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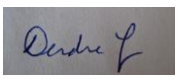
Signature: 

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Patricia Lucia Fernandez Rodriguez

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LIST OF ABBREVIATIONS:

MA	Marketing authorization

HPRA	Health Products Regulatory Authority
AGEMED	Agencia Estatal de Medicamentos y Tecnologías en Salud, (State Agency for Medicines and Health Technologies)
GMP	Good Manufacturing Practice
CTD	The Common Technical Document
EMA	European Medicines Agency
SmPC	Summary of Product Characteristics
PIL	Patient Information Leaflet
CoA	Certificate of Analysis
API	Active Pharmaceutical Ingredient
FP	Final Product
ICH	International Council for Harmonisation
RMP	Pharmacovigilance & Risk Management Plan
WHO	World Health Organization
CEP	Certificate of Suitability
QP	Qualified Person
MIA	Manufacturer's/Importer's Authorisation
PSMF	Pharmacovigilance System Master File
QPPV	Qualified Person for Pharmacovigilance

ABSTRACT

Regulatory Frameworks for Obtaining and Renewing Marketing Authorisations of Generic Paracetamol 500 mg Tablets Imported from the United States: A Comparative Analysis of HPRA (Ireland) and AGEMED (Bolivia) in 2024, Using Paracetamol as an Illustrative Example

Patricia Lucia Fernandez Rodriguez

This study compared how two national agencies, HPRA in Ireland and AGEMED in Bolivia, approve and renew the marketing authorisations of generic paracetamol 500 mg tablets imported from the United States. The research aimed to identify the main differences in legal requirements, timelines, safety measures, and documentation, in order to recommend ways to improve regulatory efficiency and public access to quality medicines in Bolivia.

A mixed-methods approach was used. First, legal and regulatory documents were reviewed. Then, an online survey was conducted with pharmaceutical professionals in Bolivia to collect both quantitative data (such as timelines) and qualitative insights (such as personal experiences and challenges). The focus was on real-life practices, especially for the approval and renewal processes.

The results showed that Ireland's regulatory process is more structured, digital, and aligned with international standards. HPRA requires bioequivalence studies, digital submissions, and ongoing safety monitoring. In contrast, AGEMED in Bolivia uses paper-based systems, does not require bioequivalence for generics, and often has slower timelines due to manual procedures. Survey participants highlighted delays, lack of clarity, and the need for system updates.

In conclusion, the study found that Bolivia could improve its regulatory framework by adopting digital tools, requiring bioequivalence studies for generic medicines, and updating outdated legal guidelines. These changes could help make the approval process faster, safer, and more transparent. By learning from Ireland's experience, Bolivia has the opportunity to modernise its system and improve public health outcomes.

Keywords: Generic medicine, Marketing authorization, Sanitary registration, HPRA, AGEMED, Bioequivalence, GMP.

CHAPTER 1: INTRODUCTION

1.1 Background and Purpose of the Study:

Medicines are very important for people's health. They help treat pain, control symptoms, and make daily life better. Generic medicines are especially helpful because they work just like the original brand-name ones but usually cost much less. This means more people can afford the treatment they need (World Health Organization, 2016).

Before any medicine can be used by patients, it must be checked and approved by a national authority. This process is called marketing authorisation or sanitary registration. It makes sure the medicine is safe, works well, and is made with good quality (ICH, 2000).

Every country has its own rules and steps for approving and renewing medicines. In Ireland, the Health Products Regulatory Authority (HPRA) is in charge. They follow European Union laws, like Directive 2001/83/EC and Regulation (EC) No. 726/2004, which set rules for all EU countries (European Parliament and Council, 2001; 2004). HPRA asks for proof that the generic medicine works the same as the original, this is called bioequivalence. They also check that medicines are made following Good Manufacturing Practices (GMP) based on international guidelines (HPRA, 2025a; ICH, 2000).

In Bolivia, the agency responsible is called AGEMED, the State Agency for Medicines and Health Technologies (Agencia Estatal de Medicamentos y Tecnologías en Salud). AGEMED uses national laws like Law No. 1737 and Supreme Decree No. 25235 to decide if a medicine can be sold (AGEMED, 1998; 2000). Their full process is written in the Manual for Sanitary Registration (AGEMED, 2005). However, unlike Ireland, Bolivia does not always require bioequivalence studies for generic medicines. This is important because bioequivalence means that the generic medicine works in the same way, with the same strength, safety, and effect as the original brand-name medicine. Without this kind of test, there is a risk that the medicine may not work as expected in the patient's body, which could affect their treatment or even their health (World Health Organization, 2016;

FDA, 2021). These studies help protect patient safety and make sure that the generic medicine offers the same quality and benefits as the original one. Also, many of the steps in Bolivia are still done on paper, which can slow the process down and make it harder to follow or manage applications (AGEMED, 2005).

This study will compare these two systems, Ireland's and Bolivia's, to understand how they handle approving and renewing generic paracetamol 500 mg tablets imported from the United States. Paracetamol is a simple and common medicine, so it is a good example to see the differences between the two countries' procedures.

1.2 Context of the Study:

Getting affordable and good-quality medicines is still a big challenge around the world. Generic medicines are one of the best answers to this problem, especially for countries with less money (World Health Organization, 2016). But before people can use these medicines, they have to go through a legal process. This process can be long, complicated, and very different depending on the country.

In Ireland, medicine approval follows European laws that have been improved over many years to make things safer, clearer, and faster (European Parliament and Council, 2001; 2004). On the other hand, Bolivia still works with older national laws and mostly paper-based systems, using rules from 1998, 2000, and a guideline from 2005 (AGEMED, 1998; 2000; 2005). These rules still guide Bolivia's medicine approval, but some parts might be a bit old-fashioned or slower compared to what other countries do today.

Because of this big difference, one country using modern digital systems, the other relying on more manual methods, this study has a great chance to learn how the way rules are set up affects the time, cost, and difficulty of getting medicines to patients.

To make this easier to understand, the study imagines two simple examples:

- Company X wants to register a generic paracetamol 500 mg tablet in Ireland, following the HPRA process.
- Company Z wants to register the same medicine in Bolivia, following AGEMED's steps.

By looking at these two stories, the research shows how the same medicine can go through very different approval journeys just because of where it is registered. This comparison helps us see the bigger picture and supports the study's main goal: finding ways Bolivia's system could improve by learning from Ireland's experience.

1.3 Justification and Significance:

This research is important because it looks at a topic that doesn't get much attention but is very important for public health: how countries handle the legal process to approve generic medicines.

Even though many people use generic medicines every day, the rules behind their approval are not always clear or well known. Some countries have modern systems that follow international standards, while others still use older rules that might need updating. This study focuses on Bolivia, which has made progress but still uses approval procedures created more than 20 years ago (AGEMED, 2000; 2005).

On the other hand, Ireland follows newer regulations as part of the European Union's shared system for medicine approval (European Parliament and Council, 2001). By

comparing these two countries, this research shows how regulatory systems develop in different ways and how learning from international best practices can help improve them.

This study is also important for public policy. The results can help Bolivian agencies and leaders think about their own system and find ways to make it faster, clearer, and more in line with global health standards. A well-organized and efficient approval process benefits both medicine companies and patients who need safe medicines quickly.

Another reason this study matters is that very few academic papers directly compare agencies like Ireland's HPRA and Bolivia's AGEMED for the same medicine. Most research looks at just one country or broader topics like medicine pricing or public opinion. For example, some studies focus on Ireland's policies and what people think about generics (O'Leary, A. et al., 2015) but don't compare them to countries like Bolivia. Studies about generics in Latin America often talk about the whole region and don't look closely at Bolivia's specific system (Badjatya, J.K. et al., 2022). This shows why this study is new and useful.

Finally, this research supports global efforts to make medicine regulations more similar across countries. Groups like the World Health Organization and the International Council for Harmonisation encourage shared rules for medicine quality and safety (WHO, 2016; ICH, 2000). This is very important when medicines are made in one country and used in another.

1.4 Aim and Objectives:

Aim:

This study wants to compare how two regulatory agencies, HPRA in Ireland and AGEMED in Bolivia, handle the approval and renewal of generic paracetamol 500 mg

tablets that come from the United States. The main goal is to understand the important differences and similarities in their processes and how each country manages the legal and technical steps needed to get this medicine to patients.

Objectives:

1. Investigate HPRA's requirements for approving and renewing marketing authorisations for generic paracetamol imported from the USA.
2. Examine AGEMED's approval and renewal process for the same product in Bolivia.
3. Compare both systems regarding documents, timelines, quality controls, and procedures.
4. Identify challenges, gaps, and opportunities to improve regulatory efficiency.
5. Provide recommendations to streamline the process and improve access to affordable generic medicines.

1.5 Research Question and Hypothesis:

Research Question:

How do the approval and renewal processes for generic paracetamol 500 mg tablets imported from the United States differ between Ireland's HPRA and Bolivia's AGEMED in 2024?

Working Hypothesis:

Ireland uses a clear and well-organized system based on European Union rules, which helps make the approval process faster and more efficient. On the other hand, Bolivia's process is less consistent and relies more on manual steps.

This idea will be checked by looking at official documents and by gathering survey answers from professionals working in Bolivia.

1.6 Key Terms and Definitions:

To help readers understand this study, here are some important terms explained simply:

- **Generic medicine:** A medicine that is the same as a brand-name one in dose, safety, quality, and effect, but usually costs less (World Health Organization, 2016).
- **Marketing authorisation:** The official permission from health authorities (like in Ireland or the EU) that allows a medicine to be sold.
- **Sanitary registration:** What Bolivia calls marketing authorization, it's the legal process to allow a medicine to be sold there.
- **HPRA (Health Products Regulatory Authority):** Ireland's national agency that checks medicines to make sure they're safe and work well before approving them.
- **AGEMED (Agencia Estatal de Medicamentos y Tecnologías en Salud):** Bolivia's government agency responsible for approving and controlling medicines.
- **Bioequivalence:** A test that proves a generic medicine works the same way and has the same effect as the original brand.
- **GMP (Good Manufacturing Practice):** International rules that make sure medicines are made in clean, safe places and pass quality checks (International Council for Harmonisation, 2000).

1.7 Structure of the Dissertation:

This dissertation is divided into six chapters, each guiding the reader through the research step by step.

- **Chapter 1: Introduction.**
  This chapter presents the study's background, aim, research question, and importance. It also defines key terms and explains the dissertation's structure.
- **Chapter 2: Literature Review.**
  This chapter covers the main laws and regulations for approving generic medicines in Ireland and Bolivia. It reviews previous studies, highlighting what is known and where gaps remain.

- **Chapter 3: Methodology.**
  This chapter explains the research methods, including study design, surveys, and document analysis. Ethical issues related to data collection and handling are also discussed.
- **Chapter 4: Findings and Analysis.**
  Here, the study results are presented, including document reviews and survey insights from Bolivian professionals. The findings are clearly organised to show similarities and differences between the systems. It also interprets the findings, compares them with existing literature, and reflects on their meaning for both countries.
- **Chapter 5: Conclusions and Recommendations.**
  The final chapter summarises key points, offers conclusions, and suggests practical improvements for Bolivia's regulatory system, as well as ideas for future research.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction:

This chapter compares how Ireland and Bolivia approve and renew generic medicines, focusing on their main procedures, strengths, and areas for improvement. To explain the process, the example of paracetamol 500 mg tablets imported from the U.S. is used, a common, low-cost medicine for pain and fever (Medicines.ie, 2020). The regulatory bodies involved are HPRA in Ireland and AGEMED in Bolivia.

Ireland follows EU laws, such as Directive 2001/83/EC and Regulation (EC) No. 726/2004 (European Parliament and Council, 2001; 2004), and international standards like ICH Q7 for manufacturing (ICH, 2000). Generic applicants must prove bioequivalence (HPRA, 2025a). Bolivia, by contrast, follows national rules, including Law 1737, Supreme Decree No. 25235, and the AGEMED Manual (AGEMED, 1998; 2000; 2005). Applications are paper-based, and bioequivalence is not required, causing delays (Badjatya et al., 2022).

The WHO supports wider use of generics to improve global access to quality treatment (WHO, 2016). However, Bolivia still faces regulatory delays, weaker controls, and limited alignment with global standards. Ireland's system is more advanced, though trust in generics remains an issue among some patients and doctors (O'Leary et al., 2015).

The chapter also compares how both countries handle imports. Ireland follows a clear, efficient process (HPRA, 2025c), while Bolivia's is slower and more complex for imported products like paracetamol.

Although many studies explore generics, few compare how Ireland and Bolivia regulate the same medicine. This research fills that gap and suggests ways Bolivia could improve approval speed and quality.

2.2 Generic Medicines Around the World:

Generic medicines are key to public health. They offer safe and effective treatment at lower cost. The WHO says generics work just as well as brand-name medicines but are much more affordable (WHO, 2016). This helps health systems care for more people with the same budget.

Agencies like the EMA and FDA also support generics, as they increase access, especially in countries with fewer resources (European Medicines Agency, 2025; FDA, 2021b; WHO, 2016). Each country has its own rules. In the U.S. and Ireland, companies must show bioequivalence, proving the generic has the same ingredient, strength, and effect as the original (FDA, 2021a; HPRA, 2025a). Without it, approval is not granted.

In many developing countries, bioequivalence is not always required, and paperwork is still manual. This slows the process and creates doubt about quality (Badjatya, J.K. et al., 2022; O'Leary, A. et al., 2015).

Europe has a more unified approach. Generics follow laws like Directive 2001/83/EC and Regulation EC No. 726/2004 (European Parliament and Council, 2001; 2004). In Ireland, the HPRA checks safety and quality, and companies must follow Good Manufacturing Practices (HPRA, 2025c; ICH, 2000).

Bolivia still uses older laws like Law No. 1737 and paper-based processes from AGEMED's Manual (AGEMED, 1998; 2000; 2005). Without digital systems, registration takes longer and is harder to follow (Badjatya, J.K. et al., 2022), making the process slower and less transparent.

In summary, generics are a powerful way to bring affordable, safe medicines to more people. But approval systems must be modern and clear. With better processes, countries can help more patients get the medicines they need, faster and with confidence.

2.3 EU and Irish Regulatory Frameworks:

Let's imagine a company in Ireland, called Company X. They want to import paracetamol 500 mg tablets from the United States to sell only in Ireland. But before they can do that, they need something very important, a Marketing Authorisation, or MA.

2.3.1 Getting a Marketing Authorisation (MA):

In the European Union, no medicine can be sold without a Marketing Authorisation (MA). This is an official approval that says the medicine is safe, works well, and can be legally sold. Without this permission, the company can't put the product on the market (Directive 2001/83/EC, Article 6(1)) (European Parliament and Council, 2001).

Since Company X plans to sell only in Ireland, they must apply directly to the Health Products Regulatory Authority (HPRA) in Ireland. Because this is a generic medicine, they don't have to do full clinical trials again. Instead, they can take a simpler path called the abridged procedure (Directive 2001/83/EC, Article 10(1)). This means they can use data from a similar medicine already approved in the EU (European Medicines Agency, 2025; HPRA, 2025a). To follow this path, the company must prove bioequivalence, basically, that their medicine works the same way, at the same dose, and gives the same results. They do this by showing studies that compare how both medicines act in the body (FDA, 2021a; WHO, 2016).

2.3.2 The Common Technical Document (CTD):

To apply for the MA, Company X needs to prepare their documents using something called the Common Technical Document, or CTD. This format is required by Directive 2001/83/EC in Article 8(3) and Annex I and helps to organise all the information clearly (European Parliament and Council, 2001) *(See Appendix A).* The CTD is used all over the EU and even in other countries. It breaks down the application into five parts (European Medicines Agency, 2021).

This system was created by the International Council for Harmonisation (ICH) to make the approval process easier and more consistent everywhere (ICH, 2021). Even if the company applies only in Ireland, they still have to use the CTD format. It's the standard for all kinds of approval routes, whether national or across several countries (EMA, 2024a).

- **Module 1: National and Administrative Information (Ireland).**

- **Cover Letter:** Company X states the product is a generic paracetamol tablet from the USA. They are applying through the Irish national procedure under Directive 2001/83/EC, Article 10(1) (European Parliament and Council, 2001).
- **Application Form:** Confirms the product is generic. Under Article 10(1), they can submit bioequivalence data instead of full clinical trials (European Parliament and Council, 2001).
- **SmPC (Summary of Product Characteristics):** Includes key information such as use, dose, and warnings. Required under Article 8(3)(j) of Directive 2001/83/EC and Irish law (Irish Statute Book, 2007).
- **Patient Information Leaflet (PIL):** Must be clear and easy to read. A readability test or justification is required, following Article 59(3) and HPRA guidance (HPRA, 2025e).

- **Labels and Outer Packaging:** Includes mock-ups. Braille must appear on the outer box (Article 56a). Design must follow HPRA national rules (European Parliament and Council, 2001; HPRA, 2025e).
- **Proof of Payment:** Proof must be included as required by SI No. 540/2007. The 2025 fee is €24,183 (HPRA, 2025d). Missing proof may delay the application. A scientific advice meeting is optional but recommended (HPRA, 2025d).
- **Manufacturing Licence and GMP Certificate:** These confirm EU GMP compliance (Directive Article 8(3)(h); EudraLex Vol. 4) (European Commission, 2022). As the product is made in the USA, FDA inspections are accepted under the EU–US Mutual Recognition Agreement (European Commission, n.d.; EMA, n.d.).
- **Environmental Risk Assessment:** In the case of simple generics like paracetamol, an it is generally not required.
- **Pharmacovigilance & Risk Management Plan (RMP):** Company X includes a simplified risk management plan, as required under EU law, even for generic products.
- **Paediatric Use Declaration:** If the product is for children, a declaration under Regulation (EC) No 1901/2006, Article 7 is needed. If not, "not applicable" must be stated (European Parliament and Council of the European Union, 2004).

➢ **Module 2: Overviews and Summaries.**

Company X must provide summaries to help HPRA understand the product. These are short versions of the full data in Modules 3–5. As this is a generic medicine, some sections are simpler (EMA, 2021; ICH, 2000).

- **Quality Overall Summary:** Explains how the medicine is made and tested, covering the active ingredient, tablet manufacturing, and quality checks. All steps follow GMP and comply with EU and international standards (European Commission, 2022; ICH, 2000; S.I. No. 540/2007; HPRA, 2025c).

- **Non-Clinical Overview**: No new animal or lab tests are required. Existing data is used under Article 10 of Directive 2001/83/EC (European Parliament and Council, 2001).
- **Clinical Overview:** The company must show bioequivalence, same absorption and effect as the original product. Studies, usually done in healthy volunteers, follow guidance from HPRA (2025a), EMA (2025), FDA (2021a), and WHO (2016).

➢ **Module 3: Quality (Pharmaceutical Information).**

Company X explains how they make sure Paracetamol 500 mg Tablets are always safe and good quality. This section has two parts: one for the active ingredient (paracetamol) and one for the final tablets. Both follow strict rules so the medicine works well and can be trusted (European Medicines Agency, 2018).

✓ **Active Ingredient (Paracetamol)**

Company X provides a Certificate of Suitability (CEP) from the European Directorate for the Quality of Medicines. This confirms paracetamol meets European standards without revealing manufacturing secrets (European Medicines Agency, 2018). The quality checks follow BP 2017 *(see Appendix C).*

- **Source:** The paracetamol supplier follows Good Manufacturing Practice (GMP) and shares full details on making and testing, ensuring safety and consistency (European Medicines Agency, 2018).
- **Batch Analysis Data for API:** From three recent production batches of paracetamol are included, confirming compliance with BP 2017 specifications. Company X provides this data as part of the CEP documentation.
- **Analytical methods:** Including identity, strength, and purity, are described and validated in accordance with ICH Q2(R1). Quality control tests confirm that paracetamol meets the specifications of the British Pharmacopoeia 2017.
- **Manufacturing Site Compliance:** The factory has a current GMP certificate, showing it follows EU medicine production rules (HPRA, 2025c).

- **Packaging and Storage:** Company X provides stability study results showing paracetamol remains stable when stored properly, protected from light and moisture (European Medicines Agency, 2018).

✓ **Finished Product (Paracetamol 500 mg Tablets)**

This explains how tablets are made and tested to meet quality standards, guided by BP 2017 *(see Appendix D).*

- **Manufacturing Process:** The process includes mixing, shaping, and coating to ensure consistent quality (European Medicines Agency, 2018).
- **Qualitative and Quantitative Formula:** All ingredients, including excipients, are listed with exact amounts for safety and consistency (European Commission, 2008).
- **Excipients Quality:** All excipients meet quality standards and are checked before use.
- **Certificate of Analysis (CoA):** A Certificate of Analysis (CoA) for the finished product is included, confirming compliance with BP 2017 specifications.
- **In-Process Controls:** During production, checks on weight and hardness maintain quality (European Medicines Agency, 2018).
- **Analytical methods:** All analytical methods used for finished product testing are fully described and follow BP 2017 monographs.
- **Validation of analytical methods:** Method validation reports are included to show accuracy, precision, linearity, and specificity, as per ICH Q2(R1) guidelines.
- **Finished Product Testing:** Tablets are tested for identity, strength, dissolution, impurities, and uniformity to ensure safety and effectiveness (BP 2016b; European Medicines Agency, 2018).
- **Packaging Materials:** Company X provides details on packaging suppliers who follow GMP (HPRA, 2025c).
- **Stability Studies:** Tests follow ICH Q1A guidelines to confirm tablets stay good under normal European and Irish storage (ICH, 2003).
- **Regulatory Compliance:** Company X holds a valid HPRA license to make or import tablets, proving legal compliance (HPRA, 2025c).

- **Batch samples:** One representative finished product sample will be submitted to the HPRA upon request (HPRA, 2023).

➢ **Module 4: Non-Clinical Reports (if available).**

For a generic medicine, animal testing is not required. Instead, Company X provides a justification letter explaining why it's not needed, supported by published safety data if available (The European Parliament and the Council of the European Union, 2001).

➢ **Module 5: Clinical Study Reports – Bioequivalence.**

This module includes clinical study data. For Company X, it contains a bioequivalence study to prove the generic acts the same as the original (EMA, 2010). HPRA follows EMA guidance. Bioequivalence means both medicines deliver the same amount of active ingredient to the bloodstream at the same speed (HPRA, 2023; EMA, 2010).

Usually, healthy volunteers take both versions on different days. Blood samples are taken to measure drug levels (EMA, 2010; WHO, 2018). Two key values are tested:

- **AUC (Area Under the Curve):** Total drug absorbed over time (EMA, 2010; HPRA, 2023).
- **Cmax (Maximum Concentration):** Highest drug level in the blood (EMA, 2010; HPRA, 2023).

The generic is accepted if results are within 80–125% of the original (EMA, 2010; HPRA, 2023). If proven, no extra clinical trials are needed, making the process faster, cheaper, and still safe (WHO, 2018).

2.3.3 Importation and the Role of the Qualified Person (QP):

Before selling a medicine in Ireland or the EU, each batch must be tested and approved. As stated in Directive 2001/83/EC, Article 51, a Qualified Person (QP) in the EU must certify the batch (The European Parliament and the Council of the European Union, 2001). The QP checks that:

- The product follows Good Manufacturing Practice (GMP),
- It matches the Marketing Authorisation (MA),
- All documents and results are correct.

If the product is made outside the EU, it must be imported by a company with a Manufacturer's/Importer's Authorisation (MIA). This company must also have a QP to certify the batch (HPRA, 2025c).

If a third party handles packaging, testing, or storage, they also need an MIA and a QP (European Commission, 2021).

