evidencia de ensayos clínicos o ausencia de tratamientos alternativos aprobados. Si está disponible, se debe proporcionar información cuantitativa sobre el uso. Para identificar patrones de uso fuera de los términos de la información de referencia del producto, el TAC debe utilizar las secciones correspondientes de la información de referencia del producto que estaba en vigor en la DLP del PBRER (por ejemplo, indicación aprobada, contraindicaciones).

Paragraph 13

Section 6.2 of the PBRER should provide background for the appendix that provides a cumulative summary tabulation of SAEs reported in the MAH's clinical trials, from the DIBD to the DLP of the current PBRER. The MAH should explain any omission of data (e.g., clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organised by System Organ Class (SOC), for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. Data can be integrated across the programme. Alternatively, when useful and feasible, tabulations of SAEs can be presented by trial, indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the SAEs.

La sección 6.2 del PBRER debe proporcionar antecedentes para el anexo que proporciona una tabla resumen acumulativa de los eventos adversos graves reportados en los ensayos clínicos del TAC, desde la DIBD hasta la DLP del PBRER actual. El TAC debe explicar cualquier omisión de datos (por ejemplo, los datos de ensayos clínicos podrían no estar disponibles para productos comercializados durante muchos años). Las tablas deben organizarse por Clasificación de Órganos y Sistemas (SOC, por sus siglas en inglés), tanto para el medicamento en

investigación como para los grupos de control (comparadores activos, placebo) utilizados en el programa de desarrollo clínico. Los datos se pueden integrar en todo el programa. Alternativamente, cuando sea útil y factible, las tablas de eventos adversos graves se pueden presentar por ensayo, indicación, vía de administración u otras variables. Esta sección no debe usarse para proporcionar análisis o conclusiones basadas en los eventos adversos graves.

Paragraph 14

The main focus of each PBRER is the evaluation of relevant new safety information from the available data sources, placed within the context of any pertinent efficacy/effectiveness information that may have become available since the International Birth Date* (IBD), the date of the first marketing approval in any country in the world, or the Development International Birth Date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country. All pertinent new safety and efficacy/effectiveness information discovered during the reporting interval should be discussed in the appropriate sections of the PBRER.

El enfoque principal de cada PBRER es la evaluación de nueva información de seguridad pertinente a partir de las fuentes de datos disponibles, situada en el contexto de cualquier información pertinente de eficacia/efectividad que pueda estar disponible desde la Fecha Internacional de Nacimiento* (IBD, por sus siglas en inglés), la fecha de la primera aprobación de comercialización en cualquier país del mundo, o la Fecha Internacional de Nacimiento de Desarrollo (DIBD, por sus siglas en inglés), la fecha de la primera autorización para la realización de un ensayo clínico de intervención en cualquier país. Toda nueva información pertinente de seguridad y eficacia/efectividad descubierta durante el intervalo de informe debe analizarse en las secciones correspondientes del PBRER.

Paragraph 15

Sections 5.1 and 5.2 of the PBRER should provide estimates of the size and nature of the population exposed to the medicinal product. Section 5.1 of the PBRER should provide information on cumulative exposure in clinical trials. Section 5.2 should provide cumulative and interval exposure in the marketed setting. Brief descriptions of the method(s) used to estimate the subject/patient exposure should be provided, as well as the limitations thereof. Consistent methods for calculating patient exposure should be used across PBRERs for the same product. If a change in the method is appropriate, both methods and calculations should be provided in the PBRER introducing the change.

Las secciones 5.1 y 5.2 del PBRER deben proporcionar estimaciones del tamaño y la naturaleza de la población expuesta al medicamento. La sección 5.1 del PBRER debe proporcionar información sobre la exposición acumulativa en ensayos clínicos. La sección 5.2 debe proporcionar la exposición acumulativa y por intervalos en el entorno de comercialización. Se deben incluir descripciones breves de los métodos utilizados para estimar la exposición sujeto/paciente, así como sus limitaciones. Se deben utilizar métodos consistentes para calcular la exposición paciente en todos los PBRERs para el mismo producto. Si es adecuado realizar un cambio en el método, se deben incluir tanto los métodos como los cálculos en el PBRER que introduce el cambio.

Chapter VI

Conclusions and Recommendations

The last chapter of this research will provide a detailed overview of the conclusions and recommendations drawn from the study's findings. It will be organized into several sections. First, the purpose of the conclusion will be explained, outlining its role in summarizing the main results and their significance. Next, the key findings will be presented in relation to each of the three specific objectives set at the beginning of the study, showing how each objective was addressed. The research question will then be restated to reflect on whether it has been fully answered, and how the findings contribute to the original question. The chapter will also discuss any unexpected results or challenges encountered during the research process. Finally, based on the researcher's experience, recommendations for future research will be offered, highlighting areas that could benefit from further investigation or improvements.

6.1 Purpose of the Conclusion

The conclusion of the research summarizes the main findings and key points discussed throughout the study. It revisits the research question and objectives and shows how the evidence and analysis have helped answer them. In this section, the researcher discusses the significance of the results and what they mean for theory and practice. The conclusion also offers recommendations for future research. Ultimately, this chapter ties everything together while pointing to possible next steps and showing how the findings contribute to the field of study.

6.2 Conclusions

In this section, the key findings will be presented concerning the three specific objectives set at the beginning of the study, showing how each objective was addressed throughout the research process. For each objective, the main results will be analyzed and discussed, showing

how the results align with or differ from the initial expectations. This will include an examination of the methods used to gather data and how effectively they contributed to achieving each objective.

6.2.1 To evaluate which methods are the most suitable for translating pharmacovigilance documentation according to translation theory

For this objective, the researcher examined two translation methods and six translation procedures to gain a comprehensive understanding of their role in the translation process. The study involved analyzing and translating two key documents: the *Reglamento de buenas prácticas de farmacovigilancia* from Spanish into English, and the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline* from English into Spanish. To identify the translation procedures used, the researcher selected fifteen paragraphs from each translation and employed the Color-Coded Text Chart explained in Chapter III. This approach allowed for a detailed analysis of how each procedure functioned in the context of these specific texts.

In the case of the text translated from Spanish into English, the translation methods varied across the fifteen paragraphs. Transposition, Modulation, and Literal Translation were used in all 15 paragraphs, making up 100% of the translations. Omission was used in 14 paragraphs (99.33%), with paragraph 15 being the exception. Amplification appeared in 10 paragraphs (66.67%), missing from paragraphs 5, 6, 10, 11, and 13. Explicitation was used in 4 paragraphs (26.67%), with certain paragraphs (1, 2, 3, 4, 7, 8, 10, 11, 13, 14, and 15) not including this method. These findings show that transposition, modulation, and literal translation were the most frequently used procedures, while omission and amplification were used less often and in specific paragraphs.

In the text translated from English into Spanish, Transposition, Amplification, and Literal Translation were used in all 15 paragraphs, representing 100% of the translations. Modulation appeared in 14 paragraphs (93.33%), with paragraph 15 being the only exception. Omission was used 8 times (53.33%), with certain paragraphs (1, 2, 5, 9, 13, 14, and 15) not including this method. Explicitation was also applied 8 times (53.33%), with some paragraphs (2, 4, 5, 6, 7, 8, and 9) excluding it. These results indicate that the most frequently used procedures were transposition, amplification, and literal translation. Hence, the researcher concluded that transposition, modulation, literal translation, and amplification are the most suitable methods for translating pharmacovigilance documentation from Spanish into English and vice versa for several reasons.

In Chapter II, it is explained that transposition allows the translator to adjust the original text to make it more natural in the target language while keeping the original meaning intact. It involves replacing one grammatical category with another or adjusting sentence structures to match the norms of the target language. Applying this method during the translation process for both documents was crucial, for both Spanish and English have grammatical and semantic differences. For example, “Buenas Prácticas de Farmacovigilancia” in Spanish becomes “Good Pharmacovigilance Practices” in English, where the word order changes. Therefore, Transposition was an essential method to provide a precise and natural translation in the target languages.

Modulation was another crucial procedure during the translation process, for it is used when a translation is grammatically correct but lacks naturalness. For instance, the word-for-word translation in Spanish for “dosage forms” would be “formas de dosificación,” which is grammatically correct; however, the correct and widely used term in Spanish is “formas

farmacéuticas." This highlights the importance of modulation in ensuring that translations not only maintain grammatical accuracy but also resonate with the target audience, which in the case of pharmacovigilance documents, includes healthcare professionals, regulators, and patients. Thus, using modulation ensured that the translated texts are both precise and easily understood.

Literal Translation is the third most suitable method for translating pharmacovigilance documentation. It involves directly converting a source-language text into a grammatically and idiomatically appropriate target-language text, maintaining close correspondence between words. This method works well for straightforward sentences, especially when the languages share similarities. For example, the English sentence "This section of the PBRER should provide a brief summary" was easily translated into Spanish as "Esta sección del PBRER debe proporcionar un breve resumen." In the context of pharmacovigilance documents, literal translation is important because it ensures the most accurate transfer of the information. By using literal translation for simpler, clear statements, translators can preserve the accuracy of the original information and help ensure that the target audience receives reliable safety data.

Lastly, Amplification is another effective method when translating these types of documents, particularly into Spanish. This is a method where translators add details or explanations to clarify implicit information from the source text, ensuring the meaning is clear in the target language. For instance, the English sentence "some ICH countries and regions accept submission of separate types of periodic reports to fulfil national and regional requirements" was translated into Spanish as "algunos países y regiones de la ICH aceptan **la** presentación de distintos tipos de informes periódicos para cumplir **con los** requisitos nacionales y regionales." In this case, the addition of the articles "la" and "los," as well as the preposition "con," was necessary to ensure the translation was both grammatically correct and natural in Spanish. This is

particularly important because Spanish uses definite articles more often than English, and their inclusion aligns with the syntactic norms of the language.

Although Omission and Explicitation were used less often than the previous methods, they still played a significant role in the translation process. Omission was employed when the researcher decided to leave out certain details from the source text, ensuring that removing them did not compromise the accuracy or meaning of the original message in the target language. On the other hand, Explicitation was applied when the researcher needed to elaborate on implicit information to make the target text more precise, understandable, and natural. Using both of these methods can also be important when translating pharmacovigilance documents, especially Explicitation. This is crucial when the target audience includes patients, who may require additional explanations for medical or technical terms that are unfamiliar to them. By elaborating on implicit details, Explicitation ensures that the translation is not only accurate but also accessible and understandable for those without specialized knowledge.

In addition, the researcher also employed two other translation methods: Semantic Translation and Communicative Translation. Both methods were found to be suitable for translating pharmacovigilance documents, and ultimately, the translation approach used in this study combines elements of both methods. Given the specialized and technical nature of the two source texts, the researcher focused on maintaining a high level of fidelity to the original content, while also ensuring the translation was clear and accurate in the target language. This combined approach demonstrates a balance between staying true to the source text and adapting to the specific needs of the target language, ensuring the final translation is exact and natural.

6.2.2 To determine the specific skills a translator needs to translate pharmacovigilance documentation

Pharmacovigilance is a highly specialized field that involves the detection, assessment, understanding, and prevention of adverse drug reactions and other drug-related problems. The documentation involved can range from safety reports to regulatory submissions and requires an elevated level of accuracy and expertise. The first document translated was the *Reglamento de buenas prácticas de farmacovigilancia*, which aims to explain the regulation of good pharmacovigilance practices. In this document, the researcher identified clear descriptions of instructions and procedures that healthcare professionals and regulatory authorities should follow when identifying and reporting adverse drug reactions. The second document, the *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline*, is intended for healthcare professionals and Marketing Authorization Holders. It emphasizes the importance of the Periodic Benefit-Risk Evaluation Report in providing an analysis of new or emerging risks and the benefits of a medicinal product in its approved uses and outlines the steps for creating one.

Hence, the researcher, as the translator of these documents, not only concluded that when translating pharmacovigilance documents, a translator needs linguistic proficiency, broad general knowledge, cultural sensitivity, a strong command of both the source and target languages, good writing skills, a rich vocabulary, and an analytical mind, but also subject matter expertise in pharmacovigilance, pharmaceuticals, and medicine to provide an accurate and natural translation. These texts include pharmaceutical and medical terminology, drug and disease names, adverse drug reactions, and clinical trial terminology. Therefore, a translator must be familiar with these subjects in order to convey them accurately in another language.

Additionally, these texts are also intended for specific audiences, one of them being regulatory authorities; thus, the researcher concluded that a translator must also have regulatory knowledge when translating these documents. Familiarity with the guidelines set by international and national regulatory bodies is crucial not only to fully understand the content but also to ensure compliance with the specific terminology, tone, style, and format required in these documents. This knowledge ensures that the translated documents are legally and technically appropriate for the target audience.

