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SINDUSFARMA

Concept and rules comparison for: CPPs, origin country, reference country in Latin America

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INTRODUCTION

Differences among Latin America (LATAM) countries on the concept of Certificate of Pharmaceutical Product (CPP), origin country and reference country as well as on the rules regarding when this document should be presented are being found.

Comparative assessment of regulatory differences is relevant to reduce complexity in completing properly the submission package and to foster convergence and possible harmonization among the markets, health authorities and pharmaceutical industries.

Countries of LATAM region considered in the assessment:

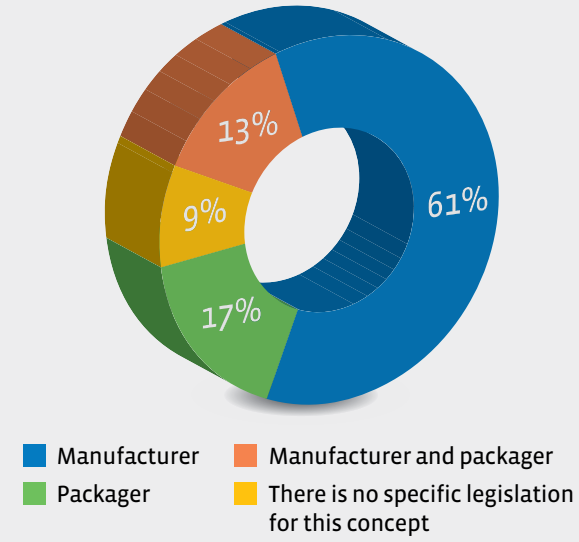
Argentina, Paraguay, Uruguay, Chile, Bolivia, Peru, Mexico, Brazil, Colombia, Venezuela, Ecuador, Costa Rica, El Salvador, Honduras, Nicaragua, Guatemala, Panama, Aruba, Curacao, Jamaica, Saint Maarten, Trinidad & Tobago and Dominican Republic.

1. DEFINITION OF COUNTRY OF ORIGIN (COO)

The country of origin (COO) is the country where a product is manufactured, packaged or exported from. There are different rules of origin under various national laws and international treaties. According to this assessment for Latin American countries, the COO is:

- Responsible for product manufacturing for Bolivia, Uruguay, Paraguay, Costa Rica, Mexico, El Salvador, Honduras, Nicaragua, Guatemala, Panama, Jamaica, Colombia, Venezuela, Ecuador and Dominican Republic;
- Responsible for product manufacturing and packaging for Chile, Peru and Trinidad & Tobago;
- Responsible for product packaging for Mexico (only sterile products), Aruba, Curacao and St Maarten.
- In Argentina and Brazil there is no specific legislation to classify this concept. In consequence, for these countries the COO can be understood as:
  - Responsible for product manufacturing or packaging for Brazil;
  - Responsible for product manufacturing, packaging or exporting for Argentina.

CONCEPT OF COUNTRY OF ORIGIN (COO)



This assessment shows that most countries have specific legislation to determine the COO. Also, almost all of them recognize the COO as the manufacturer, and the COO is only not regulated in two countries.

2. DEFINITION OF COUNTRY OF REFERENCE (COR)

The country of reference (COR) is the country with a national regulatory authority, competent and efficient in the performance of the sanitary regulation functions, to guarantee the quality, safety and efficacy of the medicines and biological products. According to this assessment for Latin American countries, the CORs are:

- Peru: United States of America (USA), United Kingdom (UK), Canada, Australia, Japan, Germany, Switzerland, France, Italy, Norway, Belgium, Switzerland, Spain, The Netherlands, Denmark, Portugal and Korean Republic;
- Chile: European Medicines Agency (EMA), Food and Drug Administration of the United States (FDA), General Medications Office of the Ministry of Health in Canada, Spanish Agency of Medicines of the Ministry of Health and Consumption (AEMPS), Japanese National Institute of Health Sciences, Medicines, Healthcare products Regulatory Agency of United Kingdom (MHRA), Agency of Medicinal Products of Sweden, Agency of Medicinal Products of Switzerland and National Health Surveillance Agency of Brazil (ANVISA);
- Uruguay: FDA, EMA, AEMPS, MHRA;
- Argentina: the local legislation lists two groups of countries of reference (Annex I and II) and establishes different criteria for registration accordingly:
  - (Annex I) USA, Japan, Sweden, Helvetic Confederation, Israel, Canada, Austria, Germany, France, United Kingdom, Netherlands, Belgium, Denmark, Spain, Italy;
  - (Annex II) Commonwealth of Australia, United States of Mexico, Federative Republic of Brazil, Republic of Cuba, The Republic of Chile, Republic of Finland, Republic of Hungary, Ireland, People´s Republic of China, Great Duchy of Luxembourg, Kingdom of Norway, New Zealand, Republic of India;
- Paraguay: Germany, Austria, Belgium, Canada, Denmark, Spain, USA, France, Israel, Italy, Japan, Netherlands, UK, Sweden and Switzerland, Australia, Chile,