For Company X, the medicine is made outside the EU and imported into Ireland. The import site must have an MIA and a QP. Any other site involved, like for labelling or storage, must also be licensed and employ a QP (HPRA, 2025c; European Commission, 2021).

After final checks, the QP signs a certificate to confirm the batch is safe and approved (European Commission, 2021; HPRA, 2025c). To avoid repeating tests, the EU has Mutual Recognition Agreements (MRAs). For example, the EU–US MRA allows the EU to accept inspections from trusted authorities like the US FDA, saving time (European Commission, n.d.).

2.3.4 Process Approval and Timeline in Ireland:

Once Company X submits the full CTD application, the HPRA reviews it to check if the product is safe, effective, and high quality. This follows Directive 2001/83/EC and S.I. No. 540/2007 (The European Parliament and the Council of the European Union, 2001; S.I. No. 540/2007). Under Article 17(1), the HPRA has 210 days to assess the file and make a decision. If more details are needed, the HPRA sends a Request for Further Information (RFI). This pauses the process (a "clock stop") until the company replies (European Medicines Agency, 2023). If all requirements are met, the HPRA grants the MA, and the medicine can be sold in Ireland

2.3.5 Safety Monitoring: Pharmacovigilance:

After receiving an MA, Company X must keep monitoring the product's safety. This is called pharmacovigilance (HPRA, 2025g; European Commission, 2025b). Pharmacovigilance means watching for, understanding, and preventing any safety problems or side effects that might appear over time or in different patients (WHO, 2025; European Commission, 2025b).

Under Regulation (EU) No 1235/2010 and Directive 2010/84/EU, Company X must follow key steps (European Commission, 2010a; 2010b). As updated in Article 104 of Directive 2001/83/EC, these include:

- **Pharmacovigilance System Master File (PSMF):** A document explaining the company’s safety monitoring system.
- **Qualified Person for Pharmacovigilance (QPPV):** A responsible EU-based person available 24/7 to oversee safety reports to EMA or the HPRA.
- **Updates to SmPC and Patient Leaflet:** If new safety data emerges, Company X must update the product’s official documents to inform doctors, pharmacists, and patients.

The HPRA provides guidelines on how to manage these duties nationally. The goal is to protect public health throughout the medicine's lifecycle (HPRA, 2025g).

2.3.6 Renewal of the Marketing Authorisation:

Marketing Authorisations (MAs) are not permanent. The first MA is valid for five years. As stated in Article 24(1) of Directive 2001/83/EC, Company X must apply for renewal at least 9 months before expiry (The European Parliament and the Council of the European Union, 2001; HPRA, 2025f). The company must send safety updates and submit:

- A renewal application form,
- Summary of safety data (European Parliament and Council of the European Union, 2010a),
- A list of any changes since the original MA (HPRA, 2025g),
- Proof of GMP/GDP compliance (European Commission, 2022),
- Updated product info, if needed (HPRA, 2025f).

If the evaluation is positive, the MA is renewed with unlimited validity (HPRA, 2025f). However, big changes, like a new manufacturer or major product update, need a variation application, submitted before or during the renewal (European Commission, 2025a; HPRA, 2025b). The renewal fee is lower than the initial application, but the final cost depends on any variations (HPRA, 2025d).

A flowchart in Figure 1 (below) shows the full Irish process for getting and renewing a generic MA.

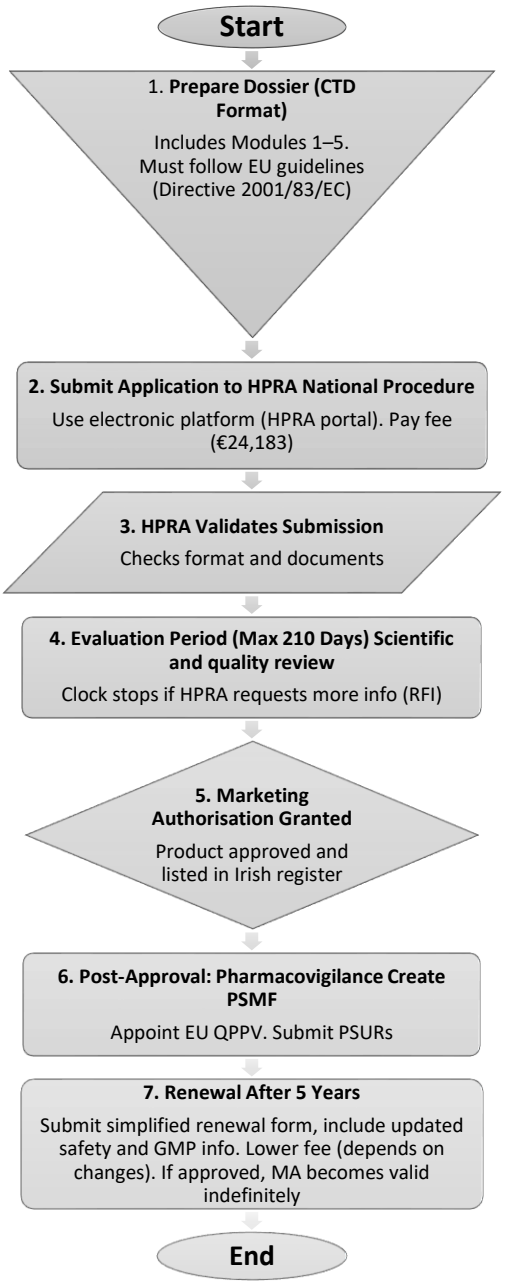

Figure 1: *Steps for Obtaining and Renewing a Generic Marketing Authorisation in Ireland HPRA, created by the author*

This flowchart shows how a generic medicine, like paracetamol, is approved and renewed in Ireland. It outlines the key steps, from preparing documents to final authorisation and

keeping the product safely on the market. By following this process, the HPRA ensures that all medicines remain safe and high quality.

2.4 Bolivian Regulatory Frameworks:

2.4.1 What is Sanitary Registration?

In Bolivia, companies must get official government permission before selling any medicine. This permission is called Sanitary Registration and works the same way as Marketing Authorisation in other countries (AGEMED, 2005). It proves that health authorities have checked the medicine's safety, effectiveness, and quality (AGEMED, 2000). Without it, the medicine cannot be legally sold, distributed, or used. The agency in charge is AGEMED, Agencia Estatal de Medicamentos y Tecnologías en Salud (State Agency of Medicines and Health Technologies) (AGEMED, 1998).

2.4.2 How is it Regulated?

In Bolivia, Sanitary Registration follows three key legal documents:

- **Law No. 1737 – Law on Medicines (2000):** This is the main legal framework for medicine regulation. It sets the rules for evaluation, distribution, and control (AGEMED, 2000).
- **Supreme Decree No. 25235 (1998):** This decree explains how to apply the law. It gives clear steps for the registration process (AGEMED, 1998).
- **Manual for Sanitary Registration (2005):** A technical guide with all details of the process, including required documents, scientific studies, and review criteria (AGEMED, 2005).

2.4.3 Requirements for Sanitary Registration in Bolivia.

To explain how sanitary registration works in Bolivia, this section uses an example: Company Y, a Bolivian-based company that wants to import Paracetamol 500 mg tablets

from the U.S. This helps show the main steps and legal requirements needed to register the product with AGEMED and sell it legally.

Preparation of the Dossier:

Company Y must submit a complete dossier, as outlined in Chapter 2, point 2.12 of the Manual for Sanitary Registration (AGEMED, 2005) *(See Appendix B).* This proves the medicine is safe, effective, and good quality.

1. Formal Request Letter.

A signed letter from the company's legal representative, officially asking AGEMED for the product's registration (AGEMED, 2005).

2. Application Form.

Filled with updated company details and signed by a qualified person (AGEMED, 2005).

3. Legal Identification.

Documents that confirm Company Y's legal status in Bolivia (AGEMED, 2005):

- Tax ID (NIT).
- Commercial registration.
- ID of the legal representative.
- Valid import licence.
- Power of Attorney (if using a third party).

4. Product Information.

This section provides technical details about the medicine. For paracetamol 500 mg tablets (AGEMED, 2005), this includes:

- The product name and complete formula, listing both the active ingredient (paracetamol) and inactive substances (excipients).
- The pharmaceutical form (tablet), dosage (500 mg), and route of administration (oral).
- A full description of the manufacturing process.
- The name and full address of both the manufacturing site and packaging facility.
- Packaging specifications, such as type of material (e.g., blister pack), size, and protective measures.
- Information on shelf-life and recommended storage conditions.

5. Quality Control Information.

Company Y must include complete evidence that the product meets quality standards (AGEMED, 2005). This includes:

a) **Specifications:**
   These are the official quality limits for both the raw materials (like the active pharmaceutical ingredient, paracetamol) and the finished tablets. For example, Company Y can follow the British Pharmacopoeia 2017 (BP 2017) to set these specifications. This includes for the final product, tests for identity, strength (assay), impurities, tablet uniformity, and how quickly the tablet dissolves in the body (British Pharmacopoeia Commission, 2016a; 2016b) *(see Appendices C and D).*

b) **Analytical Methods and Validation:**
   Company Y must describe each test used to check the quality of the ingredients and final product. These tests must be validated, which means they have been

proven to give accurate, repeatable results. This ensures the methods are scientifically reliable and suitable for their purpose (AGEMED, 2005).

c) **Certificates of Analysis (CoAs):**
These certificates are required for both the API and the finished tablets. A CoA is a document showing the results of lab tests for a specific batch of product. It proves that the batch meets all the established specifications and is safe to be used (AGEMED, 2005).

d) **Stability Studies:**
These studies show how long the medicine stays stable and safe over time. The tests must be done under conditions that match Bolivia's hot and humid climate, Zone IVb (30°C ± 2°C, 75% ± 5% relative humidity). Company Y must include the full study reports, including methods, timelines, and results, to support the claimed shelf-life and storage conditions (AGEMED, 2005).

e) **GMP Certificate:**
This is issued by the health authority in the country where the product is made. It proves that the manufacturing facility meets international quality and hygiene standards, helping protect patient safety (AGEMED, 2005).

6. Reference Standards.

Company Y must clearly state which official pharmacopoeia will be used to test and control the product's quality. In this case, the British Pharmacopoeia 2017 (BP 2017) is selected as the reference for both the active ingredient (paracetamol) and the finished tablets (AGEMED, 2005).

7. Labels and Patient Leaflets.

Samples in Spanish must include (AGEMED, 2005):

- Product name, dose, and ingredients
- Usage instructions
- Storage, warnings, expiry date, batch number

- Manufacturer and importer details

8. Pharmacological and Toxicological Data.

A summary of the product's safety and effectiveness, supported by studies and literature (AGEMED, 2005).

9. Pharmacovigilance Letter.

A signed letter confirming the company will submit Periodic Safety Update Reports (PSURs), following the Pharmacovigilance Guide (AGEMED, 2012; 2005).

10. Proof of Payment.

Receipt confirming payment of the registration fee (according to AGEMED's current tariff list, it is 1,613 Bolivianos or approx. €213), paid to AGEMED's official account (AGEMED, 2018; 2005).

2.4.4 Registration Process After Submission.

Once Company Y finishes the full dossier, it must submit it to AGEMED. As explained in Chapter 3 of the Manual for Sanitary Registration (AGEMED, 2005), the documents must be printed and delivered in person to AGEMED's office in La Paz. During the COVID-19 pandemic, AGEMED launched an online tool called MISA to help with digital steps. While some parts can still be done online, printed submission is still the official rule. Company Y should check AGEMED's website to see which steps are available online (AGEMED, 2025).

AGEMED follows a four-step evaluation process:

Step 1: Document Review.

AGEMED first checks if all documents are complete and properly formatted (AGEMED, 2005). If something is missing or incorrect, they send a written notice. Company Y then has 30 calendar days to fix the issue. If they don't reply in time, the process is cancelled and must start again.

Step 2: Technical Evaluation.

If everything is complete, AGEMED begins the technical review (AGEMED, 2005). Experts evaluate:

- The product's formula and pharmaceutical properties.
- Quality control results and method validation.
- Stability studies done under local climate (Zone IVb).
- GMP compliance.
- Labels and patient information.

Step 3: Pharmacological and Toxicological Evaluation.

Here, AGEMED checks the product's safety, how it works, and its therapeutic use (AGEMED, 2005). They also review the Summary of Product Characteristics (SmPC) and any clinical data included.

Step 4: Final Decision.

After all checks are complete, AGEMED issues a final decision on the registration of the product (a generic paracetamol 500 mg from the USA). If the application is valid, AGEMED must respond within 30 calendar days from the complete submission date (AGEMED, 2005).

There are three possible outcomes:

- **Approval:** Company Y receives a Sanitary Registration Certificate, valid for 5 years, which allows the product to be sold in Bolivia.
- **Request for Clarification:** If minor issues are found, AGEMED pauses the process and gives Company Y 30 days to send the corrections. The review resumes after that.
- **Rejection:** If serious problems are found, or corrections are not submitted in time, AGEMED rejects the application. They must explain the reasons, and the company can reapply later.

By law, the full registration process, from dossier acceptance to the final decision, must be completed in no more than 90 calendar days (AGEMED, 2005).

2.4.5 Renewal of the Sanitary Registration.

The Sanitary Registration is valid for five years (AGEMED, 2005). Company Y must begin the renewal at least three months before it expires, as described in Chapter 3 of the Manual for Sanitary Registration of Medicines (AGEMED, 2005). For renewal, the company must submit the same documents as in the first registration (Chapter 2, point 2.12), but with updated information. This includes a copy of the current Sanitary Registration Certificate, confirming that the product is already approved.

The renewal dossier must include:

- Updated stability studies and safety data.
- Certificates of Analysis.
- Current labels and patient leaflets.
- Any approved changes made in the past five years.
- A valid GMP certificate.
- A new pharmacovigilance commitment letter (AGEMED, 2005).

This is not just a minor update. Every five years, Company Y must submit a complete and updated dossier to keep the product on the Bolivian market (AGEMED, 2005). The renewal fee for imported medicines is 1,489 Bolivianos (about €198) (AGEMED, 2018).

AGEMED reviews the dossier and may pause or deny the renewal if documents are missing or incorrect (AGEMED, 2005). So, Company Y must prepare and send everything on time and complete.

Figure 2 below summarises the key steps to register and renew a generic medicine in Bolivia. The flowchart follows AGEMED's legal framework and shows the process in simple terms, from first application to final renewal.

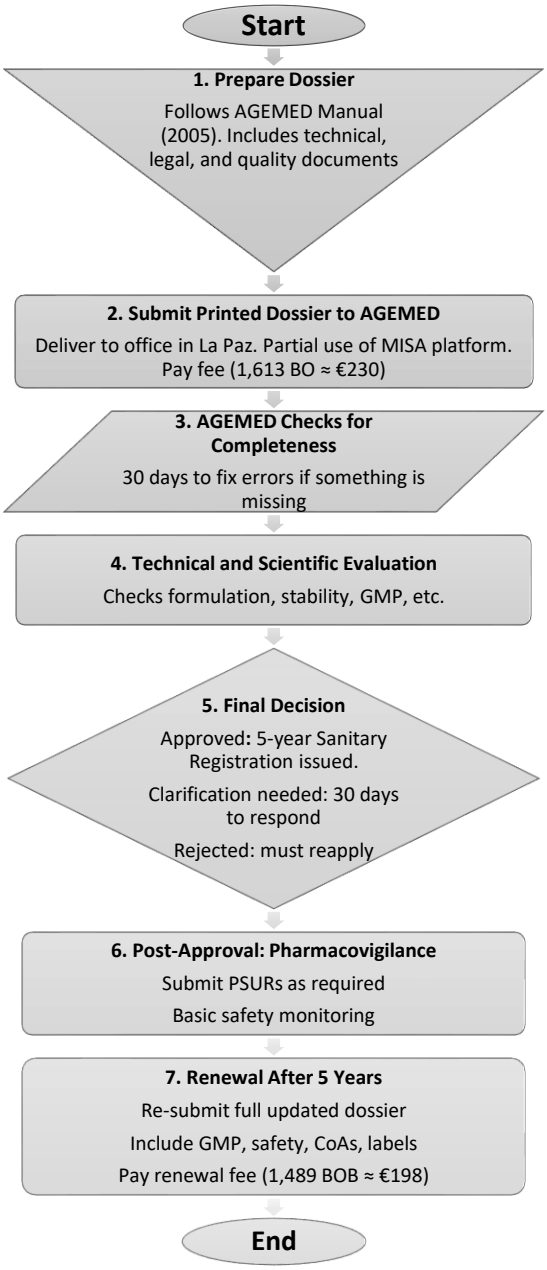

Figure 2: *Sanitary Registration and Renewal Process in Bolivia (AGEMED), created by the author.*

This flowchart shows the full process for registering and renewing a generic medicine in Bolivia. It helps explain how AGEMED reviews documents, makes decisions, and gives marketing permission. While the steps are simpler and faster than in Ireland, the system still needs updates to become more modern and efficient.

2.5 Key Themes in the Literature:

2.5.1 Bioequivalence.

Bioequivalence is very important when approving generic medicines. It means the generic medicine works in the same way, gives the same amount of drug in the blood, and has the same effect as the original (brand-name) medicine. In the European Union (EU), bioequivalence is a legal requirement for all generics (Directive 2001/83/EC, Article 10).

However, in Bolivia, this rule is not followed. The national agency AGEMED does not ask for bioequivalence studies when registering or renewing generic medicines (AGEMED, 2005). This creates a big difference between Bolivia and places like the EU or USA.

If bioequivalence is not tested, the generic medicine may not work the same or may even be unsafe. For example, it might be absorbed too slowly or too fast, or the active ingredient might not reach the blood at the correct level. This can cause the medicine to be less effective, or in some cases, cause harmful side effects. This problem is common in many countries with weaker medicine regulation. For example, da Fonseca and Shadlen (2017) explain that some Latin American countries, like Brazil in the past, did not require bioequivalence at first. This led to low-quality generics, reduced trust from doctors and patients, and higher risks to public health.

Studies show that skipping bioequivalence tests can lead to serious problems. For instance, people with epilepsy who switched from a brand-name medicine (like Lamictal®) to a generic version of lamotrigine experienced more seizures and side effects. This was seen in the EQUIGEN clinical trial (Berg et al., 2017), and also reported in other studies (Markoula et al., 2017; Dawson, 2016). These problems happened because the generic did not act exactly like the original.

Also, a global survey from the International League Against Epilepsy (ILAE) showed that doctors and patients in many countries are worried about the safety of generic seizure medicines when bioequivalence is not properly checked (Volkers, 2022).

Even for common medicines like paracetamol, the quality must be carefully controlled. If bioequivalence is not proven, there is a risk that the medicine will not reduce pain or fever correctly, or worse, it could be toxic (British Pharmacopoeia Commission, 2016a, 2016b).

This is why international agencies such as the FDA and EMA recommend pharmacokinetic studies to test bioequivalence before approving generics (FDA, 2021a; EMA, 2010). These tests help to protect patient safety and make sure the medicine will work as expected.

To improve the health system in Bolivia, it is very important to follow stronger rules. Making bioequivalence studies mandatory would help ensure that patients receive safe and effective treatment just like in the EU or other well-regulated markets.

2.5.2 Good Manufacturing Practice (GMP) Compliance.

GMP ensures medicines are made safely and consistently. In Ireland, it follows global guidelines such as ICH Q7 and Eudralex Volume 4 (European Commission, 2022). These rules are clear, updated, and strictly followed. As a result, medicines like imported paracetamol 500 mg are safer and more reliable.

In Bolivia and other Latin American countries, enforcing GMP is more difficult. As PAHO (2022) reports, many face problems like a lack of trained inspectors, weak

monitoring, or limited funding. Because of these challenges, GMP is not always fully applied in Bolivia. This raises the risk that low-quality or unsafe medicines may reach patients, a serious public health issue that calls for stronger regulation and investment.

2.5.3 Digitalisation.

Digital tools are transforming how health agencies manage data and communicate. In Ireland, the HPRA uses online systems to receive and process documents. This makes the work faster, clearer, and more efficient, reducing delays (Macdonald, J.C. et al., 2021).

In Bolivia, digitalisation is still developing. While there has been progress, many tasks still require paper documents or in-person delivery. This causes delays and complicates communication, especially with international partners (Macdonald, J.C. et al., 2021).

This contrast shows how digital tools can improve decision-making, transparency, and collaboration. But to work well, countries like Bolivia need better infrastructure, staff training, and technology access.

Digitalisation offers a key opportunity to build a more modern, connected, and flexible regulatory system that better supports public health (Macdonald, J.C. et al., 2021).

2.5.4 Comparison Between Ireland and Bolivia in the Marketing Authorisation Process.

Let’s now compare how Ireland and Bolivia manage the approval and renewal of generic medicines. Table 1 shows a side-by-side comparison of the main steps, documents, rules, timelines, costs, and safety measures. This helps highlight both strengths and challenges in each system (HPRA, 2025a; AGEMED, 2005; European Commission, 2022).

To make it clearer, this study uses one example: generic paracetamol 500 mg tablets imported from the United States. Table 1 shows how the process differs in each country.

CRITERIA	IRELAND (HPRA)	BOLIVIA (AGEMED)
Legal Framework	Directive 2001/83/EC, Regulation 726/2004	Law No. 1737, Supreme Decree No. 25235, Manual for Sanitary Registration
Dossier Format	Common Technical Document (CTD), electronic submission	Paper-based dossier, national format
Bioequivalence Requirement	Mandatory for generics	Not required
Pharmacovigilance System	Required (QPPV, PSMF, PSURs)	Basic system, less standardised
Good Manufacturing Practice (GMP)	Mandatory (EU/ICH)	Required, limited enforcement
Submission Platform	Fully digital (HPRA portal)	Partially digital (MISA system), paper still needed
Import Requirements	MIA + QP for batch release	Import licence + basic documentation
Evaluation Timeline	Up to 210 calendar days	Max 90 calendar days (often longer)
Renewal Requirements	Simplified, only updates and safety data	Full dossier re-submission
New Approval Cost	€24,183	~€213 (1,613 Bs.)
Renewal Cost	Lower than initial	~€198 (1,489 Bs.)

Table 1: *Key Differences in the Marketing Authorisation (MA) Process Between Ireland and Bolivia, created by the author.*

Ireland follows strict EU rules. It needs strong evidence that medicines are safe, effective, and made under good conditions. The process is longer and more expensive but uses digital tools and solid safety checks (HPRA, 2025a; EMA, 2025).

Bolivia's process is faster and cheaper (AGEMED, 2005; 2018). But it still uses paper documents, and its rules are less detailed. For example, no bioequivalence is required, and companies must submit the full dossier again at renewal. This can slow things down and raise safety concerns.

The big cost difference also shows how different the systems are. In Ireland, new approval costs over €24,000. In Bolivia, it's only around €213. This low cost helps with access, but weak controls could affect quality (PAHO, 2022).

In short, Bolivia has room to improve. Learning from Ireland could help build a faster, safer, and more modern system, while keeping medicines affordable.

2.6 Gaps in the Literature: Product Comparisons Across Countries.

When reviewing the academic literature on generic medicines, we notice that most research looks at how medicines are approved in big, high-income countries such as the United States or across the European Union. However, very few studies focus on smaller countries like Bolivia, or on the process of renewing generic medicines once they are already approved.

For example, Deore and Patel (2022) and Ravi Kiran et al. (2017) compared how generic medicines are approved in BRICS countries (Brazil, Russia, India, China, and South

Africa), but Bolivia was not included. Also, these studies mainly focused on initial approval and did not explain how renewals work.