6.2.3 To investigate how translators can specialize in pharmacovigilance translation

Through a review of existing literature and her experience translating the two pharmacovigilance texts, the researcher concluded that translators could specialize in this field in different ways. First, they can study pharmacovigilance or take specialized courses to familiarize themselves with the area and its texts, such as reports of adverse drug reactions, risk management, clinical trials, regulations, etc. This can help them comprehend specialized and technical terminology. In addition, the researcher used medical dictionaries, glossaries, and coding systems like the Medical Dictionary for Regulatory Activities (MedDRA) to improve her understanding of standardized medical terminology. Based on this experience, she concluded that these resources are essential tools for acquiring expertise in pharmacovigilance translation.

Translators can also specialize in this field by gaining experience through internships and working with experienced professionals. Offering translation services to pharmaceutical companies or regulatory agencies and working alongside pharmacovigilance professionals can deepen translators' understanding of the field and give them insight into how to accurately translate reports and regulatory documents. Therefore, to specialize in pharmacovigilance translation, translators need a mix of medical knowledge, an understanding of how

pharmacovigilance works, and good research skills. Translators can play a key role in helping the pharmaceutical industry disseminate safety information across the world by combining language skills with specialized knowledge.

6.3 Restatement of the Research Question

At the beginning of the study, the researcher phrased the research question: Which are the most suitable methods for translating pharmacovigilance documentation according to translation theory? This question was designed to explore how translation theories could be applied to the translation of pharmacovigilance documents. Through a careful examination of existing literature on the different translation methods, procedures, and techniques that exist, as well as a thorough analysis of the texts before and after translation, the researcher was able to successfully answer this question. It was concluded that transposition, modulation, literal translation, amplification, and both semantic and communicative translation are the most suitable methods for translating pharmacovigilance documentation.

6.4 Unexpected Results

One unexpected result from the research was that literal translation worked surprisingly well in the translation of the pharmacovigilance texts, as it was used in all 30 paragraphs that were analyzed. This is unexpected because literal translation is typically avoided in favor of more adaptive methods, such as transposition or modulation, that help write a more natural translation. However, in the case of these pharmacovigilance texts, literal translation helped maintain the accuracy of the original texts and it was successfully used in several parts of both translations.

6.5 Recommendations

As the last step of this study, the researcher would like to give some recommendations to future researchers who would like to study in more detail this topic and to translation students and professional translators who are considering specializing in this area.

Given the critical nature of pharmacovigilance documents, which include information on the risks and benefits of medicinal products, adverse drug reactions, regulatory guidelines, and clinical trials, it is highly recommended that translators work closely with experts in the field. Collaboration with these specialists is essential for ensuring the accurate translation of complex medical and regulatory terms. If a translator is having issues understanding a technical term or finding its common equivalent in the target language, being able to direct this inquiry to an expert would be beneficial for the final product. Additionally, implementing quality checks, including peer reviews by subject-matter experts, is recommended as it would help improve the consistency and accuracy of translations. This collaborative approach can help ensure that the translated documents meet the highest standards of accuracy.

Moreover, to provide high-quality specialized translation, it is recommended that translators develop a strong understanding of pharmacovigilance concepts. This can be achieved through formal education, specialized training, or self-study, using resources such as medical glossaries and pharmacovigilance books and articles. In addition, translators should familiarize themselves with international and national regulatory guidelines, as these play a crucial role in shaping the translation of pharmacovigilance documents. This will help translators be well-prepared for the challenges of this specialized field.

Last but not least, the researcher would like to recommend that Costa Rican universities consider medical translation as a mandatory course in translation majors. This approach would

be extremely beneficial, as it would provide students with essential knowledge and skills for translating specialized content. Particularly in fields like pharmacovigilance as it is an area that is constantly evolving and requires its information to be translated into global languages like Spanish and English. Medical translation as a course would help students develop a deeper understanding of medical terminology and regulatory guidelines, which are crucial for producing accurate and reliable translations. By offering formal training, students would be better equipped to handle the complexities of translating technical and specialized information, such as adverse drug reactions and clinical trial data, while ensuring clarity and precision. This approach would help students connect general translation theory with the specific needs of the healthcare and pharmaceutical sectors, ensuring graduates are well-prepared to meet industry demands and contribute effectively to patient safety across different languages. These courses could also include seminars or workshops with professional medical translators or subject-matter experts, so students can gain knowledge and receive feedback from specialists who have developed their skills through years of experience and education in the field.

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Annexes

Reglamento de buenas prácticas de farmacovigilancia

Reglamento de Buenas Prácticas de Farmacovigilancia

N° 39417-S

EL PRESIDENTE DE LA REPÚBLICA

Y EL MINISTRO DE SALUD

En uso de las facultades que le confieren los artículos 140 incisos 3), 18) y 146) de la Constitución Política; 11, 25, 27, 28, párrafo 2, inciso b) de la Ley Nº 6227 del 2 de mayo de 1978 "Ley General de la Administración Pública"; 1, 2, 4, 113 y 114, de la Ley N ° 5395 del 30 de octubre de 1973, "Ley General de Salud"; 1 y 2 inciso b) de la Ley N° 5412 del 8 de noviembre de 1973, "Ley Orgánica del Ministerio de Salud"

Considerando:

1º-Que conforme a las disposiciones contenidas en el artículo 1° de la Ley General de Salud, la salud de la población es un bien de interés público tutelado por el Estado.

2º-Que al amparo de las disposiciones legales contenidas en el artículo 2 inciso b) de la Ley Orgánica del Ministerio de Salud, son atribuciones del Ministerio dictar las normas técnicas en materia de salud particular o general; y ordenar las medidas y disposiciones que técnicamente procedan en resguardo de la salud de la población.

3º-Que en atención a lo establecido en el artículo 10 inciso f) del Decreto Ejecutivo Nº 35244-S "Reglamento del Sistema Nacional de Farmacovigilancia", el Centro Nacional de Farmacovigilancia procedió a la elaboración de las Buenas Prácticas de Farmacovigilancia.

4º-Que las Buenas Prácticas de Farmacovigilancia contribuyen a asegurar la calidad e integridad de los datos obtenidos mediante las notificaciones de reacciones adversas, como parte del seguimiento del balance beneficio/riesgo de los medicamentos cuando son utilizados en la población general, lo cual permite vigilar su idoneidad para las indicaciones y condiciones de uso aprobados. **Por tanto,**

DECRETAN:

Artículo 1°-Aprobar el siguiente reglamento:

Reglamento de Buenas Prácticas de Farmacovigilancia

CAPÍTULO I

Disposiciones Generales

1. OBJETIVO GENERAL.

Definir las bases que contribuyan a establecer un sistema de garantía de calidad en las actividades del Sistema Nacional de Farmacovigilancia, mediante el establecimiento de las obligaciones y responsabilidades que deben cumplir los diferentes agentes que lo conforman, con el fin de garantizar criterios uniformes para realizar la evaluación de las notificaciones, la generación de alertas y fomentar la comprensión y la enseñanza de la Farmacovigilancia.

2. ÁMBITO DE APLICACIÓN.

Las disposiciones del presente reglamento se aplican a cada uno de los agentes que conforman el Sistema Nacional de Farmacovigilancia y a todos los medicamentos de uso humano que se importan, fabrican, comercializan y utilizan en el país.

3. REFERENCIAS.

Para la adecuada interpretación y aplicación del presente reglamento se deben consultar los siguientes documentos:

3.1 Reglamento del Sistema Nacional de Farmacovigilancia. Decreto Ejecutivo N° 35244-S, del 13 de abril de 2009, publicado en La Gaceta N° 98 del 22/05/2009.

3.2 Reglamento Técnico Centroamericano RTCA 11.03.59:11 Productos Farmacéuticos. Medicamentos para uso Humano. Requisitos de Registro Sanitario. Anexo 1 de la Resolución Nº 333-2013 (COMIECO-LXVI), publicado en el Alcance digital Nº 20 de La Gaceta Nº 103 del 30 de mayo del 2014.

3.3 Reglamento para la autorización para la importación y adquisición de medicamentos no registrados. Decreto Ejecutivo Nº 36358-S, del 4 de octubre del 2010, publicado en La Gaceta Nº 25 del 04 de febrero del 2011.

4. ABREVIATURAS.

4.1 BPFV: Buenas Prácticas de Farmacovigilancia.

4.2 CIOMS: Consejo de Organizaciones Internacionales de las Ciencias Médicas (Council for International Organizations of Medical Sciences).

4.3 CNFV: Centro Nacional de Farmacovigilancia.

4.4 DRPIS: Dirección de Regulación de Productos de Interés Sanitario**.**

4.5 ESAVI: Evento Supuestamente Atribuible a la Vacunación o Inmunización.

4.6 FV: Farmacovigilancia.

4.7 IBD: Fecha Internacional de Nacimiento (International Birth Date).

4.8 ICH: Conferencia Internacional de Armonización (International Conference on Harmonization).

4.9 IPS: Informe Periódico de Seguridad.

4.10 OMS: Organización Mundial de la Salud.

4.11 OPS: Organización Panamericana de la Salud.

4.12 PNT: Procedimientos Normalizados de Trabajo.

4.13 RAM: Reacción Adversa Medicamentosa.

4.14 SNFV: Sistema Nacional de Farmacovigilancia.

4.15 WHO-art: Terminología de reacción adverse de la Organización Mundial de la Salud (The WHO Adverse reaction terminology).

5. DEFINICIONES.

Para efectos de interpretación del presente reglamento, se utilizan además de las definiciones establecidas en el Decreto Ejecutivo N° 35244-S Reglamento del Sistema Nacional de Farmacovigilancia, las siguientes:

5.1 Alerta: Información comunicada sobre una posible relación causal entre un evento adverso y un medicamento, cuando previamente se desconocía esta relación o estaba documentada en forma incompleta.

5.2 Auditoría: Revisión de actividades específicas efectuadas con la finalidad de verificar el cumplimiento de las Buenas Prácticas de Farmacovigilancia.

5.3 Base de datos de farmacovigilancia: Sistema informático que permite registrar notificaciones de sospechas de reacciones adversas, una vez evaluadas y codificadas.

5.4 Buenas Prácticas de Farmacovigilancia: Conjunto de reglas destinadas a garantizar la autenticidad y la calidad de los datos recolectados en Farmacovigilancia, que permitan evaluar en cada momento los riesgos atribuibles al medicamento; la confidencialidad de la información que se ha notificado sobre las reacciones adversas y el uso de criterios uniformes en la evaluación de las notificaciones y en la generación de señales de alerta.

5.5 Causalidad: Relación entre la aparición del evento adverso reportado y el consumo de un medicamento específico.

5.6 Confidencialidad: Respeto del secreto de la identidad de la persona de quien se ha notificado una sospecha de reacción adversa y que se extiende a toda la información de carácter personal o

clínico. De forma similar, se resguarda la confidencialidad de la información personal relativa a los profesionales notificadores.

5.7 Crisis: Una crisis se produce cuando se da a conocer información nueva sobre la seguridad o eficacia de un producto que puede tener un efecto importante en la salud pública y que, por tanto, requiere acciones inmediatas. También puede sobrevenir cuando los medios de comunicación difunden información en la que se expresa alguna preocupación acerca del consumo de determinado producto.

5.8 Eficacia: Aptitud de un medicamento para producir los efectos propuestos.

5.9 Estudio post-comercialización: Cualquier estudio clínico o epidemiológico realizado durante la comercialización de un medicamento según las condiciones autorizadas en el registro sanitario, o bien en condiciones normales de uso, en el que el medicamento o los medicamentos de interés son el factor de exposición fundamental investigado.

5.10 Falla terapéutica: Toda aquella situación en que no se logre el efecto terapéutico esperado en el paciente, bajo dosificaciones adecuadas según la prescripción utilizada con fines profilácticos, diagnósticos, terapéuticos o para modificar una función fisiológica.

5.11 Farmacovigilancia: Actividad de salud pública destinada a la identificación, cuantificación, evaluación y prevención de los riesgos asociados del uso de medicamentos de uso humano una vez comercializados.

5.12 Farmacovigilancia intensiva: Método de la farmacovigilancia que consiste en obtener información de sospechas de reacciones adversas a los medicamentos de manera sistemática, de calidad y completa, caracterizada por su elevada sensibilidad y fiabilidad; especialmente cuando se necesita determinar la frecuencia de las reacciones adversas e identificar agentes predisponentes y patrones de uso de medicamentos, entre otros.