Cuba, Finland, Hungary, Ireland, Luxemburg, Mexico, Norway y New Zealand, EMEA, Regional Reference Regulatory Agencies recognized by the Pan American Health Organization (PAHO);

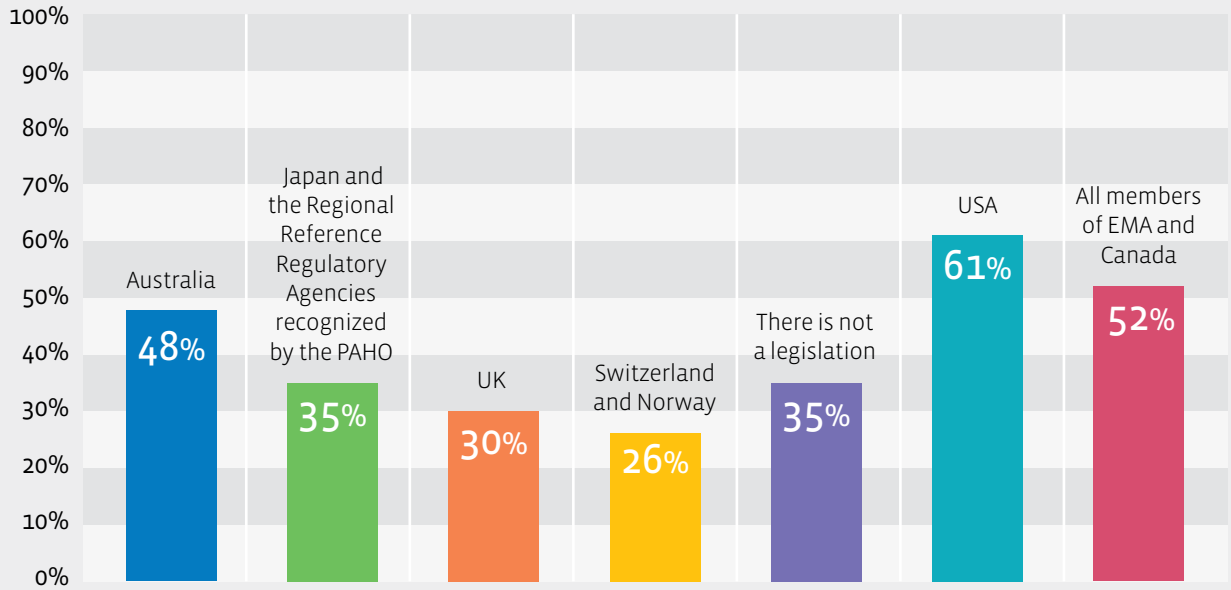
- Costa Rica, El Salvador, Honduras, Nicaragua, Guatemala and Ecuador: They can officially recognize products registered by sanitary authorities of countries whose Health Authorities have been certified at level IV by the PAHO, which are: National Administration of Drugs, Foods and Medical Devices of Argentina (ANMAT), ANVISA, State Control Center of Drug Quality from Cuba (CECMED), National Food and Drug Surveillance Institute from Colombia (INVIMA) and Federal Commission for the Protection against Sanitary Risk from Mexico (COFEPRIS), as well as products approved by FDA, EMA, Canada, Australia and Japan. For biotechnology or biosimilars and biological products, the registration will be granted if these same countries have specific regulations for them;
- Panama: USA, Canada, Japan, Switzerland, Norway, Iceland, New Zealand, Australia and all member countries of EMA;
- Trinidad & Tobago: Belgium, Netherlands, Denmark, France, Sweden;
- Colombia: USA, Canada, France, Netherlands, Sweden, Denmark, Germany Switzerland, Norway, United Kingdom and Japan;
- Dominican Republic: USA, Canada, Japan, all member countries of EMA, United Kingdom, Switzerland, Denmark, Sweden, Ireland, Norway, Iceland, New Zealand, Australia, Brazil, Argentina, Colombia, Mexico and Cuba.