The renewal process is very important. It ensures the medicine remains safe and effective after it is already in the market. Unfortunately, this part of the regulatory cycle is often ignored in academic studies. According to the Health Products Regulatory Authority (HPRA, 2025f), renewals in Ireland involve submitting updated documents like safety data and pharmacovigilance reports. In contrast, Bolivia's AGEMED also requests similar information (AGEMED, 2012), but the system is still under development, with fewer digital tools and slower procedures.

There is another gap in the literature: even though paracetamol 500 mg is one of the most commonly used generic drugs in the world (WHO, 2016), it is not usually chosen as a product for comparing regulatory systems. No research could be found comparing how countries like Ireland and Bolivia manage the approval and renewal of this medicine, even though both countries use it widely.

This research aims to fill that gap. It uses paracetamol 500 mg as a real example to compare two very different regulatory environments. Ireland has a strong and structured system with clear timelines and electronic submissions (HPRA, 2025b), while Bolivia's system is less developed and involves more manual work (AGEMED, 2005). By studying both processes, this work shows the real differences and helps identify where Bolivia could improve.

So far, no academic paper has compared HPRA and AGEMED directly. Most studies only focus on one region. For example, O'Leary et al. (2015) looked at Irish policies but did not compare them with other countries. Badjatya et al. (2022) analysed Latin America, but Bolivia was not studied in detail. Volkers (2022) highlighted global concerns about

generic medicines, especially when patients switch brands, but did not include any analysis of Bolivia or Ireland.

By comparing one medicine in two real systems, this study provides practical insights. It can support global goals promoted by the World Health Organization (WHO, 2016) and International Council for Harmonisation (ICH, 2000), which both recommend that countries align their standards, especially when medicines are exported or shared.

2.7 Conclusion:

This review showed clear differences in how Ireland and Bolivia register generic medicines. Ireland's system, managed by HPRA, is well organised and follows EU rules. It applies strong GMP guidelines (European Commission, 2022), uses the CTD format (EMA, 2021), requires bioequivalence studies (EMA, 2010), and uses digital tools for faster and more transparent processing (HPRA, 2025b).

Bolivia, managed by AGEMED, still relies on paper-based processes (AGEMED, 2005). It has laws such as Law 1737 (AGEMED, 2000), but three main issues remain:

- No requirement for bioequivalence, even for common generics like paracetamol (EMA, 2010).
- GMP standards that don't fully meet international norms (European Commission, 2022).
- Manual systems that slow down processes and reduce communication efficiency (AGEMED, 2005).

By comparing both countries, this review highlights where Bolivia could improve, by updating GMP rules, asking for bioequivalence studies, and switching to digital systems.

Overall, this review supports the main goal of the research: to show how small but smart changes can improve medicine regulation. Using one simple product, like paracetamol 500 mg, helps make this idea clear. It also offers practical suggestions that could help Bolivia modernise its regulatory system by learning from countries like Ireland.

CHAPTER 3: METHODOLOGY

3.1 Introduction:

This chapter explains how the research was carried out, step by step. It describes how the study was planned, how data were collected, and how the results were analysed. It also explains why each method was chosen and how ethical rules were followed.

The research focused on the approval and renewal process for generic paracetamol 500 mg tablets imported from the United States. It compares the regulatory systems in Ireland and Bolivia. In Ireland, this process is managed by the Health Products Regulatory Authority (HPRA), while in Bolivia, it is handled by AGEMED. Both systems aim to ensure that medicines are safe, effective, and of high quality, but they follow different procedures and have different challenges.

Because of these differences, the study used a mixed-methods approach. This means it collected two kinds of data: quantitative (numbers and facts) and qualitative (personal opinions and experiences). This method allowed the research to study not just the laws and regulations but also the real-life experiences of professionals, especially those in Bolivia. Using mixed methods provided a more complete understanding of the research topic, improving the validity of the findings by combining data from different sources (Molina-Azorín, 2016).

To collect this information, an online survey was created and sent to pharmaceutical professionals in Bolivia. These professionals were selected because they have direct experience with AGEMED and understand how the system works in practice. Their knowledge helped identify real challenges, suggest solutions, and provide useful recommendations.

This chapter outlines the research methods in a simple and clear way. First, it explains why certain methods were chosen. Then, it describes how participants were selected and how their data were kept safe. After that, it explains how the data were analysed and how the results were found. Finally, it discusses the ethical steps taken to protect the participants' rights and privacy.

The main goal of this chapter is to make the research process easy to understand and to show that every decision had a clear reason and purpose.

3.2 Research Philosophy and Approach:

This study is based on a positivist research philosophy. In simple terms, positivism means focusing on facts that can be measured, observed, and tested. It avoids personal opinions or emotions, and instead uses reliable information to find answers (Park, Konge & Artino, 2020).

According to Saunders, Lewis and Thornhill (2023), positivist research uses a method called the hypothetico-deductive method. This means starting with theories from books or laws and then testing them using real-world data. That is what this research did. First, it studied the legal documents and regulatory procedures in Ireland and Bolivia. Then, it gathered information from professionals to compare the official process with what actually happens.

The study also followed a deductive approach. This means it began with general ideas about the regulatory process and then focused on specific situations in Bolivia. The aim was to see if what is written in the law is really happening in practice.

In addition, the study used a comparative strategy. It compared two systems, one in Ireland and one in Bolivia, to understand their differences and similarities. This strategy helped identify areas where Bolivia could improve its regulatory process. A comparative

strategy is very useful when studying how different countries manage the same issue (Saunders, Lewis & Thornhill, 2023).

To support this comparison, the study used a mixed-method design. It collected:

- **Quantitative data:** Timelines, yes/no answers, and statistics.
- **Qualitative data:** Personal experiences, opinions, and suggestions.

As explained in Business Research Methodology (n.d.), positivism can include both types of data as long as the results are analysed logically and clearly.

In conclusion, this research followed a positivist philosophy, a deductive approach, and a comparative strategy. It focused on facts, tested existing knowledge, and compared real-life systems to find useful results.

3.3 Research Design:

This study used a mixed-methods research design. This means it combined quantitative data (like timelines or approval rates) and qualitative data (like opinions and challenges). The reason for using both is simple: numbers alone are not enough to understand a complex system. Real-life experiences from professionals are also important.

Molina-Azorín (2016) explains that mixed methods are ideal for complex topics, as they allow researchers to see the issue from different angles. In this case, quantitative data helped show how long approvals usually take, while qualitative data revealed common problems and improvement ideas.

The data were collected using an online survey. The survey was designed in English and shared with professionals in Bolivia who have experience working with AGEMED. The

language was kept simple and professional because many participants are used to English in their daily work.

The survey had three types of questions:

- **Quantitative questions:** for example, *"How long does the process take?"* or *"How often is bioequivalence required?"*
- **Qualitative questions:** for example, *"What are the biggest challenges with AGEMED?"*
- **Open-ended questions:** to allow extra comments or suggestions.

This design allowed the collection of both structured information and personal opinions. According to Saunders, Lewis and Thornhill (2023), combining these two types of data helps create a more complete understanding of a topic.

The online format also made it easier for professionals in different parts of Bolivia to participate. They could respond in their own time and remain anonymous. This was very important for a study like this.

Following the positivist philosophy, this design focused on collecting measurable data while also listening to the personal experiences of professionals. This balance helped provide a fuller picture of the regulatory process in Bolivia.

3.4 Target Participants:

The participants in this study were carefully selected Bolivian pharmaceutical professionals who work directly with the country's medicine approval system. They were chosen because of their knowledge and experience.

Participants had to meet three criteria:

- Have direct experience with AGEMED's registration or renewal process for generics.
- Work in areas such as regulatory affairs, quality control, or document compliance.
- Be able to understand and respond in English.

To find the right people, the study used purposive sampling. This means participants were selected on purpose because they had the exact experience needed (Saunders, Lewis & Thornhill, 2023). After the first group completed the survey, they were asked to share it with others who also fit the criteria. This is called the snowball method (Naderifar, Goli & Ghaljaie, 2017).

The goal was to get between 30 and 50 responses. This may seem small, but it is appropriate for a specialised group like this. Also, in qualitative research, useful insights often appear with just 15 to 20 participants (Creswell & Creswell, 2018). The selected professionals offered valuable views on AGEMED's regulatory practices.

3.5 Data Collection Methods:

The main tool used to collect information was an online survey created with Microsoft Forms. It included an introduction and consent section, so participants could understand the purpose and agree to take part.

There were 19 questions, divided into four sections:

1. Professional background.
2. AGEMED's approval process.
3. Comparison with HPRA/EMA.
4. Final reflections and improvement ideas.

The survey was written in English, using clear and respectful language. It included both:

- **Closed questions:** for example, yes/no or multiple choice.
- **Open questions:** where participants could write their thoughts.

The structure followed Creswell and Creswell's (2018) best practices. It was designed to collect both facts and personal views. Molina-Azorín (2016) supports this kind of design, especially for complex topics.

Online delivery made it easier for professionals to respond at their convenience. It also protected their privacy, encouraging honest feedback.

3.6 Data Analysis:

The survey responses were analysed using two techniques:

- **Quantitative data:** was reviewed using basic statistics like counts and percentages. This helped identify patterns in approval timelines or digital tool usage (Creswell & Creswell, 2018).
- **Qualitative data:** was studied using thematic analysis. This method looks for common ideas, repeated issues, or useful suggestions (Saunders, Lewis & Thornhill, 2023).

By using both methods, the study provided a more complete view. The numbers helped measure trends, while the words helped explain them. This approach matched the mixed-method design and helped achieve more trustworthy results (Molina-Azorín, 2016).

3.7 Justification of Methodology:

The mixed-methods approach was chosen because it allowed the research to explore both measurable data and personal experiences. On one side, the numbers showed how long approvals take or how often problems occur. On the other side, open-ended responses gave deeper insights into what professionals feel and think.

Using a survey was practical and safe. It allowed professionals in Bolivia to participate easily, even from different cities. It also gave them the comfort of answering anonymously, which is important when discussing sensitive systems (Creswell & Creswell, 2018).

Since the study compares two different countries, combining facts and real experiences helped to give a stronger and more balanced result (Molina-Azorín, 2016; Saunders, Lewis & Thornhill, 2023).

3.8 Conceptual Framework and Theories:

This research is based on key concepts that help understand how generic medicines are approved and renewed. The main focus is on generic paracetamol 500 mg tablets.

Key ideas include:

- Marketing authorisation.
- Generic medicine regulations.
- Bioequivalence.
- Good Manufacturing Practice (GMP).
- Regulatory efficiency.
- Use of digital platforms.

These ideas helped build a structure to compare Ireland and Bolivia. In Ireland, HPRA handles the process. In Bolivia, it is AGEMED.

The study followed international standards like European Directive 2001/83/EC and ICH Q7 (ICH, 2000), even though it did not use a specific theory. These documents show high standards for medicine approval.

Bioequivalence is especially important. In Europe, it is required (EMA, 2010; HPRA, 2025a). In Bolivia, it is not (AGEMED, 2005). This raises questions about safety and international alignment.

The study also looked at Bolivia's digital tool MISA (AGEMED, 2025), which is still new and not fully efficient. The goal was to see how technology can improve the system.

This framework supported a clear comparison, focused on practical steps and regulatory standards (WHO, 2016; EMA, 2025).

3.9 Ethical Considerations:

The research followed strict ethical standards. The survey was completely anonymous. No personal details were collected. Participants gave informed consent by clicking *"Yes"* to confirm they wanted to join.

Participation was voluntary, and no one was pressured. The questions were respectful and did not ask for sensitive information.

All data were stored safely on a password-protected computer and in a secure cloud system. Only the researcher had access. The data will be deleted two years after the research is completed.

Because the study involved minimal risk and followed all ethical guidelines, formal ethics committee approval was not required. However, to ensure transparency and protect participants, an Ethics Application & Declaration Form was completed and signed by the research supervisor on 24 June 2025. This step helped confirm that the research process respected ethical standards from the beginning. For more details, the signed form is available in Appendix E.

3.10 Materials Used:

The only tool used in the research was a short online survey in Microsoft Form. The full questionnaire is included in Appendix F, with the introduction and consent form.

The survey was designed to collect both quantitative and qualitative data. It included yes/no, multiple choice, and open-ended questions.

No interviews, video, or audio recordings were used. The survey was chosen because it was simple, clear, and respectful for participants.

3.11 Timeline and Implementation:

The research followed these steps:

- Survey design and testing (Microsoft Forms).
- Supervisor approval (24 June 2025).
- Inviting participants (LinkedIn, WhatsApp, email).
- Data collection (27 June to 27 July 2025).
- Data analysis (Microsoft Excel and Word).
- Writing and reporting (results in Chapter 4).

Every step was carefully planned and followed ethical standards. This helped ensure good quality and trustworthy results.

3.12 Conclusion:

This methodology chapter explained how the research was designed and carried out to answer the main question:

How do Ireland and Bolivia differ in their regulatory frameworks for approving and renewing generic paracetamol 500 mg tablets imported from the United States?

A respectful and organised process was used, including both open and closed survey questions. The study collected facts and real experiences from professionals in Bolivia and supported these findings with official documents (AGEMED, 2005; HPRA, 2025a).

Using mixed methods helped understand both what the laws say and what happens in practice, especially in areas like bioequivalence, GMP, and digital tools (EMA, 2010; WHO, 2016; HPRA, 2025b). International standards were used to guide the comparison and show where improvements are needed (European Parliament and Council of the European Union, 2001; ICH, 2000).

The research steps, from planning to data analysis, were completed with care, focusing on real knowledge and ethical values (Creswell & Creswell, 2018). By combining professional feedback and official regulations, the study offers practical ideas to improve the regulatory system in Bolivia.

The next chapter presents the results and connects them with the literature.

CHAPTER 4: FINDINGS AND ANALYSIS

4.1 Introduction:

This chapter presents the results of a survey completed by pharmaceutical professionals in Bolivia. The goal was to understand what is really happening in the approval and renewal process of generic medicines under AGEMED, based on the real-life experiences of people working directly in this area.

The survey gathered both quantitative data (such as how long approvals usually take or whether bioequivalence studies are required) and qualitative feedback (including professional opinions, suggestions for improvement, and challenges in the process).

The main aim of this chapter is to compare what the laws and official documents say with what professionals experience in practice. Then, these findings are linked back to the literature review from Chapter 2, to explore how Bolivia's regulatory system could be improved by learning from international best practices.

A total of 46 people answered the survey, but only 45 participants gave their consent to take part in the study. One person was excluded because they selected "No" in the consent question. Some survey questions had fewer responses because participants could skip questions or select more than one answer, depending on the type of question.

The next sections present a full analysis of the data, using graphs, tables, and quotes to explain the results. The chapter ends with a summary of conclusions that will help guide the final recommendations in Chapter 5.

4.1.1 Ethical Considerations and Participant Consent:

Before starting the survey, participants were informed about the purpose of the study, their rights, and data privacy. They were asked to give their voluntary informed consent to take part.

Out of 46 total responses, one participant selected "No" when asked to give consent. As a result, that answer was excluded from the analysis, and only 45 valid responses were

included in this chapter. Figure 3 and Table 2 show the final number of valid participants included in the study.

This step followed the ethical principles described by Creswell and Creswell (2018), which recommend excluding any data collected without consent.

Consent Given?	Participants' Responses
Yes (included)	45
No (excluded)	1
Total Responses	46

Table 2: *Consent to participate in the survey.*

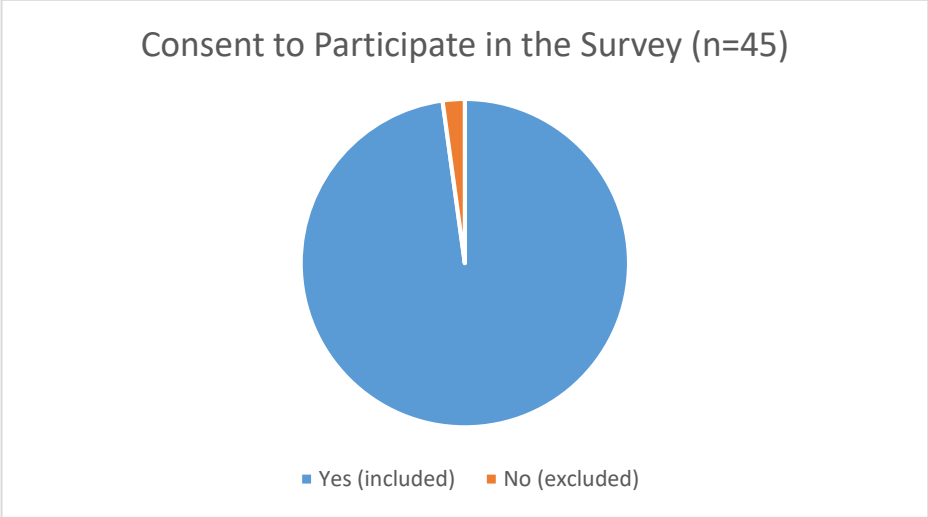

Figure 3: *Consent to participate in the study.*

4.1.2 Participants' Roles in the Regulatory Process:

The survey was completed by 45 professionals involved in the registration of generic medicines. Since participants could select more than one role**,** the total number of role selections (54) is higher than the number of respondents.

As shown in Figure 4 and Table 3**,** most participants (26 responses) said they work on preparing or submitting applications for marketing authorisation. Other common roles include compliance and documentation support (15 responses), and regulatory review (5). A few participants work in quality assurance (3) or selected "Other" (5).

Role	Responses
Preparing or submitting applications for marketing authorisation	26
Supporting companies with compliance or documentation	15
Regulatory reviewer or evaluator (e.g., AGEMED staff)	5
Quality assurance/quality control	3
Other	5

Table 3*: Roles of Participants in the generic medicines regulatory process (Multiple answers allowed).*

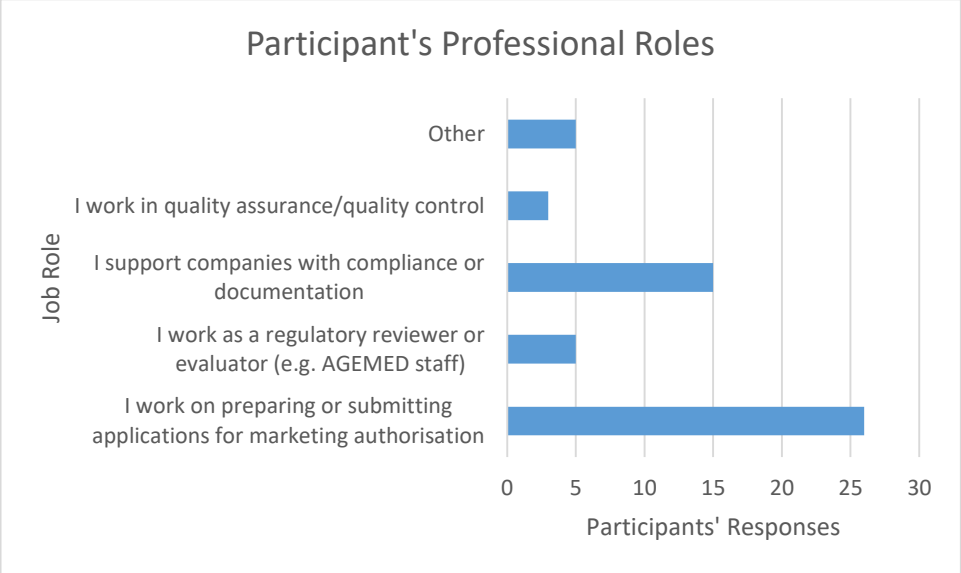

Figure 4: *Roles of participants in the regulatory process for generic medicines in Bolivia.*

4.1.3 <u>Years of Experience of Participants</u>:

The largest group of participants (38%) had 1 to 3 years of experience in regulatory work. This includes areas such as marketing authorisation, compliance, and pharmaceutical registration.

Around 24% of participants had 4 to 6 years, and 18% had 7 to 10 years. Only a few professionals (13%) had more than 10 years of experience, while 3 participants (7%) had less than 1 year.

This means the majority of responses came from professionals with a good amount of practical knowledge, especially in early and mid-career stages. Their opinions reflect real, hands-on experiences in dealing with AGEMED procedures. This adds strength and trust to the results *(see Table 4 and Figure 5).*

According to Creswell & Creswell (2018), a specialised group like this can provide valuable insights even in small samples.

Experience Level	Number of Participants	Percentage (%)
Less than 1 year	3	6.7%
1–3 years	17	37.8%
4–6 years	11	24.4%
7–10 years	8	17.8%
More than 10 years	6	13.3%
Total (n = 45)		100%

Table 4: *Expirience Level of Participants (n = 45).*

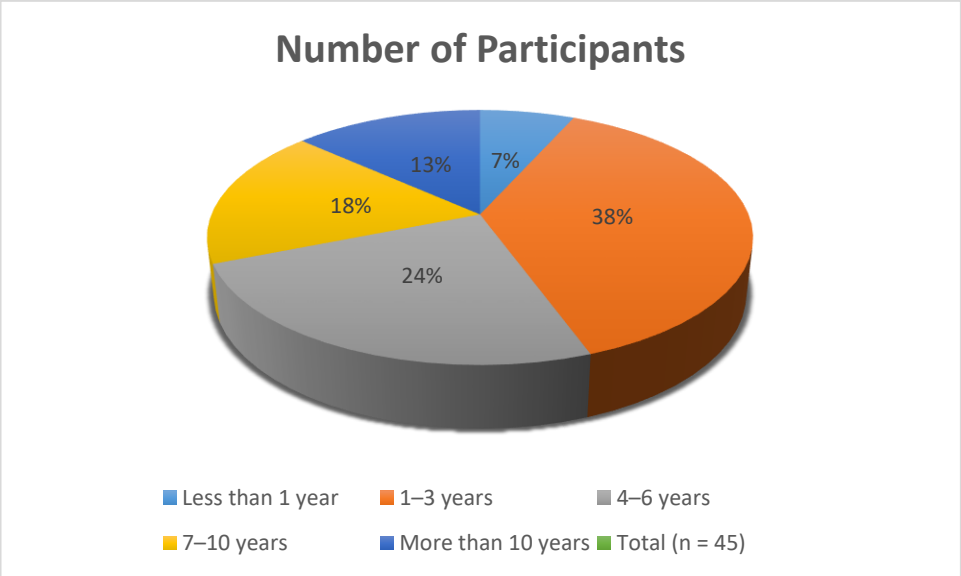

Figure 5: *Years of Experience in Regulatory Work (n = 45).*

4.1.4 Overview of Survey Questions and Where They Are Analysed:

Table 5 below shows the survey questions, their type (quantitative or qualitative), and where they are analysed in this chapter. This helps to ensure that all questions were considered.

Survey Question Topic	Type	Section
Consent to participate	Quantitative	4.1.1
Participant roles	Quantitative	4.1.2
Years of experience	Quantitative	4.1.3
Time taken for approval	Quantitative	4.2.1
Bioequivalence requirement	Quantitative	4.2.2
Regulatory clarity	Quantitative	4.2.3
Experience with international authorities	Quantitative	4.2.4
Effectiveness of digital systems	Quantitative	4.2.5
Opinion on aligning AGEMED with EU standards	Quantitative	4.2.6
Confidence in AGEMED vs HPRA/EMA	Quantitative	4.2.7
Challenges when working with AGEMED	Qualitative	4.3.1
Suggestions to improve digital/process systems	Qualitative	4.3.2

Suggestions to improve scientific/regulatory requirements	Qualitative	4.3.3
Comparison feedback from those with EU experience	Qualitative	4.3.4

Table 5: *Survey Questions, Data Type, and Location of Analysis in Chapter 4.*

4.2 Quantitative Data: Measurable Results:

4.2.1 Time to Approval:

Participants were asked how long it usually takes for AGEMED to approve a generic medicine application. The most common response was "3–6 months", selected by 26 out of 45 participants (58%). This was followed by "7–12 months" with 14 responses (31%). Only two participants (4%) said it takes less than 3 months, and another two (4%) said it takes more than one year. One participant (2%) was unsure *(see Table 6 and Figure 6).*

These results show that while many professionals experience approvals within 6 months, a large number still face delays up to 12 months. This suggests that Bolivia's approval process is inconsistent and often longer than expected, depending on the case.