5.13 Formulario CIOMS adaptado: Es el formulario creado por CIOMS y adaptado por el CNFV para el reporte de sospechas de reacciones adversas por parte de la industria farmacéutica.

5.14 Hospital: Establecimiento de salud con al menos cinco camas para internamiento de pacientes, que ofrece atención básica de diagnóstico y tratamiento; cuerpo clínico organizado, con evidencia de admisiones y asistencia permanente conducida de médicos.

5.15 Importación paralela: Importación de productos farmacéuticos patentados y registrados en Costa Rica, por parte de cualquier droguería sin el consentimiento del titular de la patente y que es comercializado conforme a las regulaciones sanitarias del país exportador.

5.16 Indicación: Los usos a los cuales se destina un medicamento, después que se ha probado científicamente que su empleo para una finalidad determinada es efectivo y seguro.

5.17 Industria farmacéutica, titular del producto o titular del registro: Persona física o jurídica propietaria del medicamento.

5.18 Informe periódico de seguridad: Documento preparado por el titular del producto, cuya finalidad es actualizar la información de seguridad del medicamento que, entre otros elementos, contiene información de las sospechas de reacciones adversas de las que haya tenido conocimiento en el período de referencia, así como una evaluación científica del balance beneficio/riesgo del medicamento.

5.19 Monografía: Descripción científico técnica de un medicamento que debe contener lo establecido en el numeral 7.6. del Reglamento Técnico Centroamericano RTCA 11.03.59:11 Productos Farmacéuticos. Medicamentos Para Uso Humano. Requisitos de Registro Sanitario:

a) Denominación común o genérica internacionalmente aceptada y concentración del medicamento.

b) Forma farmacéutica.

c) Estructura, nombre químico del principio activo o en su defecto adjuntar la ficha técnica que declare esta información.

d) Farmacología clínica.

e) Indicaciones.

f) Contraindicaciones.

g) Precauciones y advertencias.

h) Interacciones.

i) Efectos adversos.

j) Dosis y administración.

k) Recomendación en caso de sobredosificación según el perfil toxicológico.

l) Abuso y adicción.

m) Fecha de revisión de la monografía.

n) Referencias bibliográficas completas.

o) Clase terapéutica según Clasificación Anatómica Terapéutica (ATC).

p) Forma de preparación.

5.20 Notificación: Comunicación de una sospecha de reacción adversa a un medicamento al CNFV mediante los formularios de notificación de reacción adversa (Tarjeta Amarilla o Formulario CIOMS modificado) establecidos por el Ministerio de Salud.

5.21 Plan de minimización de riesgos: Documento en el que el titular del producto especifica los riesgos asociados al medicamento, identificados o potenciales y señala la información de seguridad no conocida en la literatura científica. Consiste en un programa estratégico de seguridad orientado a alcanzar metas y objetivos específicos para reducir al mínimo los riesgos conocidos de los medicamentos preservando sus beneficios.

5.22 Procedimientos Normalizados de Trabajo: Instrucciones escritas y detalladas para lograr la uniformidad en la realización de una actividad específica. Son la base fundamental para las auditorías internas o externas.

5.23 Rastreabilidad (Trazabilidad): Posibilidad de encontrar y seguir el rastro de un medicamento, a través de todas las etapas de producción, almacenamiento, distribución y comercialización.

5.24 Riesgo: Probabilidad de ocasionar un perjuicio o daño a la salud como resultado del uso de un medicamento, asociado a la magnitud del mismo.

5.25 Relación Beneficio/riesgo: Refleja la correlación entre el beneficio y el riesgo que presenta el uso de un medicamento. Sirve para expresar un juicio sobre la función del medicamento en la práctica médica, basado en datos sobre su eficacia y seguridad y en consideraciones sobre su posible uso indebido, la gravedad y el pronóstico de la enfermedad, etcétera. El concepto puede aplicarse a un solo medicamento o a las comparaciones entre dos o más medicamentos empleados para una misma indicación.

5.26 Señal: Posible relación causal entre un evento adverso y un medicamento cuando previamente se desconocía esta relación o estaba documentada en forma incompleta. Habitualmente se requiere más de una notificación para generar una señal, dependiendo de la gravedad del evento adverso y de la calidad de la información.

5.27 Sistema de notificación espontánea: Método de farmacovigilancia basado en la comunicación, reporte, recolección y evaluación de notificaciones de sospechas de reacciones

adversas a medicamentos realizadas por un profesional de la salud a través de los formularios establecidos.

5.28 WHo-art: Diccionario de reacciones adversas de la Organización Mundial de la Salud, que contiene la terminología para codificar la información clínica relacionada con los medicamentos.

6. SISTEMA NACIONAL DE FARMACOVIGILANCIA.

El SNFV está regulado por medio del Decreto Ejecutivo Nº 35244-S "Reglamento del Sistema Nacional de Farmacovigilancia", el cual aplica a la FV de todos los medicamentos de uso humano que se importan, fabrican, comercializan y utilizan en el país.

7. FUNCIONAMIENTO DEL SISTEMA NACIONAL DE FARMACOVIGILANCIA.

7.1 Los profesionales en salud deben enviar las notificaciones al CNFV en los formularios designados para la recolección de los datos.

7.2 La información de seguridad debe ser evaluada periódicamente por el CNFV según el PNT establecido con el fin de identificar de forma temprana posibles problemas de seguridad derivados del uso de los medicamentos para la generación de señales.

7.3 Las señales serán discutidas y analizadas en la Comisión Nacional de Farmacovigilancia, atendiendo al PNT establecido.

7.4 La Comisión Nacional de Farmacovigilancia debe asesorar a la DRPIS para la toma de decisiones.

7.5 La DRPIS debe tomar las medidas necesarias para mantener la relación beneficio/riesgo favorable de los medicamentos.

7.6 La DRPIS debe informar a los profesionales y al público en general sobre las medidas de seguridad adoptadas para mantener dicha relación beneficio/riesgo favorable.

CAPÍTULO II

Sobre la Información del Sistema Nacional de Farmacovigilancia

8. DOCUMENTACIÓN.

Los Agentes del SNFV deben contar con documentación completa y actualizada de acuerdo a lo establecido en el presente reglamento.

8.1 Formularios de reporte.

8.1.1 Todos los profesionales en salud deben realizar la notificación de sospechas de reacciones adversas utilizando el formulario oficial Tarjeta Amarilla, adjunto en el Anexo A del presente reglamento y procurando que la información suministrada esté completa.

8.1.2 La industria farmacéutica debe realizar la notificación de sospechas de reacciones adversas a través del formulario adaptado CIOMS, adjunto en el Anexo B del presente reglamento y procurando que la información suministrada esté completa.

8.1.3 Tanto la industria farmacéutica como los profesionales en salud deben notificar las sospechas de falla terapéutica a través de los formularios mencionados en los incisos 8.1.1 y 8.1.2 incluidos en los Anexos A y B del presente reglamento.

8.1.4 Para realizar el análisis de una notificación se requieren al menos los siguientes datos reportados con letra legible y tinta indeleble:

a) Paciente identificable: nombre o iniciales del paciente o cédula de identidad o género.

b) Medicamento sospechoso: nombre genérico o marca comercial.

c) Fecha exacta o aproximada de inicio de la administración del medicamento.

d) Reacción adversa incluyendo la localización anatómica y severidad (leve, moderada, grave o mortal), si se cuenta con ellas.

e) Fecha exacta o aproximada de inicio de la reacción.

f) Notificador identificable: nombre, firma y código profesional, teléfono de contacto y dirección de correo electrónico.

8.1.5 En caso de contar con información complementaria, los notificadores la deben documentar, enviar y conservar con el fin de que permita ampliar la información contenida en el formulario de notificación de sospechas de reacciones adversas. En el caso de que la información sea confidencial, se debe incluir en el formulario un resumen de la información obtenida.

8.1.6 La notificación debe ser entregada en forma física al CNFV a través de la Dirección de Atención al Cliente. La información puede ser enviada por fax, correo electrónico o puede ser comunicada por vía telefónica al CNFV con posterior entrega de la documentación física de acuerdo al Reglamento del Sistema Nacional de Farmacovigilancia.

8.2 Procedimientos Normalizados de Trabajo.

8.2.1 El CNFV debe contar con PNT establecidos para cada una de sus actividades.

8.2.2 Los centros prestadores de servicios de salud y la industria farmacéutica deben contar con PNT para cada actividad de FV que realicen, los cuales deben ser revisados y aprobados por los encargados de FV, estar implementados y ser del conocimiento por parte del personal involucrado.

CAPÍTULO III

Obligaciones y Responsabilidades de los Agentes del SNFV

9. CENTRO NACIONAL DE FARMACOVIGILANCIA.

El CNFV debe cumplir con las siguientes obligaciones y responsabilidades:

9.1 Recibir, evaluar, analizar y codificar las notificaciones de sospechas de RAM.

9.2 Vigilar la seguridad de los medicamentos a través del análisis de las señales.

9.3 Comunicar a la DRPIS toda información de seguridad de los medicamentos de uso humano detectada durante los análisis realizados.

9.4 Divulgar información sobre FV a los pacientes y a los profesionales de la salud.

9.5 Coordinar las actividades de FV que realicen los diferentes agentes del SNFV para lograr captar información necesaria y oportuna sobre las sospechas de RAM.

9.6 Participar en actividades de capacitación en el tema de Farmacovigilancia dirigidas principalmente a profesionales en salud y estudiantes universitarios en el área de la salud.

9.7 Realizar inspecciones a la labor del profesional encargado de FV y a la industria farmacéutica con el fin de comprobar el cumplimiento de las BPFV y evaluar su eficacia para alcanzar los objetivos específicos. Para facilitar las inspecciones de FV, el Ministerio de Salud mantendrá a disposición de los administrados la Guía de Verificación de BPFV disponible en la página web del Ministerio.

9.8 Identificar las señales generadas, analizarlas y realizar investigaciones que permitan concluir o descartar que el medicamento sea el causante del evento. Estas señales pueden ser detectadas principalmente por los siguientes métodos de FV:

a) Descripciones aisladas de pacientes.

b) Publicación de casos en la literatura científica.

c) Notificación espontánea al Sistema de Farmacovigilancia.

d) Estudios observacionales en poblaciones: estudios de cohorte o de casos y controles.

e) Estudios experimentales: investigaciones biomédicas.

Es posible que un solo caso notificado, bien documentado, pueda verse como una señal, sobre todo si describe una reexposición positiva o si el evento es desconocido en ausencia del medicamento usado.

9.9 Evaluar periódicamente la información contenida en la base de datos de FV del CNFV con el fin de detectar señales, las cuales serán evaluadas y analizadas. Cuando se considere que la señal detectada constituye un problema inminente de salud pública, se debe realizar una investigación y un informe para la toma de medidas sanitarias.

9.10 Cuantificar la fuerza de la asociación entre la reacción adversa y el medicamento, una vez identificado un riesgo y su efecto en términos de salud pública.

9.11 Evaluar los posibles beneficios y riesgos de los medicamentos para los cuales se ha cuantificado un riesgo y velar porque la relación beneficio/riesgo del medicamento siga siendo favorable.

9.12 Realizar estrategias para prevenir y minimizar los riesgos asociados a los medicamentos, dentro de las cuales se encuentran:

a) Ejecutar programas de FV Intensiva o de seguimiento sobre determinados medicamentos o grupos de riesgo.

b) Establecer mecanismos de integración de las actividades de vigilancia sanitaria en materia de promoción y publicidad, en relación con la información sobre las reacciones adversas, las advertencias y precauciones y las contraindicaciones.

c) Realizar en forma sistemática y periódica la prevención de riesgos. Los profesionales de la salud, los usuarios, la industria farmacéutica, los centros prestadores de servicios de salud, el CNFV y la DRPIS tienen responsabilidades compartidas.

Con respecto a las reacciones adversas no evitables, el objetivo debe ser su detección precoz como principal medida de prevención que reducirá la magnitud del daño.

9.13 Trabajar en forma articulada con los programas de salud pública incluyendo el de inmunizaciones, de forma tal que las notificaciones de eventos y sospechas de RAM detectadas a través de esos programas sean notificadas al CNFV para su evaluación. Los ESAVIS, aunque se remitan a otras instancias de salud pública, deben ser comunicados al CNFV en la Tarjeta Amarilla según los lineamientos establecidos para el manejo de ESAVIS.

10. CENTROS PRESTADORES DE SERVICIOS DE SALUD.

Todos los centros prestadores de servicios de salud, es decir aquellos hospitales públicos y privados así como las áreas de salud de la CCSS deben contar con un encargado de FV.