These results reveal a gap between Bolivia's legal approval timeframe and what happens in real life. According to AGEMED's own Manual for Sanitary Registration (2005), the approval process should take around 90 working days (around 4.5 calendar months). However, 31% of participants said it takes up to a year, and 4% said even longer.

This delay is not unusual in emerging markets. PAHO (2022) explains that many national regulatory authorities in Latin America face challenges like manual systems, lack of digital tools, and limited staff, all of which contribute to slower review times.

Time Range for AGEMED to Approve a Generic Medicine	Participants Responses
Less than 3 months	2

3–6 months	26
7–12 months	14
More than 1 year	2
I don't know / Not sure	1

Table 6: *Time Taken for AGEMED to Approve Generic Medicines (n = 45).*

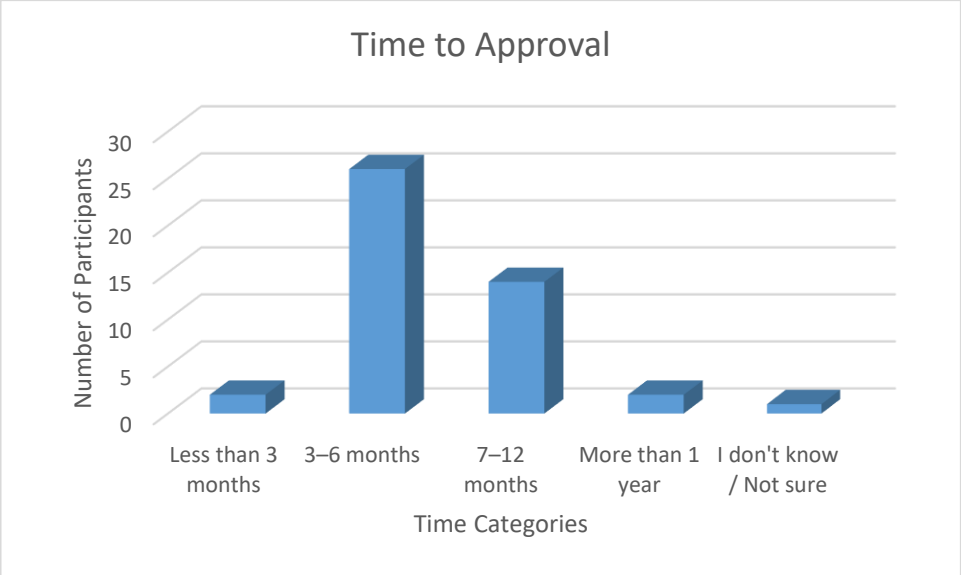

Figure 6: *Time Taken for Marketing Authorisation Approval by AGEMED (n = 45).*

4.2.2 <u>Bioequivalence Requirements</u>:

The survey results reveal that bioequivalence is not consistently required **for** generic medicines in Bolivia. When asked about their experience with AGEMED:

- 40% of respondents (n=18) said bioequivalence is never required
- 24% (n=11) said it is rarely required
- Only 11% (n=5) said always
- 13% (n=6) said sometimes
- 11% (n=5) were not sure

These responses show that 64% believe bioequivalence is rarely or never required**,** suggesting a lack of standardisation and regulatory clarity. This finding is supported by AGEMED's official Manual for Sanitary Registration (2005), which does not clearly include bioequivalence as a mandatory requirement for generic drug approval *(see Table 7 and Figure 7).*

In contrast, the Health Products Regulatory Authority (HPRA**)** in Ireland, which follows European Medicines Agency (EMA**)** regulations, requires bioequivalence studies for all generic medicines (European Medicines Agency, 2010; HPRA, 2025a). This shows a major difference between AGEMED and EU regulatory standards.

This inconsistency may lead to confusion among applicants and reduce trust in the system. As Badjatya et al. (2022) note, emerging-market regulators often show variability in how they apply key scientific standards in submissions, especially for those involved in international trade, and may slow down the registration process due to unclear expectations.

Bioequivalence Requirement	Number of Participants (n)	Percentage (%)
Always	5	11.1%
Sometimes	6	13.3%
Rarely	11	24.4%
Never	18	40.0%
I'm not sure	5	11.1%
Total	**45**	**100%**

Table 7: *AGEMED's Requirement of Bioequivalence Studies for Generic Medicines.*

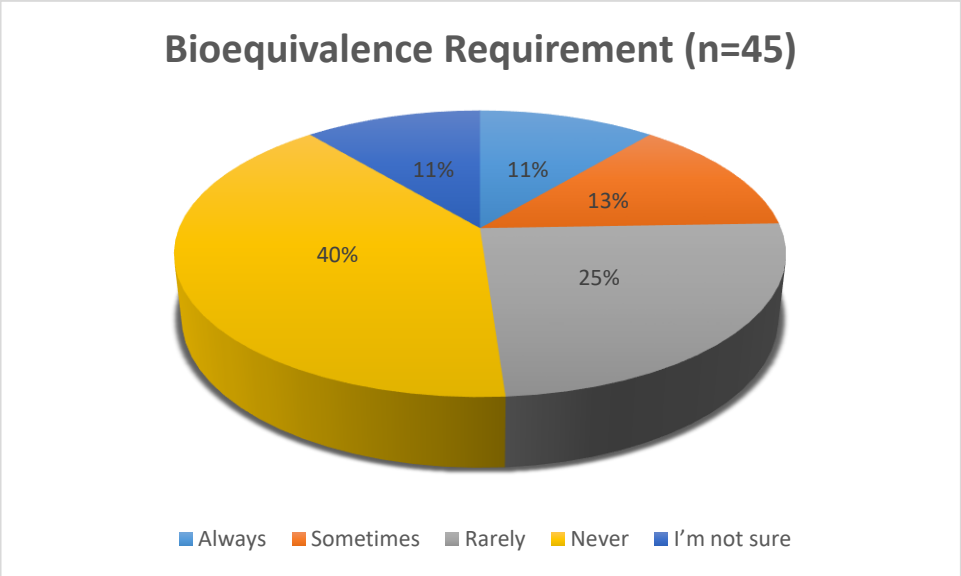

***Figure 7**: Responses on AGEMED's Requirement of Bioequivalence for Generic Medicines.*

4.2.3 Perceptions of Regulatory Clarity: Is AGEMED Easy to Understand?

Participants were asked to rate how clear and transparent AGEMED's regulatory process is for generic medicine approvals, using a scale from 1 (Very unclear) to 5 (Very clear). The average rating was 3.04**,** showing that most people see the process as moderately clear *(see Table 8 and Figure 8).*

- Most answers were level 3 (60%)**,** which suggests that the regulatory system is neither fully clear nor fully unclear.
- Only 2 people (4%) said it is very clear, and none said it is very unclear.
- A group of 9 participants (20%) gave a low rating of 2, showing some dissatisfaction or difficulty understanding the process**.**

This result suggests that the system could be improved to make the rules and steps easier to follow and more predictable**,** especially for generic medicine registration.

According to AGEMED's own documents, like the *Manual for Sanitary Registration* (AGEMED, 2005) and *the Medicine Law* (AGEMED, 2000), the agency provides rules and laws, but these may not be easy to apply in real practice**.** Also, many of the documents

are long and technical**,** which may confuse smaller pharmaceutical companies or new applicants.

In comparison, the Health Products Regulatory Authority (HPRA) in Ireland follows EU standards, which require very detailed and clear regulatory guidance (HPRA, 2025b; European Commission, 2025a). These are supported by online tools and interactive guidance documents that help applicants at every step.

Therefore, the difference in clarity and transparency between AGEMED and HPRA may show a regulatory gap**.** AGEMED could increase transparency by publishing simplified guides, checklists, or timelines**,** similar to those used by HPRA and EMA.

Clarity Level	Description	Number of Responses (n)	Percentage (%)
1	Very unclear	0	0.0%
2	Unclear	9	20.0%
3	Neutral	27	60.0%
4	Clear	7	15.6%
5	Very clear	2	4.4%
Total		**45**	**100%**

Table 8: *Participant's Ratings of AGEMED's Regulatory Clarity (Scale: 1 = Very Unclear, 5 = Very Clear).*

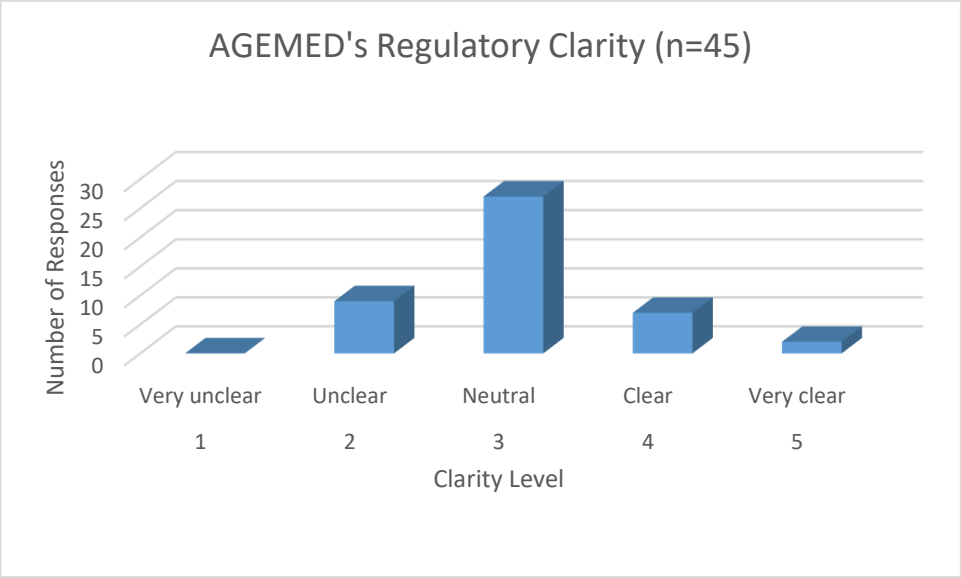

Figure 8: *Responses on How Clear AGEMED's Regulatory Process Is.*

4.2.4 Participants' Experience with Other Regulatory Authorities:

Almost half of the participants (48.9%) had experience or knowledge working with other regulatory authorities such as HPRA or EMA. This shows that many respondents were familiar with international standards, which may have influenced their views about AGEMED's system *(see Table 9 and Figure 9).*

Previous Experience with Other Authorities	Number of Participants (n)	Percentage (%)
Yes	22	48.9%
No	23	51.1%
Total	**45**	**100%**

Table 9: *Participants' Experience with Other Regulatory Authorities (e.g., HPRA or EMA).*

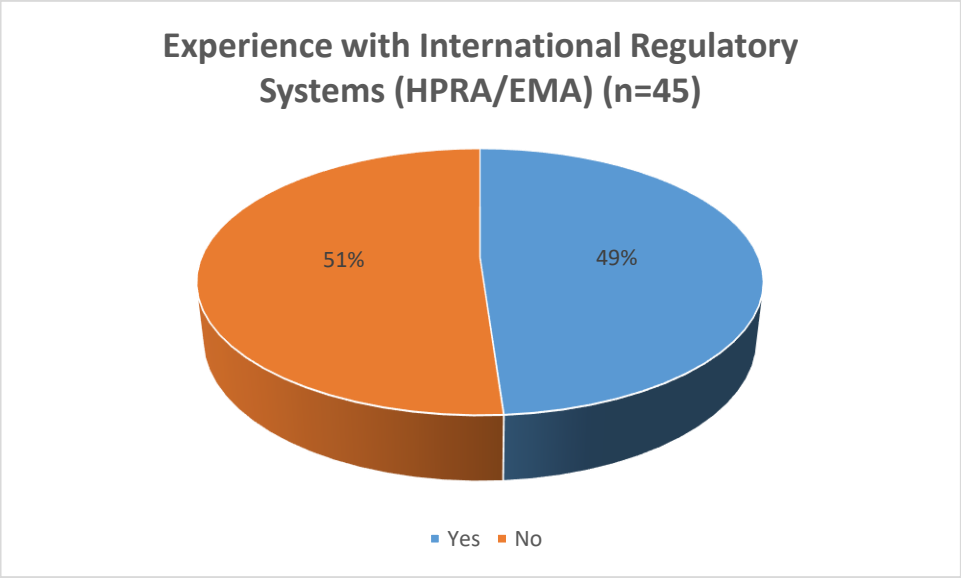

Figure 9: *Experience with International Regulatory Systems (HPRA/EMA).*

4.2.5 How Effective Are AGEMED's Digital Systems?

People were asked how well AGEMED's digital tools work, like online forms, document tracking, and communication. The average score was 2.87 out of 5, which indicates that most participants find the system to be moderately effective or needing improvement *(see Table 10 and Figure 10).*

Most answers were in the middle:

- 26 people chose Level 3,
- 13 chose Level 2,
- 5 chose Level 4,
- only 1 person gave the best score, Level 5,
- and no one gave the worst score (Level 1).

These results show that AGEMED's digital system is working, but many users don't feel satisfied. Maybe the website is hard to use, too slow, or communication is not clear. These things can make the process frustrating.

When we look at other regulators, like HPRA in Ireland or the EMA in Europe, we see more modern systems. For example, the HPRA has an easy-to-use website where companies can send documents, follow updates, and get help quickly (Health Products Regulatory Authority, 2025b). Also, Macdonald et al. (2021) explain that digital systems are now a key part of good regulation.

Rating Level	Description	Number of Responses
5	Very effective	1
4	Effective	5
3	Moderately effective	26
2	Not very effective	13
1	Not effective at all	0
	Average score	**2.87**

Table 10: *Perception of AGEMED's Digital Systems Effectiveness (Scale 1-5).*

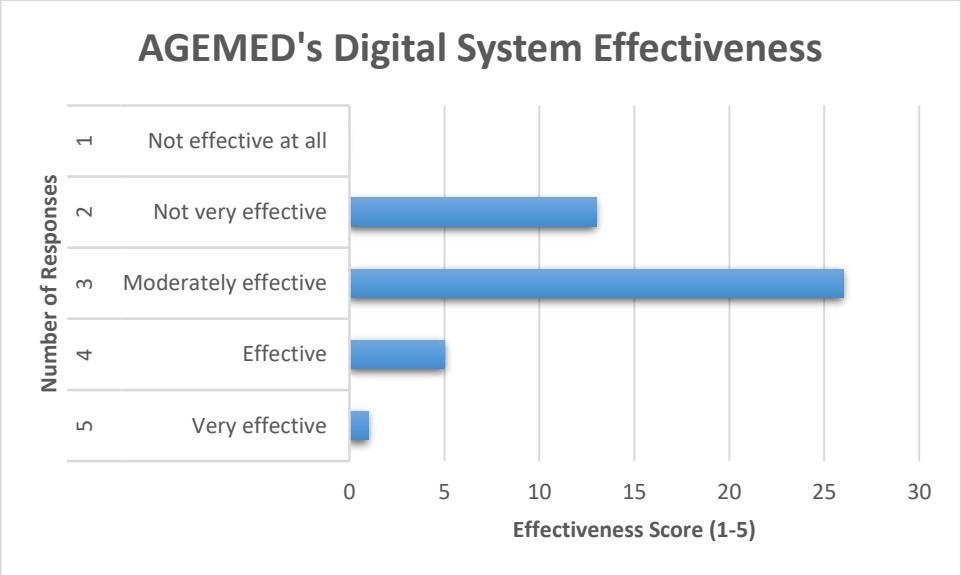

Figure 10: *Users' Ratings of AGEMED's Digital System.*

4.2.6 Support for Aligning AGEMED with EU Regulatory Standards:

In this question, participants were asked if they support changes in AGEMED's system to make it more similar to European Union (EU) standards.

- 42 people said Yes**,**
- 0 said No**,**
- 3 answered Maybe**.**

This strong support shows that people working with AGEMED want a better and more modern system, one that is more efficient, transparent, and faster, just like in Europe *(see Table 11 and Figure 11).*

At the moment, AGEMED follows rules like the Law of Medicines No. 1737 (AGEMED, 2000) and its Supreme Decree No. 25235 (AGEMED, 1998), which are good but a bit outdated. Also, some digital tools like MISA (AGEMED, 2025) help, but they still have room to improve.

In contrast, the EMA and the HPRA use clear, digital, and harmonized procedures, such as the Common Technical Document (CTD) format and strong pharmacovigilance rules (European Medicines Agency, 2021; European Commission, 2008; HPRA, 2025a). These help reduce delays and support public health.

These results show that users believe AGEMED would benefit from modernizing its system and aligning with international best practices**.**

Participants Opinion	Number of Responses
Yes	42
No	0

Maybe	3

Table 11: *Opinions on Aligning AGEMED's System with EU Standards.*

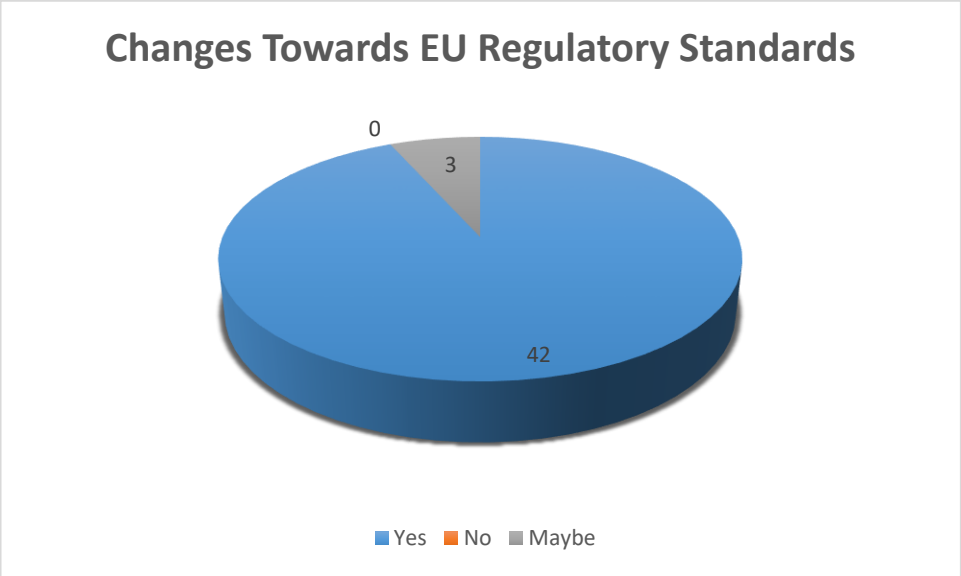

Figure 11: *Participants Support for Changes Towards EU Regulatory Standards.*

4.2.7 Confidence in AGEMED's Standards Compared to HPRA and EMA:

Participants were asked if they believe that AGEMED ensures the same level of medicine quality and safety as European authorities like the HPRA or EMA.

- 6 people said Yes,
- 25 people said No,
- 14 people were Not sure.

This response shows a low level of confidence in AGEMED's ability to match the quality and safety standards applied by European regulators *(see Table 12 and Figure 12).*

Although AGEMED has national laws and processes in place, like the Law of Medicines No. 1737 (AGEMED, 2000) and its Regulation, Supreme Decree No. 25235 (AGEMED, 1998), most of these were written many years ago and do not fully reflect today's international standards.

Meanwhile, both the HPRA and EMA operate under more current and detailed frameworks, such as:

- Directive 2001/83/EC for medicine authorization (European Parliament and Council, 2001),
- and EU Good Manufacturing Practice guidelines (European Commission, 2022).

The gap between AGEMED and these regulators may explain the perception difference. Even though AGEMED has introduced tools like MISA, which allows companies to submit their regulatory dossiers online (AGEMED, 2025), many professionals still feel uncertain about how well these tools support public health protection. This may be due to limited features, weak follow-up systems, or unclear communication within the platform.

This insight suggests that greater transparency, updated practices, and better alignment with EU standards could help AGEMED build more trust in the quality and safety of medicines in Bolivia.

Participant Belief	Number of Responses	Percentage (%)
Yes	6	13.3%
No	25	55.6%
Not sure	14	31.1%
Total	**45**	**100%**

Table 12: *Confidence in AGEMED's Quality and Safety Standards Compared to HPRA/EMA.*

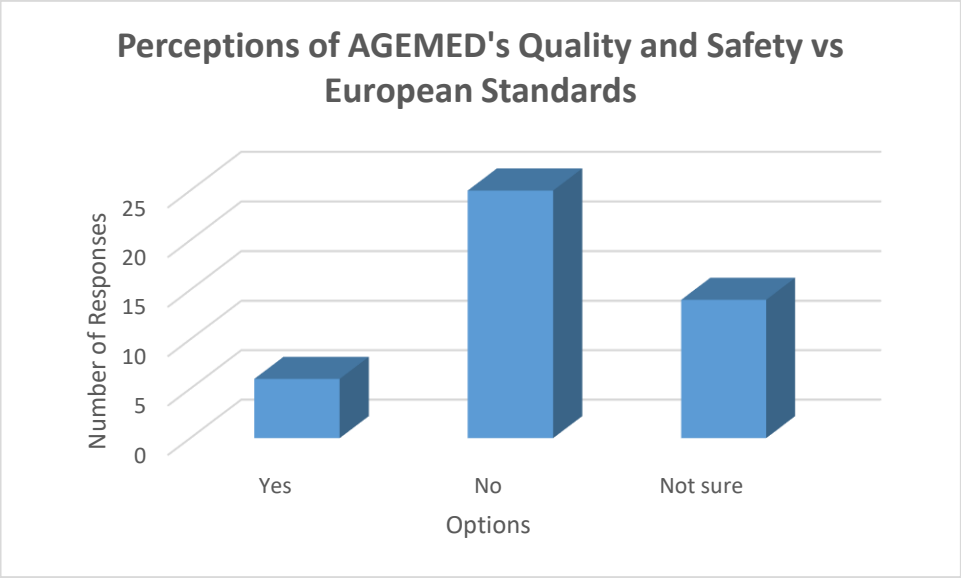

Figure 12: *Perceptions of AGEMED's Quality and Safety vs European Standards.*

4.3 Qualitative Data: Professional Experiences and Suggestions:

The following section highlights the views and suggestions of Bolivian professionals involved with AGEMED. These qualitative responses offer important context to understand the practical difficulties that may not be visible in numerical results alone.

4.3.1 Key Challenges Reported by Participants:

Participants provided detailed responses about the main problems they experience when working with AGEMED. After reviewing all 45 responses, the following eight main themes were identified. Each theme is supported with direct quotes from participants and includes the number of mentions (frequency). These results help to understand the most urgent issues in the regulatory process *(see Table 13 and Figure 13).*

A. Delays and Unclear Timelines (16 mentions).

Many participants said that the approval or renewal process takes too long. They also explained that it is difficult to know how long it will take, and there is no system to follow up the status.

Examples:

- *"The process takes too long."*
- *"Sometimes we wait more than 12 months."*
- *"The timeline is very unpredictable."*
- *"There is no tracking system."*

These responses suggest a lack of structured timelines and a need for better planning and communication in the approval process. According to AGEMED's Manual for Sanitary Registration (2005), the full registration process should be completed within approximately 90 working days, taking into account the technical evaluation, correction of observations, and final approval. The manual also states that if there are any deficiencies in the submitted documents or samples, the applicant should receive an official notification within 30 calendar days, and must correct the issues within the same period. However, many participants reported delays far beyond this timeframe, showing a clear gap between the official procedures and what happens in practice.