10.1 El director médico del centro prestador de servicios de salud debe designar y comunicar por escrito al CNFV el profesional de la salud encargado de FV y sus datos de contacto. Asimismo debe gestionar los recursos necesarios para que este encargado lleve a cabo de manera adecuada sus responsabilidades.

10.2 El encargado de FV debe cumplir con los siguientes requisitos, obligaciones y responsabilidades:

a) Servir de contacto con el CNFV.

b) Tener acceso a un teléfono, fax, computadora con internet, correo electrónico y fotocopiadora.

c) Impulsar el Sistema de Notificación Espontánea de RAM y otros programas de conformidad con las BPFV en el centro prestador de servicios de salud al cual pertenece.

d) Distribuir el formulario de notificación de sospechas de RAM (Tarjeta Amarilla) a los Profesionales en Salud dentro de su centro prestador de servicios de salud.

e) Recibir las notificaciones de sospechas de RAM generadas dentro de su centro prestador de servicios de salud con el único fin de ser remitidas al CNFV.

f) Llevar un registro de las notificaciones que recibe.

g) Verificar que los datos de las Tarjetas Amarillas estén completos, en caso contrario realizar las gestiones necesarias para completar los datos.

h) Resguardar la confidencialidad de las notificaciones realizadas por los profesionales en salud.

i) Transferir las consultas o solicitudes de información relacionadas con sospechas de RAM reacciones adversas formuladas por profesionales de salud de su centro al CNFV.

j) Responder a las solicitudes de información que le realice el CNFV.

k) Coordinar en conjunto con el CNFV actividades de capacitación a profesionales en salud.

l) Participar en las reuniones, capacitaciones y otras actividades que el CNFV programe.

m) Establecer los PNT necesarios para garantizar las BPFV en su centro prestador de servicios de salud.

11. PROFESIONALES EN CIENCIAS DE LA SALUD.

11.1. Los profesionales en ciencias de la salud deben cumplir con los siguientes requisitos, obligaciones y responsabilidades:

a) Participar activamente del SNFV para lograr captar de forma efectiva y oportuna toda la información referente a las sospechas de RAM, las cuales tienen implicación directa en la seguridad de los medicamentos que se utilizan en el país.

b) Cumplir las obligaciones establecidas en el Decreto Ejecutivo Nº 35244-S "Reglamento del Sistema Nacional de Farmacovigilancia" en su artículo 11.

c) Llenar la Tarjeta Amarilla de forma completa cuando detecte una sospecha de RAM.

d) Enviar las sospechas de RAM al CNFV en formularios oficiales y los plazos establecidos en el Decreto Ejecutivo Nº 35244-S. Este envío se puede realizar a través de las Direcciones de Áreas Rectoras de Salud del Ministerio de Salud.

e) Resguardar la confidencialidad de las notificaciones realizadas al CNFV.

f) Responder a las solicitudes de información que le realice el CNFV.

g) Participar en las reuniones, capacitaciones y otras actividades que el CNFV programe.

h) Mantenerse informado sobre los datos de seguridad relativos a los medicamentos que habitualmente prescriban, dispensen o administren.

i) Colaborar, en caso necesario, en calidad de expertos con el CNFV en la evaluación de los problemas de seguridad de los medicamentos.

11.2. Los regentes farmacéuticos de las droguerías que realizan importación de medicamentos mediante la modalidad de importación paralela y mediante la aplicación del artículo 117 de la Ley General de Salud, en particular el artículo 3 del Decreto Ejecutivo Nº 36358-S deben cumplir, además de los requisitos mencionados en el numeral anterior, los siguientes requisitos, obligaciones y responsabilidades:

a) Velar porque se establezcan y se cumplan los PNT para asegurar la FV de los productos importados mediante la modalidad indicada en el presente numeral.

b) Garantizar que todo el personal que trabaja en la droguería tenga conocimiento de los PNT.

c) Ser el encargado del Programa de Farmacovigilancia o delegar tal función en un profesional de la salud capacitado, el cual será la persona de contacto con el CNFV.

d) Establecer acuerdos en materia de FV en caso de existir cualquier transferencia de obligaciones y funciones. Estos deben estar documentados mediante un acuerdo escrito firmado y legalizado entre los representantes legales de las dos empresas, los cuales deben ser notificados al CNFV. Las funciones no transferidas mediante este acuerdo siguen siendo asumidas por el responsable de la importación.

e) Gestionar toda medida sanitaria que le sea solicitada por la DRPIS en materia de seguridad de los medicamentos.

f) Llevar un registro detallado de las sospechas de RAM detectadas que incluya toda la información contenida en el Formulario de Notificación de Sospechas de RAM. Tal registro debe mantenerse en un sistema de archivo ya sea físico o digital que permita conservar adecuadamente toda la documentación relacionada con las responsabilidades y actividades de FV por un periodo de 5 años

g) Responder en un plazo máximo de 10 días hábiles a cualquier solicitud de información de la DRPIS en materia de seguridad de medicamentos.

h) Evaluar de forma continua la relación beneficio/riesgo de los medicamentos y comunicar en un plazo máximo de 10 días hábiles a la DRPIS sobre nueva información de seguridad.

i) Identificar señales y valorar la gravedad de las mismas, las cuales deben ser comunicadas al CNFV.

j) Realizar FV intensiva a los medicamentos cuando el CNFV así lo requiera. Para facilitar el cumplimiento de los requisitos de FV intensiva, el Ministerio de Salud mantendrá a disposición de los administrados la Guía para realizar FV Intensiva en su página web.

12. INDUSTRIA FARMACÉUTICA.

Todos los titulares de registro de los medicamentos deben contar con un Programa de Farmacovigilancia. Dicho programa debe contener los roles y responsabilidades relacionadas con la seguridad de los medicamentos que comercializa y asegurar la adopción de las medidas oportunas cuando sea necesario.

12.1 Obligaciones y responsabilidades del titular del registro:

a) Garantizar que todo el personal que trabaja en la empresa tenga conocimiento en materia de Farmacovigilancia.

b) Contar con un profesional de la salud encargado del Programa de Farmacovigilancia, el cual será la persona de contacto con el CNFV.

c) Facilitar al profesional encargado del Programa de Farmacovigilancia el acceso a la monografía e información básica de seguridad actualizadas de cada medicamento.

d) Establecer acuerdos en materia de FV. En caso de existir cualquier transferencia de obligaciones y funciones, debe estar documentada mediante un acuerdo escrito firmado y legalizado entre los representantes legales de las dos empresas. Estos acuerdos deben ser notificados al CNFV y además deben adjuntarse al expediente de registro sanitario. Las funciones no transferidas mediante este acuerdo siguen siendo asumidas por el titular del registro.

e) Velar porque se establezcan y se cumplan los PNT para asegurar la FV.

f) Garantizar un sistema de archivo ya sea físico o digital que permita conservar adecuadamente toda la documentación relacionada con las responsabilidades y actividades de FV por un periodo de 5 años. Las responsabilidades en la gestión del archivo deben estar definidas por escrito.

g) Establecer un programa de auditorías internas, con el fin de garantizar que el Programa de Farmacovigilancia cumpla con lo establecido en el presente reglamento.

h) Enviar al CNFV cualquier información relacionada con la seguridad de sus medicamentos.

i) Remitir al CNFV (previo a su distribución) todo comunicado relacionado con la seguridad de sus medicamentos que se desee divulgar a los profesionales en salud o al público en general. El CNFV podrá solicitar ampliaciones o modificaciones al comunicado.

j) Todo comunicado relacionado con la seguridad de sus medicamentos debe indicar la siguiente leyenda: "Toda sospecha de reacción adversa se debe notificar al CNFV en los formularios y plazos establecidos en la normativa vigente".

12.2 Obligaciones y responsabilidades del encargado de FV:

a) Notificar las sospechas de RAM, retiro del mercado por motivos de seguridad u otro hecho relacionado con la seguridad de los medicamentos comercializados a nivel nacional o internacional al CNFV.

b) Gestionar toda medida sanitaria que le sea solicitada por la DRPIS en materia de seguridad de los medicamentos.

c) Llevar un registro detallado que incluya toda la información contenida en el Formulario de Notificación de Sospechas de RAM.

d) Remitir los IPS al CNFV. Para facilitar el cumplimiento de los requisitos para los IPS, en cuanto a contenido, el Ministerio de Salud mantendrá a disposición de los administrados la Guía de presentación de IPS para la Industria Farmacéutica en su página web.

e) Responder en un plazo máximo de 10 días hábiles a cualquier solicitud de información de la DRPIS en materia de seguridad de medicamentos.

f) Evaluar de forma continua la relación beneficio/riesgo de los medicamentos comercializados en el país y comunicar en un plazo máximo de 10 días hábiles a la DRPIS sobre nueva información de seguridad.

g) Identificar señales y valorar la gravedad de las mismas, las cuales deben ser comunicadas al CNFV.

h) Realizar FV intensiva a los medicamentos cuando el CNFV así lo requiera. Para facilitar el cumplimiento de los requisitos de FV intensiva, el Ministerio de Salud mantendrá a disposición de los administrados la Guía para realizar FV Intensiva en su página web.

i) Participar en las reuniones, capacitaciones y otras actividades que el CNFV programe.

j) Colaborar, en caso necesario, en calidad de expertos con el CNFV en la evaluación de los problemas de seguridad de los medicamentos.

k) En caso de tener conocimiento de una sospecha de RAM relacionada con medicamentos que no sean propios de su industria, debe informar al titular de ese producto.

12.3 Organización y personal:

La Industria Farmacéutica debe disponer de un organigrama actualizado en que se refleje la relación jerárquica que hay entre el Encargado de FV, la Dirección Médica y el resto de los departamentos y debe cumplir con los siguientes aspectos:

a) Debe existir una persona designada como encargada de FV y un suplente, ambos con formación y experiencia en FV.

b) El personal de FV debe conocer las funciones y responsabilidades asignadas, las cuales tienen que estar por escrito, en las descripciones de los puestos de trabajo, aprobadas por la dirección.

c) El titular del registro debe mantener actualizado el curriculum vitae, la descripción del puesto de trabajo y la capacitación del personal involucrado en las tareas de FV.

d) El titular del registro debe poner a disposición del encargado de FV los recursos humanos y materiales necesarios para llevar a cabo de manera adecuada sus responsabilidades.

12.4 Capacitación en FV al personal del titular del registro:

12.4.1 Se debe disponer de un programa de formación inicial y continua en materia de FV, el cual debe ser aprobado por la persona encargada de FV.

12.4.2 Todo el personal de la compañía relacionado con la recepción de sospechas de RAM debe recibir formación inicial y continua en materia de FV.

12.4.3 Se deben conservar los registros que validen la capacitación del personal.

12.5 Procedimientos Normalizados de Trabajo (PNT):

El titular del registro debe disponer de PNT aprobados por el encargado de FV y por la Dirección Médica, que describan las funciones y actividades que se lleven a cabo en materia de FV y deben cumplir con lo siguiente:

a) Estar actualizados de acuerdo a la información científica y la legislación vigente. Debe mantenerse un archivo histórico con las actualizaciones de los PNT.

b) El encargado, así como todas aquellas personas implicadas en el Programa de Farmacovigilancia deben de llevar a cabo las funciones y tareas de acuerdo con lo establecido en los PNT.

c) Los PNT deben de estar a disposición del personal encargado de llevar a cabo las funciones y tareas descritas en su puesto de trabajo; así como las guías y normativas vigentes sobre FV.

12.6 Gestión de las notificaciones de sospechas de RAM:

12.6.1 La información registrada en las notificaciones de sospechas de RAM tendrán carácter de declaración jurada; la veracidad de la información podrá ser verificada por el Ministerio de Salud.

12.6.2 En el momento en que un colaborador del titular del registro recibe información inicial o de seguimiento de una RAM, debe comunicarlo a más tardar un día hábil posterior a la recepción de la información, al encargado de FV y debe quedar constancia de la fecha de conocimiento de esta RAM por parte del titular de registro.

12.6.3 El encargado de FV debe asegurarse que se registra, se fecha y asigna un número de identificación correlativo único e inequívoco a cada notificación de RAM recibida.

12.6.4 Para cualquier sospecha de RAM el encargado de FV debe asegurarse que se recopile toda la información necesaria y debe evaluar los siguientes criterios: gravedad, si está referenciada o no de acuerdo con la información básica de seguridad del producto, si es esperada o inesperada de acuerdo con la monografía, cumpliendo con los plazos de reporte de acuerdo a lo establecido en el Decreto Ejecutivo N° 35244-S "Reglamento del Sistema Nacional de Farmacovigilancia". Esta información debe anotarse en el formulario adaptado CIOMS en la sección de descripción de la RAM.

12.6.5 El encargado de Farmacovigilancia debe asegurar que se realice un seguimiento de la evolución y el desenlace de cada caso individual, luego de realizar al menos 3 intentos de contacto al notificador, los cuales deben quedar documentados. La información de seguimiento adicional que se reciba quedará registrada y fechada de igual forma que la información inicial y debe ser enviada al CNFV en el formulario adaptado CIOMS en la sección de descripción de la RAM.

12.6.6 Todos los documentos y registros relacionados con una misma RAM deben conservarse conjuntamente o bien de manera que pueda localizarse fácilmente y se pueda hacer un seguimiento de todas las actividades relacionadas con la detección, evaluación y notificación.

12.6.7 Cuando se reciba información directamente de un paciente, que sugiera que se ha producido una RAM, el titular del registro debe intentar obtener el permiso del paciente para contactar con el profesional sanitario responsable del seguimiento clínico, con el fin de obtener información.

12.6.8 La información referente a sobredosis, exposición en embarazo o lactancia, uso incorrecto, dependencia, abuso de medicamentos o a errores de medicación deberá ser recolectada y enviada al CNFV, en el formulario adaptado CIOMS en los plazos establecidos en el Decreto Ejecutivo N° 35244-S "Reglamento del Sistema Nacional de Farmacovigilancia".

Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2) Guideline

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)

1. INTRODUCTION

The Periodic Benefit-Risk Evaluation Report (PBRER) described in this Guideline is intended to be a common standard for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) among the ICH regions.

This Guideline defines the recommended format and content of a PBRER and provides an outline of points to be considered in its preparation and submission.

Definitions of many technical terms used in the Guideline are included in a glossary (Appendix A); the first mention of a term in the Guideline is identified with an asterisk (*).

1.1 Background

When a new medicinal product is approved for marketing, demonstration of safety and efficacy are generally based on data from a limited number of patients, many studied under the controlled conditions of randomised trials. Often, higher risk subgroups and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited. Moreover, patients in trials are closely monitored for evidence of adverse events. In clinical practice, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, drugs, genetic abnormalities), and events too rare to occur in clinical trials may be observed (e.g., severe liver injury). These factors underlie the need for continuing analysis of relevant safety, efficacy,[1] and effectiveness[1] information throughout the lifecycle of a medicinal product – promptly, as important findings occur – and periodically – to allow an overall assessment of the accumulating data. Although the majority of new information will be safety-related, new information about effectiveness, limitations of use, alternative treatments, and many other aspects of the drug's place in therapy may be pertinent to its benefit-risk assessment.

The ICH Guideline E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, achieved *Step 4* in 1996, and was intended to harmonise the periodic reporting requirements to regulatory authorities and to provide, in a common format, the worldwide interval safety experience of a medicinal product at defined times post-approval. At that time, the focus of the Periodic Safety Update Report (PSUR) was on relevant new safety information in the context of patient exposure, to determine if changes were needed to the Reference Safety Information* (RSI) in order to optimise the continued safe use of the product. The Guideline was revised in 2003, to provide needed clarification, guidance and flexibility.

Since that time, the pharmacovigilance environment has evolved, prompting reassessment of the role of the PSUR in the spectrum of safety documents submitted to regulatory authorities. This reassessment highlighted several factors that led to consensus for revision and refocus of the Guideline, to enhance its usefulness in light of advances in the field:

- Significant progress in the technology and science of pharmacovigilance, including electronic submission of Individual Case Safety Reports (ICSRs) to regulatory authorities, automated data mining techniques, and more attention to benefit-risk evaluation;
- Greater emphasis on proactive and documented risk management planning;
- Increasing recognition that meaningful evaluation of important new risk information should be undertaken in the context of a medicinal product's benefits; and
- Overlap in the content of ICH Guidelines related to pharmacovigilance documentation.

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[1] The terms efficacy and effectiveness are not standardised, and have different meanings across some regions. See Section 2.6

As noted above, the primary objective of the PSUR was to provide a comprehensive picture of the safety of approved medicinal products. With recognition that the assessment of the risk of a medicinal product is most meaningful when considered in light of its benefits, the proposed report would provide greater emphasis on benefit than the PSUR, particularly when risk estimates change importantly. In such cases there will need to be an overall explicit evaluation of benefit-risk. Consequently the name of the proposed report is the "Periodic Benefit-Risk Evaluation Report" (PBRER). The PBRER would also provide greater emphasis on the cumulative knowledge regarding a medicinal product, while retaining a focus on new information.

A formal evaluation of benefit is a new feature of the PBRER; however, it is recognised that a concise discussion of benefit will usually be sufficient, unless the safety or benefit-risk profile has changed significantly during the reporting interval. Thus, the level of detail provided in certain sections of the PBRER (e.g., evaluation of safety and efficacy data, evaluation of safety signals,* and benefit-risk evaluation) should be proportional to the medicinal product's known or emerging important risks and to evidence of emerging important benefits.

As the scope of the PBRER has been extended to include benefit as well as safety, the reference information for the report also needs to take this new factor into account. It is generally impractical for Marketing Authorisation Holders (MAHs) to have one reference information source that:

- Encompasses all parameters that contribute towards the benefit-risk evaluation, (i.e., benefit, efficacy/effectiveness, indication(s) and safety information);
- Is common to all ICH regions; and
- Addresses all circumstances, (e.g., generics, products licensed in one country only).

Therefore, this Guideline proposes more practical options that MAHs can consider in selecting the most appropriate reference product information for the PBRER. These proposals incorporate the original ICH E2C concept of reference safety information (e.g., Company Core Safety Information* [CCSI]), with the addition of the approved indications for the product. This reference product information may be the Company Core Data Sheet* (CCDS) or another document proposed by the MAH (see Section 2.4).

The important baseline efficacy and effectiveness information summarised in Section 17.1 of the PBRER will form the basis (or "reference") for the benefit evaluation, irrespective of the reference product information used by the MAH.

The frequency of submission of reports to regulatory authorities is subject to national or regional regulatory requirements, and may differ, depending on a number of factors. The Guideline includes advice on managing different frequencies of PBRER submission in different regions.

One of the motivating factors behind revision of the ICH E2C(R1) Guideline was the desire to enhance efficiency by decreasing the duplication of effort required for the preparation of various regulatory documents. This Guideline has been developed, therefore, such that corresponding sections of the PBRER, Development Safety Update Report (DSUR, ICH E2F), and safety specification of a risk management plan (ICH E2E) can be identical in content. (See also Section 1.4, Relation of the PBRER to Other ICH Documents)

1.2 Objectives

The main objective of a PBRER is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile. The PBRER should contain an evaluation of new information relevant to the medicinal product that became available to the MAH during the reporting interval, in the context of cumulative information by:

- Summarising relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product;
- Summarising any important new efficacy/effectiveness information that has become available during the reporting interval;

- Examining whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the medicinal product's benefit and risk profile; and
- Where important new safety information has emerged, conducting an integrated benefit-risk evaluation for approved indications.

When appropriate, the PBRER should include proposed action(s) to optimise the benefit-risk profile.

Urgent safety information should be reported through the appropriate mechanism; the PBRER is not intended to be used to provide initial notification of significant new safety information or to provide the means by which new safety concerns* are detected.

1.3 Scope of the PBRER

The main focus of each PBRER is the evaluation of relevant new safety information from the available data sources,[2] placed within the context of any pertinent efficacy/effectiveness information that may have become available since the International Birth Date* (IBD), the date of the first marketing approval in any country in the world, or the Development International Birth Date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country. [3] All pertinent new safety and efficacy/effectiveness information discovered during the reporting interval[3] should be discussed in the appropriate sections of the PBRER.

For the purposes of this Guideline, sources of available information refer to data regarding the active substance(s) included in the medicinal product or the medicinal product that the MAH may reasonably be expected to have access to, and that are relevant to the evaluation of the safety or benefit-risk profile (see also Appendix E, Examples of Possible Sources of Information that May Be Used in the Preparation of the PBRER). For example, there may be less information available to the MAH regarding a generic product as compared to a product for which the MAH is the innovator, and only a published report may be accessible for a clinical trial not sponsored by the MAH. On the other hand, for a MAH-sponsored clinical trial, the MAH will have access to patient level data towards evaluation of the product's benefit-risk. When desired by the MAH, a list of the sources of information used to prepare the PBRER can be provided as an appendix to the report.

The PBRER should include cumulative knowledge of the product while retaining focus on new information, i.e., the overall safety evaluation and integrated benefit-risk evaluation will take into account cumulative information. Because clinical development of a drug frequently continues following marketing approval, relevant information from post-marketing studies or clinical trials in unapproved indications or populations should also be included in the PBRER. Similarly, as knowledge of the safety of a medicinal product may be derived from evaluation of data associated with uses other than the approved indication(s), such knowledge would be reflected in the risk evaluation, where relevant and appropriate.

1.4 Relation of the PBRER to Other ICH Documents

At present, some ICH countries and regions accept submission of separate types of periodic reports to fulfil national and regional requirements within the post-approval period: the PSUR (ICH Guideline E2C(R1)) for periodic reporting of the safety of approved medicinal products, the DSUR (ICH Guideline E2F) for periodic reporting on the safety of medicinal products that remain in clinical development, and the safety specification component of ICH Guideline E2E that might be submitted at the time of marketing application and/or PSUR submission to aid in the planning of pharmacovigilance activities. As these documents have different regulatory purposes, different periodicities, and can be reviewed by different divisions within a single regulatory authority, each document needs to be complete in its own right – a comprehensive document that can stand alone.

[2] For the purpose of this document, the terms "authorisation" and "authorised" refer to clinical trials and the terms "approval" and "approved" refer to marketing applications.

[3] This Guideline should not serve to limit the scope of information to be provided in the evaluation of benefit-risk of a medicinal product. Please refer to the applicable laws and regulations in the countries and regions in which the PBRER is to be submitted.

Nevertheless, overlap and inconsistencies between the content of the DSUR, PSUR, and safety specification can lead to inefficiencies in the production of the documents by the MAH.

Modular Approach

This Guideline aims to facilitate flexibility by encouraging the use of individual sections that are common to more than one report – "modules" that can be used for different regulatory authorities and for different purposes. Therefore, the PBRER has been developed in such a way that the content of several sections may be used for sections of other documents as a basis for a modular approach. For example, if the DIBD of a DSUR for a medicinal product is aligned to the IBD of the PBRER for the same product as suggested in ICH E2F, the content of a number of sections of the DSUR can also be used in the PBRER when the Data Lock Points (DLPs) are the same, i.e., when each report covers an interval of one year based on the IBD.

Appendix D of this Guideline lists the PBRER sections that can be shared with either the DSUR (ICH E2F) or safety specification of a risk management plan (ICH E2E), if appropriate.

The use of common sections across the PBRER, DSUR and safety specification as a modular approach has a number of advantages:

- Maximizes the utility of the modules across multiple regulatory documents;
- Promotes consistency across the PBRER, DSUR and safety specification;
- Avoids unnecessary duplication of effort;
- Is expected to improve efficiency for MAHs in the preparation of these documents;
- Facilitates flexible utilisation of existing sections (modules) when, for example, the PBRER covers different time intervals or needs to be submitted at different times to multiple different authorities. In these circumstances, only modules that include new information or new evaluation would need to be updated when submitting the PBRER.

Although currently out of scope for ICH E2C(R2), it is envisioned that the modular approach proposed, based on common sections across various documents, will ultimately facilitate development of electronic modules for use in future regulatory submissions.

2. GENERAL PRINCIPLES

2.1 Single PBRER for an Active Substance

The PBRER should provide information on all approved indications, dosage forms, and regimens for the active substance, with a single DLP. In some circumstances, it will be appropriate to present data by indication, dosage form, dosing regimen, or population (e.g., children vs. adults) within the relevant section(s) of the PBRER. In exceptional cases, submission of separate PBRERs might be appropriate, for example, an active substance used in two formulations for systemic and topical administration in entirely different indications. In these cases, the regulatory authorities should be notified and their agreement obtained, preferably at the time of approval.

2.2 PBRERs for Fixed-Dose Combination Product

For combinations of substances also marketed individually, information for the fixed combination may be reported either in a separate PBRER or included as separate presentations in the report for one of the individual substances, depending on the circumstances. Listing related PBRERs is considered important.