B. Inconsistent Criteria and Lack of Standardisation (11 mentions).

Participants highlighted that different reviewers from AGEMED give different feedback for similar cases. This creates confusion and extra work for applicants.

Examples:

- *"The different criteria of the evaluators make the process more difficult."*

- *"One reviewer says yes, another says no."*
- *"There is no consistency in observations."*

This shows that AGEMED needs to improve internal procedures to ensure all reviewers follow the same interpretation of the law (AGEMED, 1998).

C. Unnecessary or Repetitive Observations (10 mentions).

Some respondents felt that AGEMED makes repeated comments, even when requirements are already fulfilled. They said the observations sometimes do not follow the official law or are not justified.

Examples:

- *"We receive observations about documents that were already included."*
- *"Many observations are made without reading the file."*
- *"They make observations just to delay."*

This indicates that quality control in the review process is weak and needs improvement.

D. Outdated Regulations (6 mentions).

Participants pointed out that AGEMED uses very old rules, and these are not aligned with international standards.

Examples:

- *"Old regulations make the process slower."*
- *"The regulations don't include current best practices."*
- *"We are behind international systems."*

Several international sources (Deore & Patel, 2022) show that regular updates to regulations help reduce delays and improve transparency.

E. Manual and Bureaucratic Processes (6 mentions).

Several respondents said that many steps are still manual, including printing, scanning, and physical travel. This causes delays and increases costs.

Examples:

- *"Too much paperwork."*
- *"We have to resubmit everything again during renewal."*
- *"The process is very bureaucratic."*

This is especially problematic for those living outside La Paz, where AGEMED is located. A fully digital system is needed.

F. Poor Communication and Support (4 mentions).

Some participants said they felt lost during the process because AGEMED does not provide guidance or clear communication.

Examples:

- *"Poor communication from AGEMED."*
- *"There is no help desk."*
- *"You just guess."*

This shows that applicants need more support, such as a clear guide or training sessions (Creswell & Creswell, 2018).

G. Weak Legal and Technical Understanding (3 mentions).

A few participants said that some reviewers may not fully understand technical or legal documents. This affects the quality of decisions.

Examples:

- *"Some reviewers don't understand the technical documents."*
- *"They just look for reasons to reject."*

These responses highlight a need for ongoing staff training (Badjatya et al., 2022).

H. Renewal Process is a Duplicate Effort (3 mentions).

Applicants said that renewal requires them to submit all the same documents again, even when nothing has changed. This causes unnecessary delays.

Examples:

- *"We waste time resubmitting documents that haven't changed."*

- *"Renewals are a waste of time when the product is the same."*

This problem reflects the lack of a simplified renewal process (HPRA, 2025f).

Theme	Description	Frequency (Number of Participants)	Example Quote
A. Delays and Unclear Timelines	Long waiting times, no tracking, unpredictable process	16	"Sometimes we wait more than 12 months."
B. Inconsistent Criteria and Lack of Standardisation	Different reviewers apply different rules	11	"One reviewer says yes, another says no."
C. Unnecessary or Repetitive Observations	Repeated or unjustified feedback	10	"We receive observations for documents already included."
D. Outdated Regulations	Laws and rules not updated or aligned with international standards	6	"The regulations don't include current best practices."
E. Manual and Bureaucratic Processes	Need for paper-based steps, physical presence, duplication	6	"We have to resubmit everything again during renewal."
F. Poor Communication and Support	No clear help, no guidance	4	"You just guess."
G. Weak Legal and Technical Understanding	Lack of capacity or expertise in evaluation	3	"Some reviewers don't understand the technical documents."
H. Renewal Process is a Duplicate Effort	Submitting the same documents again causes delays	3	"Renewals are a waste of time when the product is the same."

Table 13: *Summary of Key Challenges Reported by Participants.*

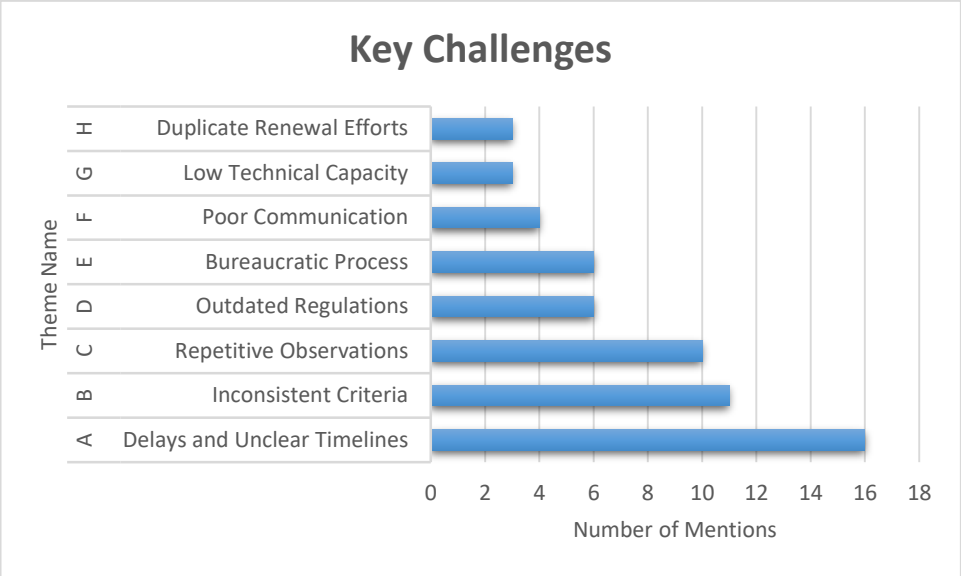

Figure 13: *Frequency of Key Challenges Faced by Applicants During Generic Medicine Registration and Renewal with AGEMED.*

Note: *The total number of mentions exceeds the number of participants (n = 45) because some participants reported multiple challenges in their responses. This highlights the complexity of the process and overlapping concerns shared by applicants.*

4.3.2 Suggestions to Improve the System:

The survey included 45 participants who shared their ideas to improve the system. Some participants gave more than one suggestion. Table 14 presents the main suggestions and the number of participants who mentioned each.

Suggestion to Improve	Number of Participants	Percentage (%) (of 45)
Improve response time	22	48.9%
Increase system reliability	18	40.0%
Add more user-friendly features	15	33.3%

Provide better training support	12	26.7%
Enhance data security	10	22.2%
Integrate with other systems	8	17.8%
Improve customer support	5	11.1%

Table 14: *Number of Participants suggesting improvements to the AGEMED's system (n = 45).*

Note: *Participants could give more than one suggestion, so percentages add up to more than 100%.*

Nearly half of the participants (48.9%) requested that the system's response time be improved because slow performance negatively affects their work. A significant number (40%) noted issues with system reliability, including frequent errors and crashes.

Around one-third (33.3%) suggested making the system more user-friendly, with easier navigation and clearer menus.

About 26.7% of participants wanted better training support, including tutorials or guides. Several participants specifically mentioned the need for improved training not only for AGEMED staff but for all users, to help them understand the system better and avoid mistakes. This training improvement was a common theme in the survey responses.

Other important suggestions included enhanced data security (22.2%) and integration with other systems (17.8%) to improve workflow efficiency.

Finally, 11.1% of participants mentioned the need for improved customer support to get faster help when problems occur.

Figure 14 illustrates these suggestions visually, showing the percentage distribution of participant responses for each improvement category.

These ideas reflect improvements already used by regulatory bodies like the HPRA's digital system in Ireland and the EMA in the European Union. These systems provide clear support for companies on what to do and when (HPRA, 2025a; HPRA, 2025b).

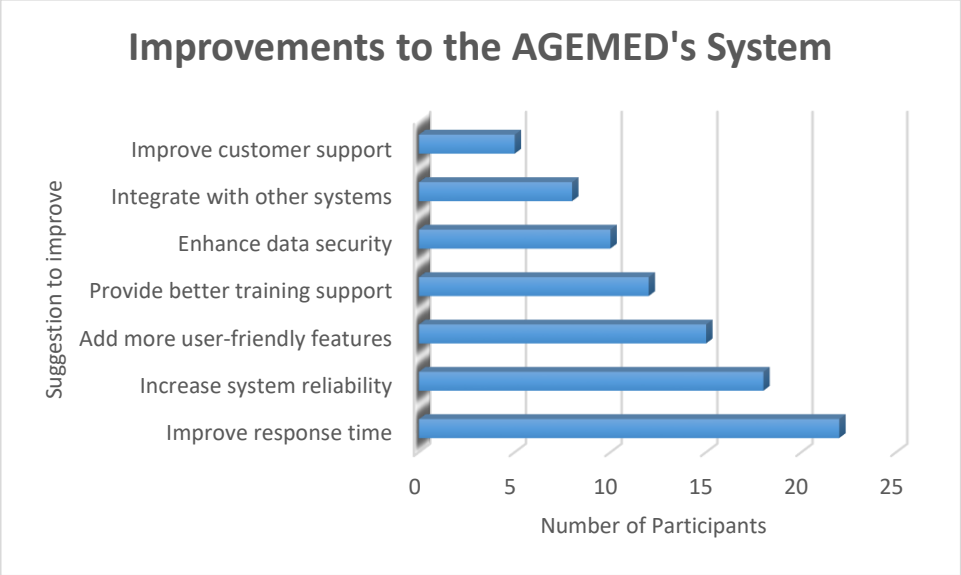

Figure 14: *Improvements to the AGEMED's system.*

4.3.3 <u>Suggestions for Scientific and Regulatory Updates</u>:

In addition to digital and procedural improvements, many participants highlighted the need to modernise AGEMED's scientific and regulatory standards. Their comments suggest that the system must evolve to ensure the safety, quality, and effectiveness of medicines in Bolivia. The main suggestions are summarised below in Table 15 and visually presented in Figure 15.

A. Make Bioequivalence Studies Mandatory for Generics.

Several participants expressed concern that bioequivalence studies are not consistently required for generic medicines in Bolivia. This contrasts with the EMA and HPRA, where bioequivalence is a basic requirement for generic approval (European Medicines Agency, 2010; HPRA, 2025a).

- *“AGEMED doesn't ask exactly for bioequivalence studies. In all the years I have been working in the area, I've never seen that.”*
- *“No, because AGEMED doesn't require bioequivalence studies in all cases, and the evaluation of dossiers is not always detailed.”*

This feedback shows a demand for stronger scientific validation of generic products to meet international standards (WHO, 2016; FDA, 2021a; EMA, 2010).

B. Update Regulations Regularly.

Several participants noted that AGEMED’s legal framework is outdated, which may slow down innovation and introduce inconsistency.

- *“In EMA or HPRA, regulations are updated regularly. AGEMED still uses rules from over 10 years ago.”*
- *“We are stuck in a system made 15 years ago. We need to move forward.”*

Updating national regulations regularly, as done in Europe, would improve transparency and regulatory certainty (European Parliament and Council, 2001; AGEMED, 2000; AGEMED, 1998).

C. Adopt International Guidelines (e.g., EU, WHO).

Some participants suggested adopting or aligning with well-established international regulatory frameworks such as EU directives or WHO standards.

- *"An adjustment to European Union (EU) regulatory standards in the AGEMED system could be beneficial."*
- *"Promoting regional harmonization and adopting digital submission platforms would greatly improve the approval process."*

This harmonisation could reduce delays, ensure quality, and facilitate global recognition of Bolivian products (European Commission, 2025a; WHO, 2016).

D. Strengthen the Pharmacovigilance System.

Participants also identified weaknesses in AGEMED's ability to monitor medicine safety after approval.

- *"There is not a good routine post-market surveillance."*
- *"AGEMED needs a strong pharmacovigilance system."*

Improving this area aligns with international requirements for medicine safety and lifecycle monitoring (WHO, 2025; European Parliament and Council, 2010a).

E. Improve Quality Control and Inspection Capacity.

Lastly, some respondents questioned the robustness of AGEMED's quality control and inspection processes.

- *"Even though the documents are reviewed, the quality control systems are not modern or connected."*

- *"Because it doesn't have inspections or audits that control its work, its standards are not consistent."*

This indicates the need for a more modern and consistent inspection system, with better tracking and control (European Commission, 2021; AGEMED, 2025).

Suggestion Type	Number of Mentions	% of Participants
Require bioequivalence studies for generics	6	13.3%
Update outdated regulations	5	11.1%
Adopt EU or WHO international standards	4	8.9%
Improve pharmacovigilance and post-market control	3	6.7%
Enhance quality control and inspection procedures	2	4.4%

Table 15: *Suggestions for Scientific and Regulatory Updates from Participants (n = 45).*

Note*: Some participants provided more than one suggestion. Percentages reflect total mentions relative to 45 participants.*

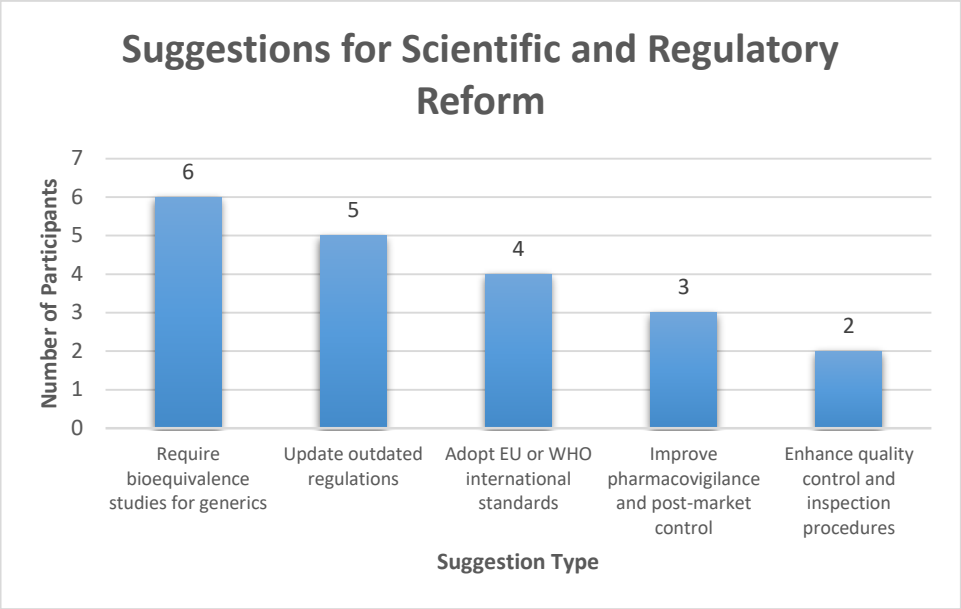

Figure 15: *Scientific and Regulatory Improvements Suggested by Participants (n = 45).*

4.3.4 Reflections from Participants with International Experience:

A total of 22 participants said they had worked with or reviewed systems from other regulatory authorities such as HPRA (Ireland) or EMA (European Union). Out of those, 16 participants shared open-ended reflections comparing AGEMED with international systems.

Their feedback revealed three key themes, as presented in Table 16 and Figure 16.

A. Clearer Processes and Documents.

Participants mentioned that EU systems are more structured, transparent, and organised. They felt it was easier to know what steps to follow and what was expected.

- *"With HPRA and EMA, if there is any observation, it's explained clearly with reference to the regulation."*

- *"EMA gives legal references. AGEMED just says 'incorrect' without a clear explanation."*

B. Faster and Simpler Procedures.

Many highlighted that international systems are faster, especially for renewals. They also noted that the procedures involve fewer unnecessary steps, saving time and resources.

- *"Renewal processes are easier and faster."*
- *"In other countries, renewal is simpler and faster."*

C. Better Digital Platforms and Tools.

Several participants praised the digital submission systems, such as CTD format and online tracking. These tools improve access and reduce printing or in-person requirements.

- *"The use of a full electronic system."*
- *"Not need to go to the office and print 100 pages."*
- *"EMA has a single portal for everything."*

These experiences support the academic literature that highlights the benefits of digitalization, harmonisation, and transparency in European regulatory systems (Deore & Patel, 2022; EMA, 2023).

Key Observations	Number of Mentions

Clearer processes and feedback	6
Faster and simpler procedures	5
Better digital platforms/tools	5

Table 16: *Key Observations Based on International Experience (HPRA/EMA).*

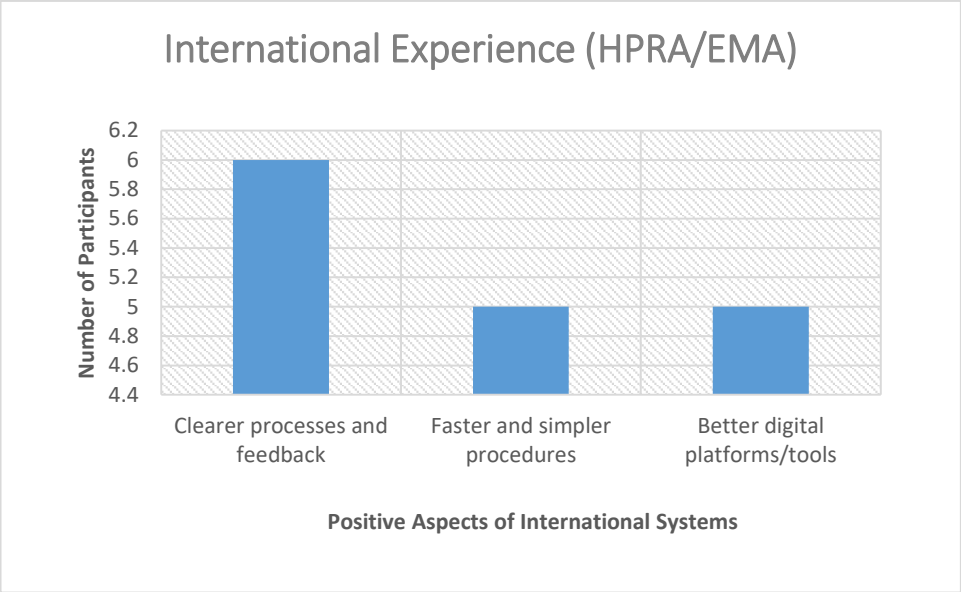

Figure 16: *Positive Aspects of EMA/HPRA According to Participants.*

4.4 Comparison with Literature Review:

This section compares the main findings from the survey with AGEMED's official regulations and international best practices. Table 17 below provides a clear summary of differences between the real experiences of professionals, AGEMED's official rules, and the systems used by HPRA and EMA. The written analysis that follows explains each point in more detail.

Key Area	What Participants Experienced with AGEMED	What AGEMED Officially Says	What HPRA/EMA Do
Approval Time	Many said it takes 6 to 12 months or	The Manual (AGEMED, 2005)	HPRA/EMA have clear timelines and

	more. Some even said it is unpredictable and slow.	says approval should take about 90 working days (≈4.5 months).	often faster processing. Renewals are simpler.
Bioequivalence Studies	64% said bioequivalence is rarely or never required. Some said it's unclear or not asked at all.	The AGEMED Manual (2005) does not clearly require bioequivalence for generics.	HPRA/EMA always require bioequivalence to prove safety and effectiveness.
Clarity of Process	Rated 3.04 out of 5. Participants said rules are not always clear, and observations are sometimes confusing.	AGEMED provides laws and manuals, but they are long and use technical language.	HPRA/EMA provide clear, step-by-step guidance with online tools.
Reviewer Consistency	Participants said reviewers give different feedback for the same case.	No formal mention of internal consistency practices.	HPRA/EMA use harmonised guidelines and standardised review systems.
Digital Tools (MISA)	Rated 2.87 out of 5. Most said the system works, but is slow and not user-friendly.	AGEMED has MISA for online submission but still uses many manual steps.	HPRA/EMA offer fast, user-friendly platforms to submit, track, and get support online.
Communication & Support	Some said there's poor communication and no help desk.	No formal system for support or applicant training is mentioned.	HPRA/EMA provide guidance documents, contact points, and training materials.
Pharmacovigilance	Some said there is little or no routine safety monitoring after approval.	AGEMED has a guide (2012), but it is limited and not regularly used.	EMA and HPRA have strong pharmacovigilance systems with reporting tools.
Renewal Process	Seen as repetitive. Applicants must re-submit unchanged documents.	No simplified renewal system. Same process as first-time registration.	HPRA has a short, simplified renewal process for unchanged products.

Table 17: *Comparison Between AGEMED Practice, Official Regulations, and International Standards (HPRA/EMA).*

- **Approval Time.**

Most participants said that AGEMED's approval process is very slow and unpredictable. Some applicants wait more than 12 months for a decision, even though the official time limit is about 90 working days (AGEMED, 2005). This delay shows that the system is not working as intended. In comparison, HPRA and EMA usually follow strict timelines,

and they have separate, simpler procedures for renewals, which helps speed up the process (HPRA, 2025f; EMA, 2021).

- **Bioequivalence Studies.**

The survey revealed that bioequivalence studies are often not required by AGEMED. In fact, 64% of participants said these studies are rarely or never requested. This matches the AGEMED manual (2005), which does not clearly state that bioequivalence is mandatory. However, this goes against international standards. Both the EMA and HPRA require bioequivalence for all generic medicines to prove that they are as safe and effective as the original drug (EMA, 2010; HPRA, 2025a; HPRA, 2025f; WHO, 2016).

- **Clarity of the Process.**

Participants gave an average score of 3.04 out of 5 when asked if AGEMED's process is clear. This shows that many users are unsure about what is expected. AGEMED does have laws and manuals, but these are long and written in complex language. In contrast, HPRA and EMA provide easy-to-follow guides, checklists, and online tools to help applicants understand each step (European Commission, 2025a; HPRA, 2025a; HPRA, 2025b).

- **Consistency of Reviewers.**

Another issue reported by participants was the lack of consistency among AGEMED reviewers. Some professionals said they received different feedback from different evaluators, even for the same type of product. This shows a lack of standardisation. International agencies like HPRA and EMA use harmonised rules and shared guidelines, which help ensure fair and consistent evaluations (Badjatya et al., 2022).

- **Digital Systems.**

Although AGEMED has a digital tool called MISA, participants rated its effectiveness as low (2.87 out of 5). Many said it was slow, not user-friendly, or lacked helpful features. Also, some parts of the process are still done manually. On the other hand, the HPRA and EMA offer complete online systems where companies can submit files, track progress, and receive updates in real time. These systems improve transparency and reduce waiting time (Macdonald et al., 2021).

- **Communication and Support.**

Several participants mentioned that AGEMED does not provide good communication or support. There is no help desk or clear way to ask questions. Some said they felt lost during the process. This is different from HPRA and EMA, which offer support materials, training, and direct contact points to help applicants (Creswell & Creswell, 2018; HPRA, 2025b).

- **Pharmacovigilance.**

Some respondents said that AGEMED's post-market surveillance is weak or almost non-existent. AGEMED does have a pharmacovigilance guide (2012), but it is not actively used. In contrast, EMA and HPRA follow strong pharmacovigilance systems that monitor medicine safety after approval using modern tools and databases (HPRA, 2025g; European Commission, 2025b; WHO, 2025).

- **Renewal Process.**

Finally, the renewal process in Bolivia was criticised by participants for being repetitive and slow. They said they must submit all the same documents again, even if nothing has changed. There is no simplified path for renewals. However, HPRA offers a fast-track system for products that have not changed, which saves time and reduces the workload for both applicants and reviewers (HPRA, 2025f).

Overall, the findings confirm that there is a clear gap between what AGEMED says in its official rules and what actually happens in practice. More importantly, when compared with HPRA and EMA, AGEMED falls behind in areas such as speed, clarity, technology, consistency, and safety monitoring. These insights support the idea that Bolivia could improve its regulatory system by following international best practices and modernising its procedures.

4.5 Conclusion:

This chapter presented the findings from the survey and open questions. The answers helped to understand how professionals see the generic medicine registration process in Bolivia, especially the work of AGEMED. Even though only a small number of people

participated, they had experience in the field and gave valuable information (Creswell & Creswell, 2018).

a) Research Conclusions

The results showed that many professionals believe the registration process in Bolivia is slow, unclear, and too manual. Several respondents said it often takes longer than the official time limits, and there is no online system to check progress, which causes frustration (AGEMED, 2005).

Some professionals said that AGEMED's communication is not clear, and the observations they receive during evaluation are sometimes repeated or not easy to understand. This makes the process difficult to follow. Also, different reviewers may use different criteria, which shows a lack of internal standardisation (PAHO, 2022).

In addition, Bolivia does not always require bioequivalence studies, which are important to prove that a generic medicine works the same as the original (PAHO, 2022). Many respondents also said that pharmacovigilance activities in Bolivia are weak, which puts patient safety at risk (WHO, 2025).

The general feeling is that the Bolivian system is not modern. It still uses paper forms, complex language, and long procedures, which are not aligned with international good practices, such as those used by the EMA or the HPRA (EMA, 2025; HPRA, 2025a).

In contrast, people with experience or knowlege working with European regulatory agencies said those systems are more organised, transparent, and supportive for applicants.

This answers the research question about the main barriers in AGEMED's system:

- Delays in the process
- Poor communication
- Lack of digital tools

- Weak post-approval monitoring
- Complex or unclear documents

b) Strategic Conclusions.

Based on the results, it is clear that Bolivia needs a stronger and more modern regulatory system. AGEMED should make improvements to provide a process that is faster, easier to understand, and aligned with international standards.

A key step is to build a digital platform, where companies can send documents, track the progress, and receive updates online. This would reduce paperwork and improve transparency.

AGEMED should also update its guidelines and procedures, using simple, clear language, and provide documents that help applicants follow the correct steps (EMA, 2025; HPRA, 2025a).

It is also important to make bioequivalence studies mandatory and create a strong pharmacovigilance system, using global tools and clear rules (PAHO, 2022; WHO, 2025).

Other changes that AGEMED should consider include:

- Giving regular training to both staff and companies
- Using a standard checklist for all evaluations
- Reviewing and improving internal processes
- Encouraging communication and feedback with applicants (HPRA, 2025d)

Without these changes, Bolivia will continue facing problems in providing fast access to safe and effective generic medicines.

Overall, these findings give a strong base for Chapter 5, where clear conclusions and useful recommendations will be proposed to help improve the approval of generic medicines in Bolivia.

4.5.1 Summary of How Objectives Were Met:

This research addressed all five objectives set at the beginning of the dissertation. The table below summarises how each objective was met:

Objective	How It Was Met
1. Investigate the HPRA regulatory requirements	Chapter 2 presented HPRA procedures for approval and renewal. These were used in Chapter 4 to compare with AGEMED (e.g., bioequivalence, timelines).
2. Examine the AGEMED approval/renewal process in Bolivia	Survey results from 45 professionals showed current challenges and delays in AGEMED's system (Sections 4.2 and 4.3).
3. Compare regulatory frameworks between HPRA and AGEMED	Multiple sections (e.g., 4.2.2, 4.2.6, 4.3.4) directly compared the two systems, based on real-world data and literature.
4. Identify challenges and opportunities	Key themes were extracted from open questions (4.3.1), and opportunities were explored through participant suggestions (4.3.2–4.3.4).
5. Provide recommendations based on best practices	Practical steps were proposed in the strategic conclusions, inspired by EU standards (e.g., digital systems, clear feedback, regular updates).

Table 18: *Summary of How Objectives Were Met.*

4.5.2 Validity, Reliability and Trustworthiness:

Although this study had a small sample (n=45), the participants had real experience working with AGEMED, which supports the validity of the results. The survey questions were clear and based on official guidelines, so the answers are reliable and reflect real challenges. Also, by combining both numbers and written responses, the findings are trustworthy (Creswell & Creswell, 2018).

Since the survey was anonymous, the exact locations of participants are unknown. However, AGEMED is based in La Paz, and many professionals from other cities either travel there or use local contacts to complete their work. Because of this, experiences and views may differ among professionals depending on their location and role, so the results may not fully represent all regulatory staff across Bolivia.

CHAPTER 5: CONCLUSIONS AND RECOMMENDATIONS

5.1 Introduction:

This final chapter brings everything together. It sums up the main conclusions based on the results from Chapter 4 and highlights what they mean for the approval and renewal of generic medicines in Bolivia. It also shares useful recommendations, both practical and academic, that could help improve AGEMED's regulatory system. The chapter also looks at the limitations of this study and gives ideas for future research. At the end, there is a short personal reflection about the knowledge and experience gained while working on this dissertation.

5.2 Summary of Key Findings and Their Implications:

Below are the key findings from the survey and how they relate to the research question:

- Most professionals said approvals often take longer than the 90 working day limit, causing delays in access to affordable medicines and affecting the healthcare system.
- A key issue is that bioequivalence studies are not clearly required by AGEMED (AGEMED, 2005). Many participants confirmed this gap. Without bioequivalence, it's harder to prove that generics are as safe and effective as the original drugs.
- Many respondents said the process lacks clarity and consistency. Similar applications often receive different feedback, leading to confusion and delays.
- AGEMED's digital system (MISA) was seen as only partly useful. Several steps still need to be done manually, like printing, delivering, or following up in person, which makes the process slow and frustrating.
- Outdated regulations were another concern. Some rules haven't been updated in over 15 years, making it difficult to meet current scientific and digital standards (Deore & Patel, 2022).
- In contrast, experts with experience in HPRA and EMA described those systems as faster, clearer, and fully digital, with modern laws and standardised procedures.

- Many professionals strongly support aligning AGEMED's system with EU standards to improve transparency, reduce delays, and increase trust in the process.

These results show that Bolivia's regulatory system needs urgent updates, such as modern laws, mandatory bioequivalence, and better digital tools, to improve efficiency, safety, and global alignment.

5.2.1 Answer to the Research Question and Hypothesis:

The main research question of this study was: *How do the approval and renewal processes for generic paracetamol 500 mg tablets differ between Ireland's HPRA and Bolivia's AGEMED in 2024?* Based on the findings, it is clear that HPRA offers a faster, more structured, and transparent system, while AGEMED faces challenges such as outdated guidelines, inconsistent requirements, and a limited digital process. These results support the working hypothesis, which suggested that Ireland's EU-based model is more efficient than Bolivia's current approach.

5.3 Summary of How Research Objectives Were Met:

This study fully met its five research objectives:

1. **Explore HPRA's requirements for generic paracetamol from the USA.** Covered in Chapter 2, this review explained HPRA and EMA rules, such as bioequivalence, CTD format, e-submissions, and strict deadlines (HPRA, 2025a; EMA, 2025).
2. **Understand AGEMED's approval and renewal process in Bolivia.** Chapters 2 and 4 addressed this. Chapter 2 looked at AGEMED's official steps.

Chapter 4 added insights from 45 professionals, who shared problems like delays, unclear rules, outdated systems, and manual work.

3. **Compare both systems: documents, timelines, quality checks, and steps.** This was done in Sections 4.2 and 4.3. Key differences were summed up in Section 4.4, using both literature and participant views.
4. **Find challenges and improvement opportunities.** Section 4.3.1 listed issues such as inconsistent reviews, weak digital systems, and slow processes. Suggestions from participants pointed to areas for improvement.
5. **Give practical recommendations to improve access to generics.** Chapter 5 gave clear suggestions to help AGEMED modernise and match global standards.

5.4 Comparison with the Literature:

The results from Chapter 4 show clear differences compared to the literature in Chapter 2. Although AGEMED has official rules, many professionals said these are not followed in practice. This creates important gaps when compared to agencies like HPRA and EMA.

- For example, AGEMED allows up to 90 working days for approvals (AGEMED, 2005), but this is often exceeded. HPRA and EMA follow strict timelines and regularly monitor them (HPRA, 2025a; HPRA, 2025b; EMA, 2021).
- Bioequivalence is another issue. AGEMED's guidelines do not clearly require it (AGEMED, 2005), while EMA and HPRA include it in all generic applications (EMA, 2010; HPRA, 2025a).
- Bolivia also uses old manuals that have not been updated in over 15 years. In contrast, HPRA and EMA review and improve their documents regularly (European Parliament and Council, 2001; HPRA, 2025a).
- The MISA digital system still needs many manual steps. This slows down the process. EU agencies use modern platforms that are fully digital (HPRA, 2025a; Macdonald et al., 2021).

- Communication from AGEMED was often described as unclear and inconsistent. Meanwhile, HPRA and EMA offer clear guidelines and helpful support (HPRA, 2025fa; Creswell & Creswell, 2018).
- Lastly, renewals in Bolivia are slow and require many repeated documents, even when nothing has changed. HPRA uses a simpler renewal for unchanged products (HPRA, 2025f).

These differences show that AGEMED needs to modernise its system, improve digital tools and communication, and align more closely with international best practices *(see Table 19).*

Key Area	Findings in AGEMED (Chapter 4)	What Literature Says About AGEMED	Comparison with HPRA	Sources
Approval Timelines	Professionals report delays far beyond the 90-day limit	Official time is 90 days, but delays are common in practice	Follows strict timelines and monitors performance	AGEMED (2005); HPRA (2025a); EMA (2021)
Bioequivalence Requirement	Participants confirm it is not requested in practice	Not mentioned as a requirement in official regulations	Mandatory for all generic submissions	EMA (2010); HPRA (2025a)
Laws and Guidelines	Considered outdated and not aligned with current standards	Manuals and laws from 1998–2005 still in use, not regularly updated	Updated regularly to match scientific and EU standards	AGEMED (2005); HPRA (2025a); EU Parliament (2001)
Digital Tools	MISA lacks full functionality; manual steps required	MISA is limited; many steps are still done manually	Fully digital systems, user-friendly, with online tracking	AGEMED (2025); HPRA (2025a); Macdonald et al. (2021)

Communication and Support	Unclear feedback, lack of standardised reviewer comments	Limited support and unclear reviewer feedback	Clear guidance documents and consistent communication	AGEMED (2005); Creswell & Creswell (2018); HPRA (2025a)
Renewal Process	Repetition of documents; same process even when product is unchanged	Not clearly differentiated from first-time approvals	Simplified renewal process for unchanged medicines	AGEMED (2005); HPRA (2025f)

Table 19: *Summary of Key Differences Between AGEMED and HPRA Based on Literature Review and Findings, created by the author.*

5.5 Practical and Academic Recommendations:

Based on the findings and comparisons with international standards, this section presents practical and academic recommendations to help improve Bolivia's regulatory system for generic medicines. These suggestions are directly connected to the problems identified in Chapter 4 and supported by the literature reviewed in Chapter 2.

5.5.1 Practical Recommendations for AGEMED:

1. **Update Old Regulations.**
   AGEMED should revise its outdated guidelines, like the Manual for Sanitary Registration (AGEMED, 2005), which hasn't changed in over 15 years. Laws must reflect new science, technology, and global standards. For example, the EMA updates its documents regularly (EMA, 2023).
2. **Require Bioequivalence.**
   Bioequivalence studies should be a clear requirement for all generic medicines, as in HPRA and EMA systems (HPRA, 2025a; EMA, 2010). This helps protect public health and ensures generics work like the original.

3. **Improve the Digital System (MISA).**
   MISA should support fully digital applications, better tracking, and clearer communication. Many users face delays due to manual steps and system issues. A better platform would improve speed, reduce costs, and support transparency (Macdonald et al., 2021).
4. **Train Reviewers and Applicants.**
   Regular training should be provided to AGEMED staff and applicants. This would reduce confusion and inconsistent feedback, which many participants highlighted as a problem.
5. **Set Clear Timelines and Updates.**
   AGEMED should publish standard timelines and give regular updates during the process. HPRA's online dashboard, which shows application progress, is a good example (HPRA, 2025a).
6. **Simplify Renewals.**
   For unchanged products, the renewal process should be simpler. Currently, companies repeat steps that are not always needed. HPRA uses a faster, risk-based approach that Bolivia could adapt (HPRA, 2025f).
7. **Improve Pharmacovigilance.**
   More effort is needed in post-approval monitoring. This includes better reporting, regular updates, and working with healthcare staff. EMA invests strongly in this area to ensure safety (European Commission, 2025b).

5.5.2 Academic Recommendations:

1. **Support Research in Latin America.**
   More academic studies are needed on regulatory timelines, digital tools, and how policies affect medicine access in Latin America. These topics are important as digital tools become central to global systems (Macdonald et al., 2021).
2. **Compare with Other Countries in the Region.**
   Studies should compare AGEMED with agencies like ANMAT (Argentina), INVIMA (Colombia), or DIGEMID (Peru). This would help Bolivia learn from shared challenges and good examples.

3. **Encourage Training Partnerships.**
   Universities, regulators, and industry can work together to offer short courses or certificates in regulatory affairs. This would help prepare new professionals and strengthen Bolivia's long-term capacity.

Area	Recommendation	Expected Impact
Legislation	Update outdated manuals and laws	Greater clarity and international alignment
Bioequivalence	Make studies mandatory for generic approval	Improved medicine safety and quality assurance
Digital Systems	Upgrade MISA for full online submissions and real-time tracking	Reduced delays, higher transparency
Reviewer Training	Regular training for AGEMED staff and external applicants	More consistent decisions and fewer rejections
Timelines	Publish clear approval timelines with follow-up communication	Better planning for applicants and improved trust
Renewal Process	Simplify for unchanged products using risk-based criteria	Saves time and resources for both AGEMED and applicants
Pharmacovigilance	Strengthen post-market monitoring tools and communication	Early detection of risks and improved patient safety
Academic Research	Encourage studies on Latin American regulatory systems	Encourages academic research and regional learning
Partnerships	Collaborate with universities for training programmes and workshops	Builds technical capacity and prepares future professionals

Table 20: *Summary of Key Recommendations for AGEMED, created by the aothor.*

These recommendations aim to support Bolivia in building a faster, fairer, and more effective regulatory system for generic medicines, which will benefit both public health and the pharmaceutical sector.

5.6 Limitations and Contributions:

5.6.1 Limitations:

Like any research, this study has some limits:

- **Small number of participants**: The survey included 45 professionals. While their answers are helpful, the group may not fully represent everyone involved in the regulatory process in Bolivia. A bigger sample could have made the results stronger.
- **Personal opinions**: The survey was based on individual experiences. This means some answers might include personal views or be affected by specific work situations. As Creswell and Creswell (2018) explain, these types of responses are rich but often shaped by personal perspective.
- **Skipped or unclear answers**: Some participants skipped questions or selected more than one option where only one was needed. This made some parts of the data harder to analyse.

Even with these limits, the study still offers useful results for both practice and academic research.

5.6.2 Contributions:

This dissertation brings several important contributions:

- **Real experience from professionals**: It shows how AGEMED's system works in everyday situations, based on the views of people who work directly with the

approval and renewal of generic medicines. These insights are often missing from official reports (Deore & Patel, 2022).

- **Useful comparisons**: The study clearly compares Bolivia's system with EU agencies like HPRA and EMA, helping to show where improvements are possible (HPRA, 2025a; EMA, 2010).
- **Practical recommendations**: The research gives clear, realistic suggestions to improve AGEMED's efficiency, communication, and digital tools. Other countries have used similar ideas with success (Macdonald et al., 2021).
- **Academic value**: This study adds to the small amount of research about regulation in Latin America. It also invites future studies on digital tools, international standards, and comparing agencies (Deore & Patel, 2022).

Together, these points show the value of this research for improving public health in Bolivia and supporting future work in pharmaceutical regulation.

5.7 Suggestions for Future Research:

Based on this study's results and limitations, several areas for future research are suggested:

- **Wider participation**: Future studies could include more professionals from different cities and departments across Bolivia to reflect a broader range of views.
- **Use of interviews or focus groups**: These methods could provide deeper insights into the experiences of regulatory staff and applicants (Creswell & Creswell, 2018).
- **Post-approval timelines**: Research could explore how long it takes for approved medicines to reach the market, helping identify delays beyond the approval stage.
- **Regional comparisons**: Studies could compare AGEMED with other Latin American agencies like ANMAT (Argentina), INVIMA (Colombia), or DIGEMID (Peru), to highlight shared challenges and good practices.

- **Digital transformation**: More research is needed on how digital tools can improve efficiency and reduce waiting times, especially in emerging markets (Macdonald et al., 2021).
-

These areas could support future improvements in generic medicine regulation across Latin America.

5.8 Personal Reflection:

This dissertation helped me learn how to design surveys, analyse data, and understand medicine regulation in real-life situations. Listening to professionals gave deeper insight, especially into the approval and renewal of generic medicines. I have a clear interest in the regulatory field and now feel more confident giving practical suggestions to improve systems. The research made me more aware of Bolivia's challenges, where delays and outdated processes limit access to affordable treatment. This experience inspired me to keep learning and support better regulation in my country and beyond.

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APPENDICES

The following appendices include official regulatory extracts and reference standards that support the literature review in Chapter 2. These documents were used to explain the approval and renewal process for generic paracetamol 500 mg tablets in Ireland and Bolivia.

- ✓ Appendix A presents the key requirements for a marketing authorisation application in Ireland according to Directive 2001/83/EC.
- ✓ Appendix B contains the official list of documents required by AGEMED in Bolivia. This text remains in Spanish, the official language of Bolivia.
- ✓ Appendices C and D provide the British Pharmacopoeia 2017 monographs used in both case studies, to explain the expected quality standards for paracetamol as an active ingredient and as a finished product.

Appendix A: *Key Application Requirements According to Directive 2001/83/EC Article 8(3).*

2. Member States may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

3. Without prejudice to paragraph 1, Member States shall lay down provisions in order to ensure that marketing authorisation holders, manufacturers and health professionals are not subject to civil or administrative liability for any consequences resulting from the use of a medicinal product otherwise than for the authorised indications or from the use of an unauthorised medicinal product, when such use is recommended or required by a competent authority in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm. Such provisions shall apply whether or not national or Community authorisation has been granted.

4. Liability for defective products, as provided for by Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States, concerning liability for defective products[27], shall not be affected by paragraph 3.

TITLE III

PLACING ON THE MARKET

CHAPTER 1

Marketing authorisation

Article 6

1. No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93.

When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1).

1a. The marketing authorisation holder shall be responsible for marketing the medicinal product. The designation of a representative shall not relieve the marketing authorisation holder of his legal responsibility.

2. The authorisation referred to in paragraph 1 shall also be required for radionuclide generators, kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals.

Article 7

A marketing authorization shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorized, according to national legislation, to use such medicinal products in an approved health care establishment exclusively from authorized radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions.

Article 8

1. In order to obtain an authorization to place a medicinal product on the market regardless of the procedure established by Regulation (EEC) No 2309/93, an application shall be made to the competent authority of the Member State concerned.

[27] OJ L 210, 7.8.1985, p. 29. Directive as last amended by Directive 1999/34/EC of the European Parliament and of the Council (OJ L 141, 4.6.1999, p. 20).

2. A marketing authorization may only be granted to an applicant established in the Community.

3. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

(a) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.

(b) Name of the medicinal product.

(c) Qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the WHO, where an INN for the medicinal product exists, or a reference to the relevant chemical name.

(ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.

(d) Description of the manufacturing method.

(e) Therapeutic indications, contra-indications and adverse reactions.

(f) Posology, pharmaceutical form, method and route of administration and expected shelf life.

(g) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.

(h) Description of the control methods employed by the manufacturer.

(i) Results of:

- pharmaceutical (physico-chemical, biological or microbiological) tests,

- pre-clinical (toxicological and pharmacological) tests,

- clinical trials.

(ia) A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce.

(ib) A statement to the effect that clinical trials carried out outside the European Union meets the ethical requirements of Directive 2001/20/EC.

(j) A summary, in accordance with Article 11, of the product characteristics, a mock-up of the outer packaging, containing the details provided for in Article 54, and of the immediate packaging of the medicinal product, containing the details provided for in Article 55, together with a package leaflet in accordance with Article 59.

(k) A document showing that the manufacturer is authorised in his own country to produce medicinal products.

(l) Copies of any authorisation obtained in another Member State or in a third country to place the medicinal product on the market, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination. Copies of the summary of the product characteristics proposed by the applicant in accordance with Article 11 or approved by the competent authorities of the Member State in accordance with Article 21. Copies of the package leaflet proposed in accordance with Article 59 or

2. A marketing authorization may only be granted to an applicant established in the Community.

3. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

(a) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.

(b) Name of the medicinal product.

(c) Qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the WHO, where an INN for the medicinal product exists, or a reference to the relevant chemical name.

(ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.

(d) Description of the manufacturing method.

(e) Therapeutic indications, contra-indications and adverse reactions.

(f) Posology, pharmaceutical form, method and route of administration and expected shelf life.

(g) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.

(h) Description of the control methods employed by the manufacturer.

(i) Results of:

- pharmaceutical (physico-chemical, biological or microbiological) tests,

- pre-clinical (toxicological and pharmacological) tests,

- clinical trials.

(ia) A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce.

(ib) A statement to the effect that clinical trials carried out outside the European Union meets the ethical requirements of Directive 2001/20/EC.

(j) A summary, in accordance with Article 11, of the product characteristics, a mock-up of the outer packaging, containing the details provided for in Article 54, and of the immediate packaging of the medicinal product, containing the details provided for in Article 55, together with a package leaflet in accordance with Article 59.

(k) A document showing that the manufacturer is authorised in his own country to produce medicinal products.

(l) Copies of any authorisation obtained in another Member State or in a third country to place the medicinal product on the market, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination. Copies of the summary of the product characteristics proposed by the applicant in accordance with Article 11 or approved by the competent authorities of the Member State in accordance with Article 21. Copies of the package leaflet proposed in accordance with Article 59 or

approved by the competent authorities of the Member State in accordance with Article 61. Details of any decision to refuse authorization, whether in the Community or in a third country, and the reasons for such a decision.

This information shall be updated on a regular basis.

(m) A copy of any designation of the medicinal product as an orphan medicinal product under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products[28], accompanied by a copy of the relevant Agency opinion.

(n) Proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The documents and information concerning the results of the pharmaceutical and pre-clinical tests and the clinical trials referred to in point (i) of the first subparagraph shall be accompanied by detailed summaries in accordance with Article 12.

Article 9

In addition to the requirements set out in Articles 8 and 10(1), an application for authorization to market a radionuclide generator shall also contain the following information and particulars:

- a general description of the system together with a detailed description of the components of the system which may affect the composition or quality of the daughter nucleid preparation,

- qualitative and quantitative particulars of the eluate or the sublimate.

[28] OJ L 18, 22.1.2000, p. 1.

Article 10

1. By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.

The first subparagraph shall also apply if the reference medicinal product was not authorised in the Member State in which the application for the generic medicinal product is submitted. In this case, the applicant shall indicate in the application form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference product and if necessary other relevant documentation.

The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.