2.3 Products Manufactured and/or Marketed by More than One Company

Each MAH is responsible for submitting PBRERs for its own products.

When companies are involved in contractual relationships (e.g., licensor-licensee), respective responsibilities for preparation and submission of the PBRER to the regulatory authorities should be clearly specified in the written agreement.

When data received from a partner company(ies) might contribute meaningfully to the safety, benefit, and/or benefit-risk analyses and influence the reporting company's product information, these data should be included and discussed in the PBRER.

2.4 Reference Information

An objective of a PBRER is to evaluate whether information obtained during the reporting interval is in accord with previous knowledge on the product's benefit and risk profile, and to indicate whether changes should be made to the reference product information. Having one reference source of information that can be applied across the three ICH regions would facilitate a practical, efficient, and consistent approach to the benefit-risk evaluation and make the PBRER a unique report accepted in all countries and regions.

The reference product information for the PBRER would include "core safety" and "approved indications" components. In order to facilitate the assessment of benefit and benefit-risk by indication in the evaluation sections of the PBRER, the reference product information document should list all approved indications in ICH countries or regions. It is likely that these indications will also apply in other countries or regions. However, when the PBRER is also to be submitted to other countries in which there are additional locally approved indications, these indications may either be added to the reference product information or handled as a regional appendix/appendices as considered most appropriate by the MAH. The basis for the benefit evaluation should be the baseline important efficacy/effectiveness information summarised in Section 17.1 of the PBRER.

The following possible options can be considered by MAHs in selecting the most appropriate reference product information for a PBRER:

- Company Core Data Sheet

In accordance with ICH E2C(R1) recommendations, it is a common practice for MAHs to prepare their own CCDS, which includes sections relating to safety, indications, dosing, pharmacology, and other information concerning the medicinal product. The core safety information contained within the CCDS is referred to as the CCSI. A practical option is for MAHs to use the latest CCDS in effect at the end of the reporting interval as the reference product information for both the risk sections of the PBRER as well as the main approved indications for which benefit is evaluated.

When the CCDS for a medicinal product does not contain information on approved indications, the MAH should clearly specify which document is used as the reference information for the approved indications in the PBRER.

- Other options for the reference product information

When there is no CCDS or CCSI for a product, e.g., where the product is approved in only one country or region, or for established/generic products on the market for many years, the MAH should clearly specify the reference information being used. This may comprise national or regional product information such as the US Package Insert (USPI) or European Summary of Product Characteristics (SmPC), or the Japanese package insert, as appropriate. The basis for the benefit evaluation should be the baseline important efficacy/effectiveness information summarised in Section 17.1 of the PBRER.

Where the reference information for approved indications is a separate document to the RSI, the version current at the DLP of the PBRER should be included in Appendix 1.

The MAH should continuously evaluate whether any revision of the reference product information/RSI is needed whenever new safety information is obtained throughout the reporting interval. Significant changes to the reference product information/RSI made during the interval should be described in Section 4 of the PBRER ("Changes to Reference Safety Information") and include:

- Changes to contraindications, warnings/precautions sections of the RSI;
- Addition of Adverse Drug Reaction(s) (ADR) and interactions;
- Addition of important new information on use in overdose; and
- Removal of an indication or other restrictions for safety or lack of efficacy reasons.

Significant changes to the RSI made after the DLP but before submission of the PBRER should be included in Section 14 of the report (Late-Breaking Information), if feasible.

If stipulated by applicable regional requirements, the MAH should provide, in a regional appendix, information on any final, ongoing, or proposed changes to the national or local authorised product information.

2.5 Level of Detail Within PBRER

The level of detail provided in certain sections of the PBRER should depend on the medicinal product's known or emerging important benefits and risks. This approach is applicable to those sections of the PBRER in which there is evaluation of safety data, efficacy/effectiveness data, safety signals, and benefit-risk. Therefore, the extent of information provided in such PBRER sections will vary among individual PBRERs.

For example, when there is important new safety information, a detailed presentation of that information should be included, plus the relevant benefit information, in order to facilitate a robust benefit-risk analysis. Conversely, when little new important safety information has become available during the reporting interval, a concise summary of baseline benefit information should be sufficient, and the benefit-risk evaluation would consist primarily of an evaluation of updated interval safety data.

2.6 Efficacy/Effectiveness

For the purpose of this Guideline, evidence on benefits in clinical trials and in everyday medical practice should be reported. Because the terms are not harmonized across regions, the terms "efficacy/effectiveness" are used in this Guideline to clarify that information from both clinical trials and everyday medical practice are within the scope of the information on benefit to be included within the PBRER. In some regions, efficacy refers to evidence of benefit from controlled clinical trials while effectiveness implies use in everyday medical practice. Conversely, in other regions, this distinction is not made.

2.7 Benefit-Risk Evaluation

When a drug is approved for marketing, a conclusion has been reached that, when used in accordance with approved product information, its benefits outweigh its risks. As new information about the drug emerges during marketing experience, benefit-risk evaluation should be carried out to determine whether benefits continue to outweigh risks, and to consider whether steps need to be taken to improve the benefit-risk balance through risk minimisation activities, e.g., labelling changes, communications with prescribers, or other steps.

2.8 Periodicity and PBRER Data Lock Point

2.8.1 International Birth Date and Data Lock Point

Each medicinal product should have an IBD: the IBD is the date of the first marketing approval for any product containing the active substance granted to any company in any country in the world. When a report contains information on different dosage forms, formulations, or uses (indications, routes and/or populations), the date of the first marketing approval for any of the various authorisations should be regarded as the IBD and, therefore, determine the DLP for purposes of the PBRER. The DLP is the date designated as the cut-off for data to be included in a PBRER. Through PBRERs prepared with harmonised DLPs based on a common IBD, the same updated safety and benefit-risk information can be reviewed globally by different regulatory authorities.

When a separate PBRER is prepared for a fixed-dose combination product (see Section 2.2), the DLP for that PBRER can be based on either the earliest IBD of one of the component active substances, or the IBD of the first marketing approval anywhere in the world for the fixed-dose combination.

When clinical development of a medicinal product continues following marketing approval, if desired by the sponsor/MAH, the beginning of the DSUR reporting interval can be synchronized with the IBD-based cycle, so that both the DSUR and PBRER can be prepared at the same time, using the same

DLP. This approach will facilitate use of the proposed common sections/modules for both the PBRER and DSUR when both are submitted annually (see Appendix D).

2.8.2 Managing Different Frequencies of PBRER Submission

The need for the submission of a PBRER and the frequency of report submission to regulatory authorities are subject to national or regional regulatory requirements, and usually depend on such factors as approval dates, the length of time the product has been on the market, and the extent of knowledge of the benefit-risk profile of the product. The PBRER format and content are intended to apply to periodic reports that cover reporting periods of 6 months or longer. Once a drug has been marketed for several years, national or regional regulation may allow the frequency of submission to be extended to longer time intervals, e.g., greater than one year for products considered to have an established and acceptable profile or considered to be low risk; however, more frequent PBRERs may continue to be required in other regions. As a result, the following scenarios may be encountered by MAHs:

- PBRERs may be required on 6-monthly, annual, and less frequent submission timetables simultaneously across different regions.
- Changes in reporting frequency may also apply after important additions or changes in clinical use are approved (e.g., new indication[s] and/or new population[s]). In these circumstances, it is possible that the reporting interval will be shortened, even for older products with a previously reduced frequency of PBRER submission.
- An *ad hoc* PBRER may be requested by a regulatory authority (see Section 2.8.2.1 of this Guideline).

Independent of the length of the interval covered by the report:

- Each PBRER should be stand-alone and reflect new and cumulative information currently available to the MAH.
- Regulators will normally accept use of the IBD to determine the DLP for PBRERs. Where national or regional requirements differ from this, the MAH may wish to discuss with the relevant regulatory authority. Use of a single harmonised IBD and DLP for each product is important in order to reduce the burden of work involved in preparing PBRERs, and respects the original purpose of the PBRER – to prepare a single worldwide summary on a product that can be submitted to different regulatory authorities.
- For newly approved products, a 6-monthly periodicity applies in many regions, for at least the first 2 years after approval.
- For PBRERs submitted on a routine/regular basis, the reports should be based on cumulative data, with interval data sets of 6 months, or multiples thereof.
- Sections that provide interval information are likely to need to be updated for each PBRER, and the content used in the previous PBRER can be reviewed and reused for sections where no new information has arisen since preparation of the last PBRER, if appropriate. Following review, it may be determined that sections providing evaluation of cumulative data may not need to be updated if the content remains up to date with current information. See Figure 1.
- In situations when an MAH is preparing PBRERs on both a six-monthly and annual basis for different regulatory authorities, the regulatory authority requiring a PBRER on a six-month cycle may accept PBRERs containing 12-month interval data. See Figure 2. MAHs should discuss the acceptability of this approach with the relevant regulatory authority(ies).

2.8.2.1 Ad hoc ("for cause") PBRERs

Ad hoc PBRERs are reports outside the routine reporting requirements, and may be requested by some regulatory authorities. Where an *ad hoc* report is requested and a PBRER has not been prepared for a number of years, it is likely that a completely new report will need to be prepared by the MAH.

2.8.3 Time Interval Between Data Lock Point and the Submission

As a result of the expanded scope of the PBRER, the time interval between the DLP and submission of PBRERs should be as follows:

- PBRERs covering intervals of 6 or 12 months: within 70 calendar days;
- PBRERs covering intervals in excess of 12 months: within 90 calendar days;
- *ad hoc* PBRERs: 90 calendar days, unless otherwise specified in the *ad hoc* request.

The day of DLP is day 0 of the 70- or 90-calendar day interval between the DLP and report submission. Where national or regional requirements differ from the above, the MAH should discuss the timeline for submission with the relevant regulatory authority.

2.9 Format and Presentation of PBRER

2.9.1 Format

The recommended format and content of the PBRER, including table of contents, section numbering, and content of each section, is outlined below.

The full ICH Guideline E2C(R2) format should be used for all PBRERs. When no relevant information is available or a PBRER section is not applicable, this should be stated. Particular sections of the PBRER may share content with other regulatory reports, e.g., documents described in ICH Guidelines E2E and E2F. It may be possible for the MAHs to take advantage of the modular approach of the PBRER (i.e., sections that can be separated and submitted independently or combined with other documents) to facilitate such regulatory needs, maximize the utility of the content, and reduce duplicate work.

2.9.2 Presentation

The recommended table of contents, including section numbering, for the PBRER is provided below:

Title Page

Executive Summary

Table of Contents

1. Introduction
2. Worldwide Marketing Approval Status
3. Actions Taken in the Reporting Interval for Safety Reasons
4. Changes to Reference Safety Information
5. Estimated Exposure and Use Patterns
   - 5.1 Cumulative Subject Exposure in Clinical Trials
   - 5.2 Cumulative and Interval Patient Exposure from Marketing Experience
6. Data in Summary Tabulations
   - 6.1 Reference Information
   - 6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials
   - 6.3 Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources
7. Summaries of Significant Findings from Clinical Trials during the Reporting Period
   - 7.1 Completed Clinical Trials
   - 7.2 Ongoing Clinical Trials

3. GUIDANCE ON CONTENTS OF THE PBRER

All sections should be completed, and when no information is available, this should be stated. Note that Section "3.N" of this Guideline provides guidance on the content of Section "N" of the PBRER. For example, "Reference Information," described in Section 3.6.1 of this Guideline corresponds to Section 6.1 of the PBRER.

Title Page

The title page of the PBRER should include the following information:

- Date of the report;
- Medicinal product(s);
- IBD;
- Reporting interval;
- MAH(s) name(s) and address(es); and
- Any statement on the confidentiality of the information included in the PBRER.

Executive Summary

This section should provide a concise summary of the most important information contained in the report.

The following information should be included in the Executive Summary:

- Introduction;
- Reporting interval;
- Medicinal product(s) – mode(s) of action, therapeutic class(es), indication(s), dose(s), route(s) of administration, formulation(s);
- Estimated cumulative exposure of clinical trial subjects; interval and cumulative post-approval exposure;
- Number of countries in which the medicinal product is approved;
- Summary of overall benefit-risk evaluation (based on Section 18.2 of the PBRER);
- Actions taken or proposed for safety reasons, e.g., significant changes to the reference product information, other risk minimisation activities; and
- Conclusions.

Table of Contents

3.1 Introduction

Section 1 of the PBRER should include:

- IBD;
- Reporting interval;
- Medicinal product(s) – mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s);
- A brief description of the approved indication(s) and population(s);
- A brief description and explanation of any information that has not been included in the PBRER; and
- The rationale for submission of multiple PBRERs for the medicinal product, if applicable.

3.2 Worldwide Marketing Approval Status

Section 2 of the PBRER should provide a brief narrative overview including date of first approval, indication(s), approved dose(s), and where approved, if applicable.

3.3 Actions Taken in the Reporting Interval for Safety Reasons

Section 3 of the PBRER should include a description of significant actions related to safety that have been taken during the reporting interval, related to either investigational uses or marketing experience by the MAH, sponsor of a clinical trial(s), regulatory authorities, data monitoring committees, or ethics committees that had:

- A significant influence on the benefit-risk profile of the approved medicinal product; and/or
- An impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme.

The reason(s) for each action should be provided, if known, and additional relevant information should be provided when appropriate. Relevant updates to previous actions should also be summarised in this section. Examples of significant actions taken for safety reasons include:

Actions related to investigational drugs:*

- Refusal to authorise a clinical trial for ethical or safety reasons;
- Partial[4] or complete clinical trial suspension or early termination of an ongoing clinical trial* because of safety findings or lack of efficacy;

[4] "Partial suspension" might include several actions (e.g., suspension of repeat dose studies, but continuation of single dose studies; suspension of trials in one indication, but continuation in another, and/or suspension of a particular dosing regimen in a trial but continuation of other doses).

- Recall of investigational drug or comparator;
- Failure to obtain marketing approval for a tested indication, including voluntary withdrawal of a marketing application;
- Risk management activities, including:
  - Protocol modifications due to safety or efficacy concerns (e.g., dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);
  - Restrictions in study population or indications;
  - Changes to the informed consent document relating to safety concerns;
  - Formulation changes;
  - Addition by regulators of a special safety-related reporting requirement;
  - Issuance of a communication to investigators or healthcare professionals; and
  - Plans for new studies to address safety concerns.

Actions related to marketed drugs:

- Failure to obtain or apply for a marketing approval renewal;
- Withdrawal or suspension of a marketing approval;
- Suspension of supply by the MAH;
- Risk management activities including:
  - Significant restrictions on distribution or introduction of other risk minimisation measures;
  - Significant safety-related changes in labelling documents that could affect the development programme, including restrictions on use or population treated;
  - Communications to health care professionals; and
  - New post-marketing study requirement(s) imposed by regulator(s).

3.4 Changes to Reference Safety Information

Section 4 of the PBRER should list any significant changes to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, ADRs, overdose, and interactions; important findings from ongoing and completed clinical trials;* and significant non-clinical findings (e.g., carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PBRER.

A clean version of the reference document that is current at the DLP of the PBRER should be included in Appendix 1. A track change version of the reference information is not required.

3.5 Estimated Exposure and Use Patterns

Sections 5.1 and 5.2 of the PBRER should provide estimates of the size and nature of the population exposed to the medicinal product. Section 5.1 of the PBRER should provide information on cumulative exposure in clinical trials. Section 5.2 should provide cumulative and interval exposure in the marketed setting. Brief descriptions of the method(s) used to estimate the subject/patient exposure should be provided, as well as the limitations thereof. Consistent methods for calculating patient exposure should be used across PBRERs for the same product. If a change in the method is appropriate, both methods and calculations should be provided in the PBRER introducing the change.

3.5.1 Cumulative Subject Exposure in Clinical Trials

Section 5.1 of the PBRER should include the following information, if applicable, presented in tabular format (see Appendix B, Tables 1-3 for examples):

- Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the DIBD. It is recognised that for older products, precise data might not be available.

- More detailed cumulative subject exposure in clinical trials should be presented if available, e.g., sub-grouped by age, sex, and racial/ethnic group for the entire development programme.
- Important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered.
- If clinical trials have been or are being performed in special populations (e.g., pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided, as appropriate.
- When there are substantial differences in duration of exposure between subjects randomised to the investigational medicinal product or comparator(s), or disparities in duration of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or -years).
- Investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate.
- If the Serious Adverse Events (SAEs) from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available.
- For individual trials of particular importance, demographic characteristics should be provided separately.

3.5.2 Cumulative and Interval Patient Exposure from Marketing Experience

Separate estimations should be provided for interval exposure (since the DLP of the previous PBRER) and, when possible, cumulative exposure (since the IBD). See Appendix B, Tables 4 and 5 for examples. The estimated number of patients exposed should be provided when possible, along with the method(s) used to determine the estimate. If an estimate of the number of patients is not available, alternative estimated measures of exposure should be presented along with the method(s) used to derive them, if available. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a defined daily dose may also be used to estimate patient exposure.

The data should be presented according to the following categories:

1. *Post-approval (non-clinical trial) exposure:*

An overall estimation of patient exposure should be provided.

In addition, the data should be routinely presented by indication, sex, age, dose, formulation, and region, where applicable.

Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment.

When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.

2. *Post-approval use in special populations:*

Where post-approval use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data include non-interventional studies designed to obtain this information, including registries. Populations to be considered for discussion include, but might not be limited to:

- Paediatric population;
- Elderly population;
- Pregnant or lactating women;
- Patients with hepatic and/or renal impairment;

- Patients with other relevant co-morbidity;
- Patients with disease severity different from that studied in clinical trials;
- Sub-populations carrying relevant genetic polymorphism(s); and
- Patients of different racial and/or ethnic origins.

3. Other post-approval use:

If the MAH becomes aware of patterns of use of the medicinal product considered relevant for the interpretation of safety data, provide a brief description thereof. Examples of such patterns of use may include overdose, drug abuse, misuse, and use beyond that recommended in the reference product information (e.g., an anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). Such patterns may be regional. If known, the MAH may briefly comment on whether use beyond that recommended in the reference product information is supported by clinical guidelines, clinical trial evidence, or an absence of approved alternative treatments. Quantitative use information should be provided, if available. For purposes of identifying patterns of use outside the terms of the reference product information, the MAH should use the appropriate sections of the reference product information that was in effect at the DLP of the PBRER (e.g., approved indication, contraindications).

3.6 Data in Summary Tabulations

PBRER Sections 6.1 to 6.3 should present cumulative summary tabulations of SAEs from clinical trials and post-marketing sources that have been reported to the MAH since the DIBD. At the discretion of the MAH, graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

3.6.1 Reference Information

Section 6.1 of the PBRER should specify the version(s) of the coding dictionary used for analyses of adverse reactions.

3.6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

Section 6.2 of the PBRER should provide background for the appendix that provides a cumulative summary tabulation of SAEs reported in the MAH's clinical trials, from the DIBD to the DLP of the current PBRER. The MAH should explain any omission of data (e.g., clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organised by System Organ Class (SOC), for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. Data can be integrated across the programme. Alternatively, when useful and feasible, tabulations of SAEs can be presented by trial, indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the SAEs.

Appendix B, Table 6 of this Guideline provides an example of summary tabulations of SAEs from clinical trials. The following points should be considered:

- In general, the tabulation(s) of SAEs from clinical trials should include only those terms that were used in defining the case as serious; they should not include non-serious events.
- When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the Preferred Term (PT) level and SOC should be presented in the summary tabulations.
- The tabulations should include blinded and unblinded clinical trial data. Unblinded SAEs might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g., expedited reporting), if applicable. Sponsors/MAHs should not unblind data for the specific purpose of preparing the PBRER.
- Certain adverse events in clinical trials can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as "exempt" from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study

endpoints, can be excluded (e.g., deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

- Causality assessment is generally useful for the evaluation of individual rare ADRs. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations should include all SAEs for the investigational drug, active controls, and placebo. It may be useful to give rates by dose.

3.6.3 Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

Section 6.3 of the PBRER should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the DLP of the current PBRER. As described in ICH Guideline E2D, for marketed medicinal products, spontaneously reported* adverse events usually imply at least a suspicion of causality by the reporter, and should be considered to be adverse reactions for regulatory reporting purposes. The tabulation should include:

- Serious and non-serious adverse drug reactions from spontaneous ICSRs, including reports from healthcare professionals, consumers, scientific literature, and regulatory authorities;
- Serious adverse reactions from non-interventional studies; and
- Solicited reports* of serious adverse reactions.

The tabulation should include interval and cumulative data presented side-by-side (see Appendix B, Table 7), and should be organised by SOC.

For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the data presented.

3.7 Summaries of Significant Safety Findings from Clinical Trials during the Reporting Interval

This section of the PBRER should provide a brief summary of clinically important emerging efficacy/effectiveness and safety findings obtained from the MAH's sponsored clinical trials that became available during the reporting interval of the report. The safety signals arising from clinical trial sources should be tabulated in Section 15 of the PBRER. Evaluation of the signals (whether or not categorised as refuted signals or either potential* or identified risks*) that were closed during the reporting interval should be presented in Section 16.2 of the PBRER. New information in relation to any previously known potential or identified risks and not considered to constitute a newly indentified signal should be evaluated and characterised in Sections 16.3 and 16.4, respectively. Findings from clinical trials not sponsored by the MAH should be described in the relevant sections of the PBRER.

When relevant to the benefit-risk evaluation, information on lack of efficacy from clinical trials for treatments of non-life-threatening diseases in approved indications should also be summarised in this section. Information on lack of efficacy from clinical trials with products intended to treat or prevent serious or life-threatening illnesses should be summarised in Section 13 of the PBRER.

When possible and relevant, data categorized by sex and age (particularly children versus adult), indication, dose, and region should be presented.

A listing of any MAH-sponsored post-marketing interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard, or confirming the safety profile of the medicinal product that were completed or ongoing during the reporting interval should be included in an appendix. The listing should include the following information for each trial:

- Study ID (e.g., protocol number or other identifier);
- Study title (abbreviated study title, if applicable);
- Study type (e.g., randomized clinical trial, cohort study, case-control study);
- Population studied (including country and other relevant population descriptors, e.g., paediatric population or trial subjects with impaired renal function);

- Study start (as defined by the MAH) and projected completion dates;
- Status:
  - Ongoing (clinical trial has begun);
  - Completed (clinical study report is finalised).

3.7.1 Completed Clinical Trials

Section 7.1 of the PBRER should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in narrative format or as a synopsis.[5] It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

3.7.2 Ongoing Clinical Trials

If the MAH is aware of clinically important information that has arisen from ongoing clinical trials (e.g., learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this section should briefly summarise the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

3.7.3 Long-Term Follow-up

Where applicable, this section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products.

3.7.4 Other Therapeutic Use of Medicinal Product

This section of the PBRER should include clinically important safety information from other programmes conducted by the MAH that follow a specific protocol, with solicited reporting as per ICH Guideline E2D (e.g., expanded access programmes, compassionate use programmes, particular patient use, single-patient Investigational New Drug applications [INDs], treatment INDs, and other organised data collection).

3.7.5 New Safety Data Related to Fixed Combination Therapies

Unless otherwise specified by national or regional regulatory requirements, the following options can be used to present data from combination therapies:

- If the product that is the subject of a PBRER is also approved or under development as a component of a fixed combination product or a multi-drug regimen, this section should summarise important safety findings from use of the combination therapy.
- If this PBRER is for a fixed combination product, this section should summarise important safety information arising from the individual components.

The information specific to the combination can be incorporated into a separate section(s) of the PBRER for one or all of the individual components of the combination.

3.8 Findings from Non-Interventional Studies

This section should summarise relevant safety information or information with potential impact on the benefit or risk evaluations, from MAH-sponsored non-interventional studies that became available during the reporting interval (e.g., observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from drug utilisation studies when applicable to multiple regions.

A listing of any MAH-sponsored post-marketing non-interventional study(ies) with the primary aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures that were completed

[5] Examples of synopses are provided in ICH E3 and CIOMS VII.

or ongoing during the reporting interval should be included in an appendix (see Section 3.7 of this Guideline for the information that should be included in the listing).

Final study reports completed during the reporting interval for the studies mentioned in the paragraph above should also be included in the regional appendix of the report where stipulated by regional requirements.

3.9 Information from Other Clinical Trials and Sources

3.9.1 Other Clinical Trials

This subsection should summarise information accessible to the MAH with reasonable and appropriate effort from any other clinical trial/study sources, including results from pooled analyses or meta-analyses of randomised clinical trials, and safety information provided by co-development partners or from investigator-initiated trials.

3.9.2 Medication Errors

This subsection should summarise relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. A potential medication error is the recognition of circumstances that could lead to a medication error, and may or may not involve a patient. Such information may be relevant to the interpretation of safety data or the overall benefit-risk evaluation of the medicinal product. A medication error may arise at any stage in the medication use process, and may involve patients, consumers, or healthcare professionals.