2. For the purposes of this Article:

(a) "reference medicinal product" shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8;

Appendix B: *Requirements for the Sanitary Registration of Medicines in Bolivia (Chapter 2, Section 2.12 of the Manual for Sanitary Registration, AGEMED).*

Note: *The following document is presented in Spanish, as it is the official language of Bolivian law.*

ITEM	REQUISITOS	1ra. PARTE	2da. PARTE
2.1	**FORMULARIO**		
	Formulario de Solicitud para Registro y Control de Calidad de Medicamentos (DINAMED Form. 005)	X	X
2.2.	**DOCUMENTACIÓN LEGAL – ADMINISTRATIVA DE LAS EMPRESAS**	1ra. PARTE	2da. PARTE
2.2.1.	Fotocopia de Resolución Ministerial o Secretarial	X	
2.2.2.	Fotocopia de Certificado de Empresa Vigente	X	
2.2.3.	Información General de Licencia y Fabricantes	X	
2.2.4.	Formato para Aclaración de Particularidades	X	
2.3.	**DOCUMENTACIÓN GENERAL DEL PRODUCTO**	1ra. PARTE	2da. PARTE
2.3.1.	Certificación del Director Técnico-Regente Farmacéutico	X	
2.3.2.	Certificado de Buenas Prácticas de Manufactura (BPM)	X	
2.3.3.	Contrato de Fabricación o Control de Calidad por Terceros	X	
2.3.4.	Certificado de Producto Farmacéutico Sujeto a Comercio Internacional Consularizado	X	
2.3.5.	Fotocopia de Registro Sanitario Anterior	X	
2.3.6.	Representación Legal	X	
2.3.7.	Fotocopia de Certificado de Despacho Aduanero, solo para los casos de (psicotrópicos o estupefacientes)	X	
2.4.	**INFORMACIÓN TÉCNICA DEL PRINCIPIO ACTIVO**	1ra. PARTE	2da. PARTE
2.4.1.	Fotocopia de Certificado de Análisis de la Materia Prima	X	X
2.4.2.	Nombre Genérico (D.C.I.) y Clasificación Anátomo Terapéutica (A.T.Q.)	X	X
2.4.3.	Nombre Químico, Formula Estructural, Formula Molecular y Peso Molecular		X
2.4.4.	Características Físicas y Químicas del Principio Activo		X
2.4.5.	Características Organolépticas		X
2.4.6.	Vías de Síntesis o de Obtención de Productos Biológicos		X
2.4.7.	Impurezas y Productos de Degradación		X
2.4.8.	Estabilidad de Principios Activos	X	X
2.4.9.	Metodología Analítica		X
2.4.10.	Validación del Método Analítico		X
2.5.	**INFORMACIÓN TÉCNICA DEL PRODUCTO TERMINADO**	1ra. PARTE	2da. PARTE
2.5.1.	Desarrollo Galénico del Producto	X	X
2.5.2.	Fórmula Cuali-Cuantitativa	X	X
2.5.3.	Fotocopia del Certificado de Análisis del Producto Terminado	X	X
2.5.4.	Fotocopia del Certificado de Control de Calidad Emitido por el Laboratorio de Control de Calidad de Medicamentos y Toxicología (CONCAMYT)	X	
2.5.5.	Características Fisicoquímicas de los Excipientes	X	X
2.5.6.	Métodos de Manufactura (un resumen o flujograma)	X	X
2.5.7.	Metodología Analítica	X	X
2.5.8.	Validación del Método Analítico		X
2.5.9.	Patrón(es) de Referencia Primarios o Secundarios		X
2.5.10.	Liberación del Producto Terminado	X	X
2.5.11.	Estudios de Estabilidad	X	X
2.5.12.	Condiciones de Almacenamiento	X	X
2.5.13.	Características del Material de Envase	X	X
2.5.14.	Codificación del Lote	X	X
2.6.	**DOCUMENTACIÓN TÈCNICA BIOFARMACÈUTICA**		
2.6.1.	Estudios de Biodisponobilidad *		
2.6.2.	Estudios de Bioequivalencia *		
2.7.	**ETIQUETAS Y RÓTULOS, INSERTOS O PROSPECTOS**		
2.7.1.	Etiquetas, Rótulos y Estuches	X	X
2.7.2.	Insertos o Prospectos	X	X
2.8.	**EVALUACION FARMACOLOGICA**		
2.8.1.	Formulario de Solicitud Calificación DINAMED form. 007	X	
2.8.2	Formulario de Calificación de Eficacia y Seguridad DINAMED form. 019	X	
		X	
		X	
2.10.	**PAGO POR CONCEPTO DE SERVICIO**	X	

* Según Norma a ser establecida

Appendix C: *BP 2017 Monograph – Paracetamol (API).*

impurity C = about 0.75; impurity B = about 0.8; impurity A = about 0.9; impurity F = about 1.1; impurity D = about 1.2.

System suitability: reference solution (b):
- *resolution*: minimum 1.5 between the peaks due to impurity A and papaverine.

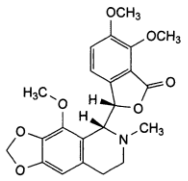
Limits:
- *correction factors*: for the calculation of contents, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 6.2; impurity C = 2.7; impurity D = 0.5;
- *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
- *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*)
Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

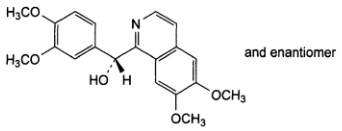
Sulfated ash (*2.4.14*)
Maximum 0.1 per cent, determined on the residue from the test for loss on drying.

ASSAY
Dissolve 0.300 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *alcohol R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.
1 mL of *0.1 M sodium hydroxide* is equivalent to 37.59 mg of $C_{20}H_{22}ClNO_4$.

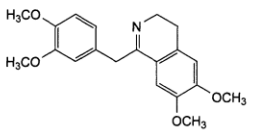
IMPURITIES



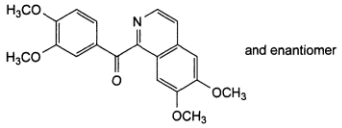
A. (3*S*)-6,7-dimethoxy-3-[(5*R*)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]isobenzofuran-1(3*H*)-one (noscapine),



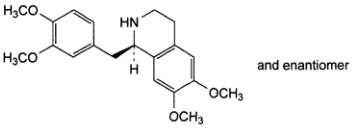
B. (*RS*)-(3,4-dimethoxyphenyl)(6,7-dimethoxyisoquinolin-1-yl)methanol (papaverinol),



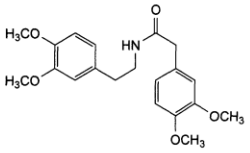
C. 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (dihydropapaverine),



D. (3,4-dimethoxyphenyl)(6,7-dimethoxyisoquinolin-1-yl)methanone (papaveraldine),



E. (1*RS*)-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (tetrahydropapaverine),

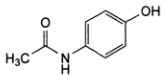


F. 2-(3,4-dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]acetamide.

Ph Eur

Paracetamol

(Ph. Eur. monograph 0049)



$C_8H_9NO_2$ 151.2 *103-90-2*

Action and use
Analgesic; antipyretic.

Preparations
Co-codamol Tablets
Co-codamol Capsules
Effervescent Co-codamol Tablets
Effervescent Paracetamol Tablets
Co-dydramol Tablets
Co-proxamol Tablets
Paracetamol Capsules
Paediatric Paracetamol Oral Solution
Paediatric Paracetamol Oral Suspension
Paracetamol Oral Suspension
Paracetamol Suppositories
Paracetamol Tablets
Paracetamol and Caffeine Tablets
Soluble Paracetamol and Caffeine Tablets
Dispersible Paracetamol Tablets
Soluble Paracetamol Tablets
Paracetamol, Codeine Phosphate and Caffeine Capsules
Paracetamol, Codeine Phosphate and Caffeine Tablets

Ph Eur

DEFINITION

N-(4-Hydroxyphenyl)acetamide.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride.

IDENTIFICATION

First identification A, C

Second identification A, B, D, E

A. Melting point (*2.2.14*): 168 °C to 172 °C.

B. Dissolve 0.1 g in *methanol R* and dilute to 100.0 mL with the same solvent. To 1.0 mL of the solution add 0.5 mL of a 10.3 g/L solution of *hydrochloric acid R* and dilute to 100.0 mL with *methanol R*. Protect the solution from bright light and immediately measure the absorbance (*2.2.25*) at the absorption maximum at 249 nm. The specific absorbance at the maximum is 860 to 980.

C. Infrared absorption spectrophotometry (*2.2.24*).

Preparation Discs.

Comparison paracetamol CRS.

D. To 0.1 g add 1 mL of *hydrochloric acid R*, heat to boiling for 3 min, add 1 mL of *water R* and cool in an ice bath. No precipitate is formed. Add 0.05 mL of a 4.9 g/L solution of *potassium dichromate R*. A violet colour develops which does not change to red.

E. It gives the reaction of acetyl (*2.3.1*). Heat over a naked flame.

TESTS

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution Dissolve 0.200 g of the substance to be examined in 2.5 mL of *methanol R* containing 4.6 g/L of a 400 g/L solution of *tetrabutylammonium hydroxide R* and dilute to 10.0 mL with a mixture of equal volumes of a 17.9 g/L solution of *disodium hydrogen phosphate R* and of a 7.8 g/L solution of *sodium dihydrogen phosphate R*.

Reference solution (a) Dilute 1.0 mL of the test solution to 50.0 mL with the mobile phase. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 5.0 mg of *4-aminophenol R*, 5 mg of *paracetamol CRS* and 5.0 mg of *chloroacetanilide R* in *methanol R* and dilute to 20.0 mL with the same solvent. Dilute 1.0 mL to 250.0 mL with the mobile phase.

Reference solution (d) Dissolve 20.0 mg of *4-nitrophenol R* in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 1.0 mL to 20.0 mL with the mobile phase.

Column:
- *size*: *l* = 0.25 m, Ø = 4.6 mm,
- *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm),
- *temperature*: 35 °C.

Mobile phase Mix 375 volumes of a 17.9 g/L solution of *disodium hydrogen phosphate R*, 375 volumes of a 7.8 g/L solution of *sodium dihydrogen phosphate R* and 250 volumes of *methanol R* containing 4.6 g/L of a 400 g/L solution of *tetrabutylammonium hydroxide R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 245 nm.

Injection 20 µL.

Run time 12 times the retention time of paracetamol.

Relative retentions With reference to paracetamol (retention time = about 4 min): impurity K = about 0.8; impurity F = about 3; impurity J = about 7.

System suitability: reference solution (c):
- *resolution*: minimum 4.0 between the peaks due to impurity K and to paracetamol,
- *signal-to-noise ratio*: minimum 50 for the peak due to impurity J.

Limits:
- *impurity J*: not more than 0.2 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (10 ppm),
- *impurity K*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (50 ppm),
- *impurity F*: not more than half the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.05 per cent),
- *any other impurity*: not more than half the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent),
- *total of other impurities*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),
- *disregard limit* for the calculation of the total of other impurities: the area of the principal peak in the chromatogram obtained with reference solution (b) (0.01 per cent).

Heavy metals (*2.4.8*)

Maximum 20 ppm.

Dissolve 1.0 g in a mixture of 15 volumes of *water R* and 85 volumes of *acetone R* and dilute to 20 mL with the same mixture of solvents. 12 mL of the solution complies with test B. Prepare the reference solution using lead standard solution (1 ppm Pb) obtained by diluting *lead standard solution (100 ppm Pb) R* with a mixture of 15 volumes of *water R* and 85 volumes of *acetone R*.

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

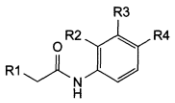
Dissolve 0.300 g in a mixture of 10 mL of *water R* and 30 mL of *dilute sulfuric acid R*. Boil under a reflux condenser for 1 h, cool and dilute to 100.0 mL with *water R*. To 20.0 mL of the solution add 40 mL of *water R*, 40 g of ice, 15 mL of *dilute hydrochloric acid R* and 0.1 mL of *ferroin R*. Titrate with *0.1 M cerium sulfate* until a greenish-yellow colour is obtained. Carry out a blank titration.

1 mL of *0.1 M cerium sulfate* is equivalent to 7.56 mg of $C_8H_9NO_2$.

STORAGE

Protected from light.

IMPURITIES



A. R1 = R3 = R4 = H, R2 = OH: *N*-(2-hydroxyphenyl)acetamide,

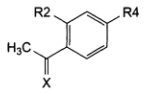
B. R1 = CH_3, R2 = R3 = H, R4 = OH: *N*-(4-hydroxyphenyl)propanamide,

C. R1 = R2 = H, R3 = Cl, R4 = OH: *N*-(3-chloro-4-hydroxyphenyl)acetamide,

D. R1 = R2 = R3 = R4 = H: *N*-phenylacetamide,

H. R1 = R2 = R3 = H, R4 = O-CO-CH_3: 4-(acetylamino)phenyl acetate,

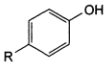
J. R1 = R2 = R3 = H, R4 = Cl: *N*-(4-chlorophenyl)acetamide (chloroacetanilide),



E. X = O, R2 = H, R4 = OH: 1-(4-hydroxyphenyl)ethanone,

G. X = N-OH, R2 = H, R4 = OH: 1-(4-hydroxyphenyl)ethanone oxime,

I. X = O, R2 = OH, R4 = H: 1-(2-hydroxyphenyl)ethanone,



F. R = NO_2: 4-nitrophenol,

K. R = NH_2: 4-aminophenol.

Ph Eur

Hard Paraffin

(Ph. Eur. monograph 1034)

Ph Eur

DEFINITION

A purified mixture of solid saturated hydrocarbons generally obtained from petroleum. It may contain a suitable antioxidant.

CHARACTERS

Appearance

Colourless or white or almost white mass; the melted substance is free from fluorescence in daylight.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

First identification A, C

Second identification B, C

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison hard paraffin CRS.

Preparation Place about 2 mg on a sodium chloride plate, heat in an oven at 100 °C for 10 min, spread the melted substance with another sodium chloride plate and remove one of the plates.

B. Acidity or alkalinity (see Tests).

C. Melting point (*2.2.16*): 50 °C to 61 °C.

TESTS

Acidity or alkalinity

To 15 g add 30 mL of boiling *water R* and shake vigorously for 1 min. Allow to cool and to separate. To 10 mL of the aqueous layer add 0.1 mL of *phenolphthalein solution R*. The solution is colourless. Not more than 1.0 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to red. To a further 10 mL of the aqueous layer add 0.1 mL of *methyl red solution R*. The solution is yellow. Not more than 0.5 mL of *0.01 M hydrochloric acid* is required to change the colour of the indicator to red.

Polycyclic aromatic hydrocarbons

Use reagents for ultraviolet absorption spectrophotometry. Dissolve 0.50 g in 25 mL of *heptane R* and place in a 125 mL separating funnel with unlubricated ground-glass parts (stopper, stopcock). Add 5.0 mL of *dimethyl sulfoxide R*. Shake vigorously for 1 min and allow to stand until 2 clear layers are formed. Transfer the lower layer to a 2nd separating funnel, add 2 mL of *heptane R* and shake the mixture vigorously. Allow to stand until 2 clear layers are formed. Separate the lower layer and measure its absorbance (*2.2.25*) between 265 nm and 420 nm using as the compensation liquid the clear lower layer obtained by vigorously shaking 5.0 mL of *dimethyl sulfoxide R* with 25 mL of *heptane R* for 1 min. Prepare a 7.0 mg/L reference solution of *naphthalene R* in *dimethyl sulfoxide R* and measure the absorbance of this solution at the absorption maximum at 278 nm using *dimethyl sulfoxide R* as the compensation liquid. At wavelengths from 265 nm to 420 nm, the absorbance of the test solution is not greater than one-third that of the reference solution at 278 nm.

Sulfates (*2.4.13*)

Maximum 150 ppm.

Introduce 2.0 g of the melted substance to be examined into a 50 mL ground-glass-stoppered separating funnel. Add 30 mL of boiling *distilled water R*, shake vigorously for 1 min and filter.

STORAGE

Protected from light.

Ph Eur

Light Liquid Paraffin

(Ph. Eur. monograph 0240)

Preparation

Light Liquid Paraffin Eye Drops

Ph Eur

DEFINITION

Purified mixture of liquid saturated hydrocarbons obtained from petroleum.

CHARACTERS

Appearance

Colourless, transparent, oily liquid, free from fluorescence in daylight.

Solubility

Practically insoluble in water, slightly soluble in ethanol (96 per cent), miscible with hydrocarbons.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 1 volume of the resulting solution to 10 volumes with the mobile phase.

(3) 0.0005% w/v each of *4-aminophenol* and *paracetamol BPCRS* in the mobile phase.

(4) Dilute a 0.005% w/v solution of *4′-chloroacetanilide* in *methanol* with the mobile phase to produce a solution containing 0.000005% w/v of *4′-chloroacetanilide*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C8 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 245 nm.

(f) Inject 50 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for 12 times the retention time of the principal peak.

MOBILE PHASE

250 volumes of *methanol* containing 1.15 g of a 40% w/v solution of *tetrabutylammonium hydroxide*, 375 volumes of 0.05M *disodium hydrogen orthophosphate* and 375 volumes of 0.05M *sodium dihydrogen orthophosphate*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to 4-aminophenol is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.1%);

the area of any peak corresponding to 4′-chloroacetanilide is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (10 ppm);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%);

the sum of the areas of any other *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.03%).

ASSAY

For suppositories containing 150 mg or more

To 1 suppository add 30 mL of *water* and 100 mL of 1M *sulfuric acid*. Boil under a reflux condenser for 1 hour, cool and add 100 mL of *water*, 50 g of ice, 50 mL of *dilute hydrochloric acid* and 0.2 mL of *ferroin solution*. Titrate with 0.2M *ammonium cerium(IV) sulfate VS* until a yellow colour is obtained. Each mL of 0.2M *ammonium cerium(IV) sulfate VS* is equivalent to 15.12 mg of $C_8H_9NO_2$. Repeat the test using a further 4 suppositories and calculate the average content per suppository from the 5 individual results thus obtained.

For suppositories containing less than 150 mg and more than 60 mg

To 1 suppository add 10 mL of *water* and 30 mL of *dilute sulfuric acid*. Boil under a reflux condenser for 1 hour, cool and add 40 mL of *water*, 40 g of ice, 15 mL of *dilute hydrochloric acid* and 0.1 mL of *ferroin solution*. Titrate with 0.1M *ammonium cerium(IV) sulfate VS* until a yellow colour is obtained. Each mL of 0.1M *ammonium cerium(IV) sulfate VS* is equivalent to 7.56 mg of $C_8H_9NO_2$. Repeat the test using a further 4 suppositories and calculate the average content per suppository from the 5 individual results thus obtained.

For suppositories containing 60 mg or less

To 1 suppository add 10 mL of *water* and 30 mL of *dilute sulfuric acid*. Boil under a reflux condenser for 1 hour, cool and add 40 mL of *water*, 40 g of ice, 15 mL of *dilute hydrochloric acid* and 0.1 mL of *ferroin solution*. Titrate with 0.025M *ammonium cerium(IV) sulfate VS* until a yellow colour is obtained. Each mL of 0.025M *ammonium cerium(IV) sulfate VS* is equivalent to 1.89 mg of $C_8H_9NO_2$. Repeat the test using a further 4 suppositories and calculate the average content per suppository from the 5 individual results thus obtained.

Paracetamol Tablets

Action and use

Analgesic; antipyretic.

DEFINITION

Paracetamol Tablets contain Paracetamol.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a quantity of the powdered tablets containing 0.5 g of Paracetamol with 20 mL of *acetone*, filter, evaporate the filtrate to dryness and dry at 105°. The residue complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of paracetamol (*RS 258*).

B. Boil 0.1 g with 1 mL of *hydrochloric acid* for 3 minutes, add 10 mL of *water* and cool; no precipitate is produced. Add 0.05 mL of 0.0167M *potassium dichromate*; a violet colour is produced slowly which does not turn red.

C. *Melting point*, about 169°, Appendix V A.

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1, using Apparatus 2. Use as the medium 900 mL of *phosphate buffer pH 5.8* and rotate the paddle at 50 revolutions per minute. Withdraw a sample of 20 mL of the medium and filter. Dilute the filtrate with 0.1M *sodium hydroxide* to give a solution expected to contain about 0.00075% w/v of Paracetamol. Measure the *absorbance* of this solution, Appendix II B, at the maximum at 257 nm using 0.1M *sodium hydroxide* in the reference cell. Calculate the total content of paracetamol, $C_8H_9NO_2$, in the medium taking 715 as the value of A(1%, 1 cm) at the maximum at 257 nm.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. *Prepare the solutions immediately before use and protect from light.*

For solution (1) disperse a quantity of powdered tablets containing 0.2 g of Paracetamol in 8 mL of the mobile phase with the aid of ultrasound, add sufficient mobile phase to produce 10 mL, mix well and filter. For solution (2) dilute 1 volume of solution (1) to 20 volumes with mobile phase and dilute 1 volume of this solution to 20 volumes with mobile phase. Solution (3) contains 0.002% w/v each of *4-aminophenol* and *paracetamol BPCRS* in the mobile phase. For solution (4) dilute a 0.02% w/v solution of *4′-chloroacetanilide* in *methanol* with the mobile phase to produce a solution containing 0.00002% w/v of *4′-chloroacetanilide*.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C8 is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute, at a temperature of 35°C, a mixture of 250 volumes of *methanol* containing 1.15 g of a 40% w/v solution of *tetrabutylammonium hydroxide* with 375 volumes of 0.05M *disodium hydrogen orthophosphate* and 375 volumes of 0.05M *sodium dihydrogen orthophosphate* and (c) a detection wavelength of 245 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 4.0.

Inject solution (1) and allow the chromatography to proceed for 12 times the retention time of the principal peak. In the chromatogram obtained with solution (1) the area of any peak corresponding to 4-aminophenol is not greater than the area of the corresponding peak in solution (3) (0.1%), the area of any peak corresponding to 4′-chloroacetanilide is not greater than the area of the principal peak in solution (4) (10 ppm) and no other impurity is greater than the area of the principal peak obtained with solution (2) (0.25%).

ASSAY

Weigh and powder 20 tablets. Add a quantity of the powder containing 0.15 g of Paracetamol to 50 mL of 0.1M *sodium hydroxide*, dilute with 100 mL of *water*, shake for 15 minutes and add sufficient *water* to produce 200 mL. Mix, filter and dilute 10 mL of the filtrate to 100 mL with *water*. Add 10 mL of the resulting solution to 10 mL of 0.1M *sodium hydroxide*, dilute to 100 mL with *water* and measure the *absorbance* of the resulting solution at the maximum at 257 nm, Appendix II B. Calculate the content of $C_8H_9NO_2$ taking 715 as the value of A(1%, 1 cm) at the maximum at 257 nm.

STORAGE

Paracetamol Tablets should be protected from light.

Dispersible Paracetamol Tablets

Action and use

Analgesic; antipyretic.

DEFINITION

Dispersible Paracetamol Tablets contain Paracetamol in a suitable dispersible basis.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of paracetamol, $C_8H_9NO_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Disperse in *water* to form a uniform suspension.

B. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the final solution obtained in the Assay exhibits a maximum only at 257 nm.

C. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel* GF_{254} as the coating substance and a mixture of 10 volumes of *toluene*, 25 volumes of *acetone* and 65 volumes of *chloroform* as the mobile phase but allowing the solvent front to ascend 14 cm above the line of application. Apply separately to the plate 40 µL of each of solutions (1), (2) and (3). Pour the mobile phase into the unlined tank, immediately place the prepared plate in the tank and close the tank. For solution (1) add 50 mL of *ethanol* (*96%*) to a quantity of the powdered tablets containing 0.10 g of Paracetamol, shake for 10 minutes, add sufficient *ethanol* (*96%*) to produce 100 mL and filter. Solution (2) contains 0.10% w/v of *paracetamol BPCRS* in *ethanol* (*96%*). For solution (3) dissolve 0.25 g of *4′-chloroacetanilide* and 0.10 g of *paracetamol* in sufficient *ethanol* (*96%*) to produce 100 mL. After removal of the plate, dry it in a current of warm air and examine under *ultraviolet light* (*254 nm*). The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated principal spots, the spot corresponding to 4′-chloroacetanilide having the higher Rf value.