This information may be received by the MAH via spontaneous reporting systems, medical information queries, customer complaints, screening of digital media, patient support programmes, or other available information sources.

Signals or risks identified from any information source and/or category of reports should be presented and evaluated in the relevant section of the PBRER.

3.10 Non-Clinical Data

This section should summarise major safety findings from non-clinical *in vivo* and *in vitro* studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies) ongoing or completed during the reporting interval. Results from studies designed to address specific safety concerns should be included in the PBRER, regardless of the outcome. Implications of the findings presented in PBRER Section 10 should be discussed in the relevant evaluation sections of the report.

3.11 Literature

This section should summarise new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts, relevant to the approved medicinal product that the MAH became aware of during the reporting interval. Literature searches for PBRERs should be wider than those for individual adverse reaction cases, and include studies reporting safety outcomes in groups of subjects. If relevant, information on active substances of the same class should be considered.

3.12 Other Periodic Reports

Unless otherwise specified by national or regional regulatory requirements, the MAH should prepare a single PBRER for a single active substance. However, if an MAH prepares multiple PBRERs for a single active substance (e.g., covering different indications, or formulations), this section should summarise significant findings from the other periodic reports if they are not presented elsewhere within this report.

When available, based on contractual agreements, the MAH should summarise significant findings from periodic reports provided during the reporting interval by other parties (e.g., sponsors, MAHs, other contractual partners).

3.13 Lack of Efficacy in Controlled Clinical Trials

Data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening illnesses (e.g., excess cardiovascular adverse events in a trial of a new anti-platelet drug for acute coronary syndromes) could reflect a significant risk to the treated population and should be summarised in this section.

3.14 Late-Breaking Information

This section should summarise information on potentially important safety and efficacy/effectiveness findings that arise after the DLP but while the PBRER is in preparation. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the MAH, a data monitoring committee, or a regulatory authority has taken for safety reasons. New individual case reports should not be included unless they are considered to constitute an important index case (i.e., the first instance of an important event), an important safety signal, or where they may add information to the evaluation of safety concerns already presented in the PBRER (e.g., a well documented and unconfounded case report of aplastic anaemia in a medicinal product known to be associated with adverse effects on the bone marrow).

Any significant change proposed to the reference product information which has occurred after the DLP of the report but before submission should also be included in this section, where feasible. Such changes could include a new contraindication, warning/precaution, or new adverse drug reaction.

The data presented in this section should also be taken into account in the evaluation of risks and new information (see Section 3.16.3 of this Guideline).

3.15 Overview of Signals: New, Ongoing, or Closed

The general location for presentation of information on signals and risks within the PBRER is shown in Appendix F of this Guideline. The purpose of Section 15 of the PBRER is to provide a high level overview of safety signals that were closed (i.e., the evaluation was completed) during the reporting interval as well as ongoing signals* that were undergoing evaluation, at the end of reporting interval. For the purposes of the PBRER, a signal should be included once it has undergone the initial screening or clarification step, and a determination made to conduct further evaluation by the MAH. It should be noted that a safety signal is not synonymous with a statistic of disproportionate reporting for a specific drug/event combination as a validation step is required. Signals may be qualitative (e.g., a pivotal individual safety case report, case series) or quantitative (e.g., a disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the form of an information request or inquiry on a safety issue from a regulatory authority.

Decisions regarding the subsequent classification of these signals and the conclusions of the evaluation involve medical judgement and scientific interpretation of available data, which is presented in Section 16 of the PBRER.

A new signal is a signal that the MAH became aware of during the reporting interval. New clinically important information on a previously closed signal* that became available during the reporting period of the PBRER (i.e., a new aspect of a previously refuted signal or recognised risk likely to warrant further action to verify) would also constitute a new signal. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the DLP of the PBRER. Examples would include new information on a previously:

- Closed and refuted signal, which would result in the signal being re-opened;
- Identified risk which is indicative of a clinically significant difference in the severity of the risk, e.g., transient liver enzyme increases are identified risks and new information is received indicative of a more severe outcome such as hepatic failure; neutropenia is an identified risk and a well documented and unconfounded case report of agranulocytosis is received;
- Identified risk for which a higher frequency of the risk is newly found, e.g., in a subpopulation; and

- Potential risk* which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimisation activities.

Within this section, or as an appendix, include a tabular listing of all signals ongoing or closed at the DLP of the PBRER. This table should include the following information: See Appendix C for an example.

- A brief description of the signal;
- Date when the MAH became aware of the signal;
- Status of the signal (closed or ongoing at the DLP);
- Date when the signal was closed, if applicable;
- Source of the signal;
- A brief summary of key data;
- Plans for further evaluation; and
- Actions taken or planned.

Detailed signal evaluations for closed signals are not to be included in this section but instead should be presented in Section 16.2 of the PBRER (Signal Evaluation). Evaluation of new information in relation to any previously known identified and potential risks and not considered to constitute a newly identified signal* should be provided in Section 16.3 of the PBRER (Evaluation of Risks and New Information).

When a regulatory authority has requested that a specific topic (not considered a signal) be monitored and reported in a PBRER, the MAH should summarize the result of the analysis in PBRER Section 15 if it is negative. If the specific topic becomes a signal, include it instead in the signal tabulation and discuss in PBRER Section 16.2.

3.16 Signal and Risk Evaluation

The purpose of Section 16 of the PBRER is to provide:

- A succinct summary of what is known about important identified and potential risks and important missing information* at the beginning of the reporting interval covered by the report (16.1);
- An evaluation of all signals closed during the reporting interval (16.2);
- An evaluation of new information with respect to previously recognised identified and potential risks (16.3);
- An updated characterisation of important potential and identified risks ,where applicable (16.4); and
- A summary of the effectiveness of risk minimisation activities in any country or region which may have utility in other countries or regions (16.5).

Appendix F of this Guideline provides a flowchart to illustrate the mapping of signals and risks to specific sections of the PBRER.

The evaluation subsections should not summarise or repeat information presented in previous sections of the PBRER, but should instead provide an interpretation of the information, with a view towards characterising the profile of those risks assessed as important. As a general rule, it is not necessary to include individual case narratives in the evaluation sections of the PBRER; however, when integral to the scientific analysis of a signal or risk, a clinical evaluation of pivotal or illustrative cases (e.g., the first case of suspected agranulocytosis with an active substance belonging to a class known to be associated with this adverse reaction) should be provided.

3.16.1 Summary of Safety Concerns

The purpose of this section is to provide a summary of safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. These comprise:

- Important identified risks;*
- Important potential risks;* and
- Important missing information.

The following factors should be considered when determining whether or not a risk is important:

- Medical seriousness of the risk, including the impact on individual patients;
- Its frequency, predictability, preventability, and reversibility;
- Potential impact on public health (frequency; size of treated population); and
- Potential for avoidance of a medical product with a preventive benefit as a result of public perception of risk.

For products with an existing safety specification, this section can be either the same as, or be derived from, the safety specification summary (according to ICH Guideline E2E) at the start of the reporting interval of the current PBRER. For products without an existing safety specification, this section should provide information on the important identified and potential risks and important missing information associated with use of the product, based on pre- and post-approval experience. Important identified and potential risks may include, for example:

- Important adverse reactions;
- Interactions with other medicinal products;
- Interactions with foods and other substances;
- Medication errors;
- Effects of occupational exposure; and
- Pharmacological class effects.

The summary on important missing information should take into account whether there are critical gaps in knowledge for specific safety issues or populations that use the medicinal product.

3.16.2 Signal Evaluation

Section 16.2 of the PBRER should summarize the results of evaluations of all safety signals (whether or not classified as important) that were closed during the reporting interval. A safety signal can be closed either because it is refuted or because it is determined to be a potential or identified risk following evaluation. Therefore, the two main categories to be included in this section are:

1. Those signals that, following evaluation, have been refuted as "false" signals based on medical judgment and a scientific evaluation of the currently available information.

2. Those signals that, following evaluation, have been categorised as either a potential or identified risk, including lack of efficacy.

For both categories of closed signals, a concise description of each signal evaluation should be included in order to provide to the regulatory authorities the basis upon which the signal was either refuted or considered to be a potential or identified risk by the MAH.

It is recommended that the level of detail provided in the description of the signal evaluation be proportionate to the medical significance of the signal, its public health importance, and the extent of the available evidence. When multiple evaluations are included under both categories of closed signals, they can be presented in the following order:

- Closed and refuted signals;
- Closed signals that are categorised as important potential risks;
- Closed signals that are categorised as important identified risks;
- Closed signals that are potential risks not categorised as important; and
- Closed signals that are identified risks not categorised as important.

Where applicable the closed signal evaluations can be presented by indication or population.

The description(s) of the signal evaluations can be included in this section of the PBRER, or in an appendix. Each signal evaluation should include the following information as appropriate:

- Source of the signal;
- Background relevant to the evaluation;
- Method(s) of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms [e.g., PTs, HLTs, SOCs, etc.] or Standardised MedDRA Queries [SMQs] that were reviewed), and analytical approaches;
- Results – a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an ICSR, e.g., an index case of well documented agranulocytosis or Stevens Johnson syndrome;
- Discussion; and
- Conclusion.

3.16.3 Evaluation of Risks and New Information

This section should provide a critical appraisal of new information relevant to previously recognised risks that is not already included in Section 16.2 of the PBRER (Signal Evaluation).

New information that constitutes a signal with respect to a previously recognised risk or previously refuted signal should be presented in the tabular summary in Appendix C and evaluated in Section 16.2 of the PBRER, if the signal is also closed during the interval of the PBRER.

Updated information on a previously recognised risk that does not constitute a signal should be included in this section. Examples include information that confirms a potential risk as an identified risk, or information that allows further characterisation of a previously recognised risk.

New information can be organised as follows:

1. New information on important potential risks;
2. New information on important identified risks;
3. New information on other potential risks not categorised as important;
4. New information on other identified risks not categorised as important;
5. Update on important missing information.

The focus of the evaluation(s) is on new information which has emerged during the reporting interval of the PBRER. This should be concise and interpret the impact, if any, on the understanding and characterisation of the risk. Where applicable, the evaluation will form the basis for an updated characterisation of important potential and identified risks in Section 16.4 of the report. It is recommended that the level of detail of the evaluation included in this section should be proportional to the available evidence on the risk and its medical significance and public health relevance.

The evaluation(s) of new information and missing information update(s) can be included in this section of the PBRER, or in an appendix. Each evaluation should include the following information as appropriate:

- Source of the new information;
- Background relevant to the evaluation;
- Method(s) of evaluation, including data sources, search criteria, and analytical approaches;
- Results – a summary and critical analysis of the data considered in the risk evaluation;
- Discussion; and
- Conclusion including whether or not the evaluation supports an update of the characterisation of any of the important potential and identified risks in Section 16.4 of the PBRER.

Any new information on populations exposed or data generated to address previously missing information should be critically assessed in this section. Unresolved concerns and uncertainties should be acknowledged.

3.16.4 Characterisation of Risks

This section will characterise important identified and important potential risks based on cumulative data (i.e., not restricted to the reporting interval), and describe important missing information.

Depending on the nature of the data source, the characterisation of risk may include, where applicable:

- Frequency;
- Numbers of cases (numerator); precision of estimate, taking into account the source of the data;
- Extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
- Estimate of relative risk; precision of estimate;
- Estimate of absolute risk; precision of estimate;
- Impact on the individual patient (effects on symptoms, quality or quantity of life);
- Public health impact;
- Patient characteristics relevant to risk (e.g., age, pregnancy/lactation, disease severity, hepatic/renal impairment, relevant co-morbidity, genetic polymorphism),
- Dose, route of administration;
- Duration of treatment, risk period;
- Preventability (i.e., predictability, ability to monitor for a "sentinel" adverse reaction or laboratory marker);
- Reversibility;
- Potential mechanism; and
- Strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

When missing information could constitute an important risk, it should be included as a safety concern. The limitations of the safety database (in terms of number of patients studied, cumulative exposure or long term use, etc.) should be discussed.

For PBRERs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration. Headings that could be considered include:

- Risks relating to the active substance;
- Risks related to a specific formulation or route of administration (including occupational exposure);
- Risks relating to a specific population; and
- Risks associated with non-prescription use (for substances that are available as both prescription and non-prescription products).

3.16.5 Effectiveness of Risk Minimisation (if applicable)

Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important identified risks that has become available during the reporting interval should be summarised in this section.

Insights into the effectiveness of risk minimisation activities in any country or region that may have utility in other countries or regions are of particular interest. Information may be summarised by region, if applicable and relevant.