TESTS

Disintegration

Comply with the requirements for Dispersible Tablets.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light. For solution (1) disperse a quantity of powdered tablets containing to 0.2 g of Paracetamol in 8 mL of the mobile phase with the aid of ultrasound, add sufficient mobile phase to produce 10 mL, mix well and filter. For solution (2) dilute 1 volume of solution (1) to 20 volumes with mobile phase and dilute 1 volume of this solution to 20 volumes with mobile phase. Solution (3) contains 0.002% w/v each of *4-aminophenol* and *paracetamol BPCRS* in the mobile phase. Solution (4) contains 0.00002% w/v of *4′-chloroacetanilide* in the mobile phase.

The chromatographic procedure may be carried out using (a) a stainless steel column (25 cm × 4.6 mm) packed with *octylsilyl silica gel for chromatography* (5 µm) (Zorbax Rx C8 is suitable), (b) as the mobile phase with a flow rate of 1.5 mL per minute, with a temperature of 35°C, a mixture of 250 volumes of *methanol* containing 1.15 g of a 40% v/v solution of *tetrabutylammonium hydroxide* with 375 volumes of 0.05M *disodium hydrogen orthophosphate* and 375 volumes of 0.05M *sodium dihydrogen orthophosphate* and (c) a detection wavelength of 245 nm.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution factor* between the two principal peaks is at least 4.0.

Inject solution (1) and allow the chromatography to proceed for 12 times the retention time of the principal peak. In the chromatogram obtained with solution (1) the area of any peak corresponding to 4-aminophenol is not greater than the area of the corresponding peak in solution (3) (0.1%), the area of any peak corresponding to 4′-chloroacetanilide is not greater than the area of the principal peak in solution (4) (10 ppm) and no other impurity is greater than the area of the principal peak obtained with solution (2) (0.25%).

The following appendices include supporting documents related to the research methods discussed in Chapter 3. These materials show the ethical approval process and the main data collection tool used in the study.

- ✓ Appendix 5 presents the signed Ethics Application and Declaration Form, which confirms that the research followed ethical standards and was approved by the academic supervisor on 24 June 2025.
- ✓ Appendix 6 includes the full online survey questionnaire, used to gather primary data for this study. It contains the participant information, consent section, and all survey questions. Screenshots of the survey as it appeared in Microsoft Forms are also provided for reference.

Appendix E: *Ethics Application & Declaration Form.*

Innopharma education

GRIFFITH COLLEGE

Ethics Application & Declaration Form

DISSERTATION TITLE: Regulatory Frameworks for Obtaining and Renewing Marketing Authorisations of Generic Paracetamol 500 mg Tablets Imported from the United States: A Comparative Analysis of HPRA (Ireland) and AGEMED (Bolivia) in 2024, Using Paracetamol as an Illustrative Example.

RESEARCHER'S NAME: Patricia Lucia Fernandez Rodriguez.

PROGRAMME OF STUDY: MSc in Pharmaceutical Business and Technology.

SUPERVISOR'S NAME: Deirdre Finn.

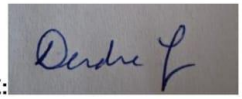
DECLARATION:
The information in this application form is accurate to the best of my knowledge. I undertake to abide by the principles outlined by Innopharma/Griffith College ethics policy in my research dissertation. I confirm that I have completed a full ethics assessment for my research dissertation as per the college guidelines. I will not begin my primary research until such approval from my supervisor and/or ethics Committee has been obtained.
I pledge to carry out my research according to the Innopharma/Griffith College academic integrity standards. Any results presented in my dissertation will be from my own, original research, I will reference and/or acknowledge any material or sources used in its preparation and I will not plagiarise the work of anyone else.

For Student:
STUDENT SIGNATURE: 

DATE: 23/06/2025

The research contained within this research dissertation proposal has been approved.

For Supervisor:
Ethics Committee Approval Required: Yes ☐ **X** No

SUPERVISOR SIGNATURE: 

DATE:24/06/2025

For Ethics Committee (if required):
Ethics Committee Approval Given: Yes ☐ No ☐

ETHICS COMMITTEE MEMBER SIGNATURE:

DATE:

NOTE: Supervisors are responsible for ensuring their students fill in this form correctly and that all ethical areas have been considered.

SECTION 1: DESCRIPTION OF RESEARCH STUDY

1.1 **Purpose and objectives of research:**

Purpose: This study compares the medicine approval systems in two countries: Ireland and Bolivia. It focuses on how each country gives permission to sell and renew generic paracetamol 500 mg tablets that are imported from the United States. In Ireland, the process is done through the HPRA, which follows clear and modern rules from the European Union. The system is digital, organised, and usually faster. In Bolivia, the agency is AGEMED, and it follows older national rules. The process there is mostly manual and uses paper, which can take longer and is more difficult to track. The goal of this study is to find the main differences between the two systems, to understand the challenges that professionals face in Bolivia, and to give helpful suggestions. These suggestions can support Bolivia in making its system more modern, so that people can have better and faster access to safe and affordable medicines.

Objectives:

- Investigate the regulatory requirements set by the HPRA for the initial approval and renewal for obtaining the marketing authorisation for generic paracetamol 500 mg tablets imported from the United States.
- Examine the approval and renewal for obtaining the marketing authorisation for generic paracetamol 500 mg tablets imported from the United States under AGEMED in Bolivia.
- Compare the regulatory frameworks of HPRA and AGEMED concerning to the approval and renewal of marketing authorisations for generic paracetamol 500 mg tablets imported from the United States.
- Identify potential challenges and opportunities arising from the regulatory differences between Ireland and Bolivia in the approval and renewal processes for marketing authorisations of generic paracetamol 500 mg tablets.
- Provide recommendations based on best practices from HPRA and AGEMED to enhance the efficiency of importation and authorisation procedures, ensuring the access to generic paracetamol 500 mg tablets for the population.

1.2 **Research methodology**:

This study will use a positivist and deductive approach, which means it will focus on real facts and compare what is written in the regulations with what actually happens in real life. The main goal is to understand how generic paracetamol 500 mg tablets are approved and renewed in two countries: Ireland, through the HPRA, and Bolivia, through AGEMED.

Two types of information will be used: primary and secondary data.

- Primary data will be collected through an online survey. The people invited to answer the survey will be pharmaceutical professionals in Bolivia who work directly with marketing authorisations and know AGEMED's process well. These professionals will be able to complete the survey in English, because many documents they work with, such as product files, technical information, and international regulations are already written in English. They are used to reading and working with this kind of content, so they can understand and answer the questions without any problem.

- Secondary data will include official documents, laws, and procedures from both HPRA and AGEMED. These will help compare both systems.

The survey will include quantitative questions (like: "How long does approval take?") and qualitative questions (like: "What are the biggest challenges you face?"). The answers will be studied using content comparison and thematic analysis, to find common ideas, repeated problems, and suggestions for improvement.

The plan is to collect 30 to 50 surveys. In studies like this, saturation usually happens after 15 to 20 responses, when no new information is coming. This number is enough to explore the topic and give useful recommendations.

SECTION 2: POSSIBLE ETHICAL ISSUES

Answer 'yes' or 'no' to the following questions.

SUBJECT MATTER

Does the research proposal involve:

Research into specific company activities that would be deemed sensitive or confidential	No
Research into politically and/or racially/ethnically and/or commercially sensitive areas	No
Sensitive, personal, professional or corporate issues	No

RESEARCH PROCEDURES

Does the research proposal involve:

Research that might damage the reputation of companies or participants	No
Research that may negatively affect the reputation of Griffith College/Innopharma	No
Use of personal records without consent	No
Use of company data without consent	No
The offer of any inducements to participate	No
Audio or visual recording without consent	No
Using a language other than English	No

PARTICIPANTS

Does the research proposal involve:

People who are not competent and/or fluent in English	No
Does your research group include any of the following vulnerable groups	No

(Adults with psychological impairments; Adults with learning difficulties; Adults under the protection/control /influence of others (e.g. in care/prison); Relatives of ill people (e.g. parents of sick children); Hospital or GP participants recruited in a medical facility; persons under the age of 18)

If you have answered NO to ALL questions, please go straight to Section 4.

If you have answered YES to ANY question in SECTION 2, you must fill in SECTION 3.

SECTION 3: STEPS TAKEN TO AVOID ETHICAL ISSUES

[Only fill in this section if you answered YES to ANY of the questions in Section 3. For example, if you answered yes to including participants who are not fluent in English, you might put forward a plan that offers your survey in two languages to take this into account. Another example could be a study where the researcher wants to include information about the care received by children with a long-term condition but it would not be ethical to approach the children directly but it might be acceptable to instead ask parents questions about their child's care. If these plans are acceptable to your supervisor, you may not need to apply for ethical approval from the Ethics Committee].

3.1. If your ethics relates to ***Subject Matter***, outline your action plan to work around any sensitive issues.
3.2. If your ethics relates to ***Research Procedures***, outline your action plan to deal with possible ethical issues in your research procedures.
3.3. If your ethics relates to ***Participants***, outline how you will protect vulnerable persons or those that do not have English as their first language.

SECTION 4: ABOUT YOUR PARTICIPANTS

4.1. **Outline your participant profile and why you have chosen them for this study.**
The people invited to take part in this study are pharmaceutical professionals based in Bolivia. They must have direct experience working with AGEMED, especially in the process of getting or renewing marketing authorisations for imported medicines, such as generic paracetamol 500 mg tablets. These participants are important because they know the real challenges that can happen when dealing with regulations. Many of them work with technical documents and communication in English, as part of their job. Because of this, they are able to understand the survey questions and respond in English without difficulty. Their honest opinions and knowledge will help identify practical problems, gaps, and ideas to improve the regulatory process in Bolivia. Their input is very valuable for the study, as it brings the real-world side of the system.

4.2 **How do you plan to gain access to/contact/approach your participant(s).**
Participants will be contacted using professional networks such as LinkedIn, email, and WhatsApp. A short and respectful message will be sent, clearly explaining the purpose of the research, what the survey is about, and that participation is completely voluntary. The message will also explain that all responses will stay anonymous, and no names or personal details will be collected. To reach more people, I will also use snowball sampling, this means that after someone completes the survey, they can share it with other professionals they know who meet the same criteria. This helps to reach the right people who are involved in the regulatory process and can share useful insights.

SECTION 5: INFORMATION, CONSENT AND CONFIDENTIALITY

5.1 **Participant Information Letter (PIL) for participants**

Please confirm below that your information letter covers:

Description of the research topic and method	N/A
Details of what participation will involve	N/A
Rights to anonymity	N/A
Confidentiality	N/A
Rights to withdraw from the research	N/A
The contact details of the researcher and supervisor (if necessary)	N/A

5.2 **Informed Consent Form (ICF) for participants**
Please indicate below if your research requires a signed consent form by selecting the relevant option only:

No: my research study involves an online survey only and/or does not require signed consent. Consent will be asked in the online survey:

Do you consent to participate in this study?

☐ Yes ☐ No

SECTION 6: STORAGE OF DATA

6.1. **How will you store the research data and for how long? How will you manage data protection issues?**

- All data collected for this research will be stored in a safe and secure way. The survey responses will be saved on a password-protected laptop, and a backup copy will also be saved in secure cloud storage, such as Microsoft OneDrive, to prevent any data loss.
- Only the researcher (Patricia Fernandez) will have access to the data. It will not be shared with anyone else, including classmates or third parties. The survey is designed to be anonymous, meaning no names, email addresses, or personal details will be collected. This helps to protect the privacy of everyone who takes part.
- All responses will be anonymised and treated with strict confidentiality. The data will only be used for academic purposes, such as writing the final dissertation and presenting the results. The research findings may include general comments or quotes, but no participant will ever be identified.
- The data will be kept for a maximum of two years after the project is submitted, in line with ethical and data protection guidelines. After this period, the data will be permanently deleted from both the laptop and the cloud storage. Any files that include raw data or analysis will be securely removed to make sure the information is not accessed again in the future.

This careful process will help ensure that participant privacy is protected and that all data is managed in an ethical and responsible way.

SECTION 7: NON-DISCLOSURE AGREEMENT & STUDENT CONSENT

7.1 **Non-Disclosure Agreement (NDA)**
Will the final dissertation contain any information pertaining to any source what would warrant the use of a Non-Disclosure Agreement (NDA) e.g. industry-based research?

No

7.2 **Student consent**
If a Non-Disclosure Agreement (NDA) is not required, does the Student consent to allow their completed dissertation to be held/published by Innopharma/Griffith College?

Yes

SECTION 8: RECORDING AND RETENTION OF DISSERTATION VIVA

8.1 **Viva Recording**
The Dissertation viva will be recorded. This recording may be used to facilitate assessment by Innopharma staff, a third reader if necessary and/or if requested by the external examiner for the Programme. The recording will be held in line with current GDPR guidelines and will not be made publicly available.

SECTION 9: DOCUMENT CHECKLIST

NOTE: Applicants must attach the following documents in electronic format to the appendix.

Which documents are added to the appendix? Please tick N/A if not applicable:

9.1 Participant Information Letter (PIL) for participant	N/A
9.2 Informed Consent Form (ICF) for participant	N/A
9.3 Questions/survey for interviewees/focus groups etc *(can be in draft form)*	Yes
9.4 Any other documents e.g. Non-Disclosure Agreement	N/A

I confirm that this application is complete and all required documents are included in the appendix.

For Student:
STUDENT SIGNATURE: 

DATE: 23/06/2025

SECTION 10: APPENDIX

10.1: Survey

Introduction for Participants (before starting the survey):

Dear Participant,

You are invited to take part in a short, anonymous survey as part of a research study for a Master's dissertation at Griffith College, Dublin. The purpose of this study is to understand the process of approving and renewing marketing authorisations for generic medicines imported from the United States, using the case of paracetamol 500 mg tablets, and to explore how this process works in Bolivia through AGEMED.

The survey is for pharmaceutical professionals who have experience working with AGEMED's regulatory system. Your participation is voluntary, and all responses are completely anonymous. No personal data will be collected. The survey will take around 10–15 minutes to complete.

Thank you for your time and support!

Consent Section (at the start of the Microsoft Form):

Do you consent to take part in this anonymous survey?

- Yes, I agree to participate.
- No, I do not agree.

Survey Questions:

Section 1: About Your Professional Background (Quantitative)

1. **What best describes your current role in the regulatory process for generic medicines? (You may select more than one if it applies)**

   - I work on preparing or submitting applications for marketing authorisation
   - I work as a regulatory reviewer or evaluator (e.g. AGEMED staff)
   - I support companies with compliance or documentation
   - I work in quality assurance/quality control
   - Other: _____

2. **How many years of experience do you have working in the regulatory area (e.g. marketing authorisation, compliance, or pharmaceutical registration)?**

   - Less than 1 year
   - 1–3 years
   - 4–6 years
   - 7–10 years
   - More than 10 years

3. **Are you currently involved in the importation of generic medicines that require marketing authorisation in Bolivia?**

   - Yes, regularly
   - Occasionally

- No
- Not applicable to my current role

Section 2: Approval and Renewal Process (Regulatory Procedures)

4. **On average, how long does it take for AGEMED to approve a marketing authorisation for a generic medicine? (Quantitative)**

   - Less than 3 months
   - 3–6 months
   - 7–12 months
   - More than 1 year
   - I don't know / Not sure

5. **In your experience, how clear and transparent is AGEMED's regulatory process for approving generic medicines? (Quantitative)**

   Scale: 1 (Very unclear) to 5 (Very clear)

   1 2 3 4 5

6. **What are the biggest challenges you face during the approval or renewal process of generic medicines with AGEMED? (Qualitative – Open question)**

   [Write your answer below]

Section 3: Comparison and Opportunities

7. **Have you ever worked with or reviewed the systems of other regulatory authorities (e.g., HPRA or EMA)? (Quantitative)**

   - Yes
   - No

8. **From your experience, which parts of the HPRA or EMA systems do you find more efficient or better structured compared to AGEMED?**

   [Write your answer below]

9. **In your opinion, what are the main differences between AGEMED and regulatory authorities in more developed systems (e.g., HPRA, EMA)? (Qualitative – Open question)**

[Write your answer below]

10. **What aspects of AGEMED's process could be improved to make the system more efficient and transparent? (Qualitative – Open question)**

[Write your answer below]

11. **From your experience, does AGEMED require bioequivalence studies when approving generic medicines? (Quantitative)**

- Always
- Sometimes
- Rarely
- Never
- I'm not sure

12. **Do you think AGEMED's use of digital systems (such as online applications, document tracking, communication) is effective? (Quantitative)**

Scale: 1 (Not effective at all) to 5 (Very effective)

1 2 3 4 5

13. **What digital improvements would help AGEMED increase transparency or speed in the process? (Open-ended)**

[Write your answer below]

14. **In your opinion, how do differences between AGEMED and EU regulatory systems affect access to generic medicines in Bolivia? (Open-ended)**

[Write your answer below]

Section 4: Final Reflections

15. **Would you support changes in AGEMED's system that align more closely with EU regulatory standards? (Quantitative)**

- Yes
- No
- Maybe

16. Do you believe AGEMED ensures the same level of medicine quality and safety as the HPRA or EMA?

- Yes
- No
- Not sure

17. Why or why not?

[Write your answer below]

18. In your view, what would be the biggest benefit of improving AGEMED's regulatory system? (Qualitative – Open question)

[Write your answer below]

19. Is there anything else you would like to add about your experience or suggestions for improving the approval of generic medicines in Bolivia? (Optional – Open question)

[Write your answer below]

10.2 Sample Size Calculations

In Bolivia, it is very difficult to find exact numbers of people who work only in the area of pharmaceutical regulation, especially those involved in the approval or renewal of generic medicines like Paracetamol. Most pharmacists in Bolivia usually work in pharmacies, hospitals, or the pharmaceutical industry. In many cases, companies that import generic medicines do not have a full-time regulatory expert. Instead, they hire someone only when needed, such as a consultant or an external expert. Because of this, the number of people in Bolivia who are qualified and actively working in this regulatory area is very small and hard to reach.

To calculate how many people should answer the survey, the following was used:

- **Confidence level:** 95% (Z = 1.96), this shows how sure we want to be.
- **Margin of error**: 5% (E = 0.05), this is how much error we can accept.
- **Estimated proportion:** 8% (P = 0.08), this is an estimate of how many people work in this area, based on experience and what is known about the Bolivian market.

The formula used was:

$$n = \frac{Z^2 \cdot P\,(1 - P)}{E^2} = \frac{1.96^2 \cdot 0.08\,(1 - 0.08)}{0.05^2} = \frac{0.2825}{0.0025} = 113$$

So, the result shows that the ideal number of participants would be 113 people.

However, in real life, it may not be possible to get 113 responses, because the number of qualified professionals in Bolivia is very small. Also, many of them are not easy to contact, since they don't always work directly for companies, they may work independently or only be hired for short periods. Because of this, this research will try to collect answers from at least 30 to 50 professionals who have experience in the regulatory area. Even though this is a smaller sample, a small number of participants can offer meaningful results in qualitative research (Creswell and Creswell, 2018). The study will still be valuable because it uses a mixed-method exploratory approach. That means it focuses not just on numbers, but also on people's opinions, experiences, and suggestions, which can give a lot of insight, especially for a Master's research project.

References:

Creswell, J.W. and Creswell, J.D. (2018) *Research design: Qualitative, quantitative, and mixed methods approaches*. 5th edn. Thousand Oaks, CA: SAGE Publications.

Appendix F: *Survey Questionnaire Including Participant Information and Consent Section.*

Available at: https://forms.office.com/e/Ufdqvf8t05?origin=lprLink

Survey on AGEMED's Approval Process for Generic Medicines in Bolivia

Dear Participant,
You are invited to take part in a short, anonymous survey as part of a research study for a Master's dissertation at Griffith College, Dublin. The purpose of this study is to understand the process of approving and renewing marketing authorisations for generic medicines imported from the United States, using the case of paracetamol 500 mg tablets, and to explore how this process works in Bolivia through AGEMED. The survey is for pharmaceutical professionals who have experience working with AGEMED's regulatory system. Your participation is voluntary, and all responses are completely anonymous. No personal data will be collected. The survey will take around 10–15 minutes to complete.
Thank you for your time and support!

* Required

Consent Section

1. Do you consent to take part in this anonymous survey? *

- ◯ Yes, I agree to participate
- ◯ No, I do not agree

Section 1: About Your Professional Background

2. **What best describes your current role in the regulatory process for generic medicines? (You may select more than one if it applies)** *

- [ ] I work on preparing or submitting applications for marketing authorisation
- [ ] I work as a regulatory reviewer or evaluator (e.g. AGEMED staff)
- [ ] I support companies with compliance or documentation
- [ ] I work in quality assurance/quality control
- [ ] Other

3. **How many years of experience do you have working in the regulatory area (e.g. marketing authorisation, compliance, or pharmaceutical registration)?** *

- ◯ Less than 1 year
- ◯ 1–3 years
- ◯ 4–6 years
- ◯ 7–10 years
- ◯ More than 10 years

Section 2: Approval and Renewal Process (Regulatory Procedures)

4. **On average, how long does it take for AGEMED to approve a marketing authorisation for a generic medicine?** *

- ◯ Less than 3 months
- ◯ 3–6 months
- ◯ 7–12 months
- ◯ More than 1 year
- ◯ I don't know / Not sure

5. **In your experience, how clear and transparent is AGEMED's regulatory process for approving generic medicines?**
Scale: 1 (Very unclear) to 5 (Very clear) *

1	2	3	4	5

6. **What are the biggest challenges you face during the approval or renewal process of generic medicines with AGEMED?** *

Section 3: Comparison and Opportunities

7. **Have you ever worked with or reviewed the systems of other regulatory authorities (e.g., HPRA or EMA)?** *

   ◯ Yes

   ◯ No

8. **From your experience, which parts of the HPRA or EMA systems do you find more efficient or better structured compared to AGEMED?** *

9. **In your opinion, what are the main differences between AGEMED and regulatory authorities in more developed systems (e.g., HPRA, EMA)?** *

10. **What aspects of AGEMED's process could be improved to make the system more efficient and transparent?** *

11. **From your experience, does AGEMED require bioequivalence studies when approving generic medicines?** *

- ◯ Always
- ◯ Sometimes
- ◯ Rarely
- ◯ Never
- ◯ I'm not sure

12. **Do you think AGEMED's use of digital systems (such as online applications, document tracking, communication) is effective?**
Scale: 1 (Not effective at all) to 5 (Very effective) *

1	2	3	4	5

13. **What digital improvements would help AGEMED increase transparency or speed in the process?** *

14. **In your opinion, how do differences between AGEMED and EU regulatory systems affect access to generic medicines in Bolivia?** *

Section 4: Final Reflections

15. **Would you support changes in AGEMED's system that align more closely with EU regulatory standards?** *

- ◯ Yes
- ◯ No
- ◯ Maybe

16. **Do you believe AGEMED ensures the same level of medicine quality and safety as the HPRA or EMA?** *

- ◯ Yes
- ◯ No
- ◯ Not sure

17. **Why or why not?** *

18. **In your view, what would be the biggest benefit of improving AGEMED's regulatory system?** *

19. **Is there anything else you would like to add about your experience or suggestions for improving the approval of generic medicines in Bolivia?**