In Brazil, Bolivia, Mexico, St Maarten, Aruba, Curacao, Jamaica and Venezuela, the regulation does not contemplate a concept of reference country. Usually FDA and EMA are accepted as regulatory authorities of reference to all those countries.

With these results it is possible to conclude that the USA, Australia, all members of EMA and Canada are reference countries for most of the Latin American countries. To a lesser degree, the following are considered: Japan, Switzerland and Norway, UK and the regional reference regulatory Agencies recognized by the PAHO.

These Health Authorities can support, based on its experiences, the strengthening of other regulatory agencies, as well as to promote exchange and technical cooperation between countries.

CONCEPT OF REFERENCE COUNTRY
(WHICH ARE THE HEALTH AUTHORITIES CONSIDERED AS REFERENCE IN THE COUNTRY)



3. IMPACT OF REGISTRATIONS IN COO OR COR ON THE ABILITY TO REGISTER PRODUCTS IN LATAM REGION

3.1. Approval in the COO

The regulation and control of new marketing applications require, in some countries, that the product is approved in the COO as a condition to grant a new registration in the Latin America country. This requirement may have as goal to provide additional basis to the Health Authority in the new marketing application.

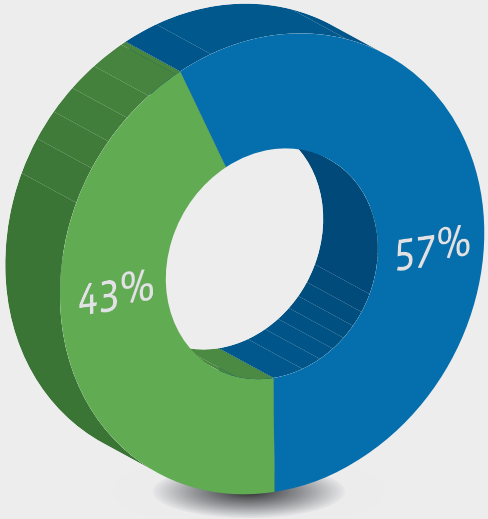
After the analysis of LATAM region, it is possible to affirm that:

- In 11 out of 23 countries (Panama, Curacao, Aruba, Jamaica, Saint Maarten, Trinidad & Tobago, Colombia, Paraguay, Venezuela, Ecuador and Dominican Republic) it is mandatory to have the product approved in the COO in order to have a new registration approved
- In 12 out of 23 countries (Brazil, Chile, Bolivia, Mexico, Uruguay, Argentina, Peru, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua) it is not mandatory to have the product approved in the product in the COO to obtain a new registration.

Furthermore, some specifications per country can be described:

- Brazil: it is mandatory to present proof (with the information about the manufacturing site) that the product is registered in any country to obtain approval;
- Peru: it is mandatory to submit a CPP issued by any country with a Positive Marketing Status. Submission of the manufacturing agreement between the proposed holder of registration and the manufacturing site is also accepted as long as the CPP is presented afterwards during the process dossier review;
- Uruguay: it is not mandatory to have approval in the COO, but the process is more complex and there is a risk of rejection;
- Paraguay, Aruba, Curacao, Trinidad & Tobago, Jamaica, Saint Maarten: the product must be approved and marketed in the COO;
- Costa Rica: the CPP could be from the COO or from the country of the proposed holder of the registration in Costa Rica (if the product is not marketed in the COO);
- Guatemala: it is mandatory to submit a CPP issued by any country with Positive Marketing Status;
- Colombia: the CPP should be issued by HA of the manufacturing country, of the exporting country, of one of the reference countries, or of one country for which there is Mutual Recognition (countries that are members of the European Union).

IS THIS MANDATORY THAT THE PRODUCT BE APPROVED IN THE ORIGIN COUNTRY TO SUBMIT A NEW MARKETING APPLICATION?



Approval in COO is not mandatory: Brazil, Chile, Bolivia, Mexico, Uruguay, Argentina, Peru, Costa Rica, El Salvador, Honduras, Nicaragua, Guatemala

Approval in COO is mandatory: Panama, Curacao, Aruba, Jamaica, St Marteen, Trinidad & Tobago, Colombia, Paraguay, Venezuela, Ecuador and Dominican Republic

In conclusion, for 57% (12/23) of the markets it is mandatory to have the product approved in the COO before submission or approval and for 43% (11/23) of the markets it is not a mandatory requirement. Therefore, it is important to take it into account when planning the submissions in this region.

3.2 Approval in a COR

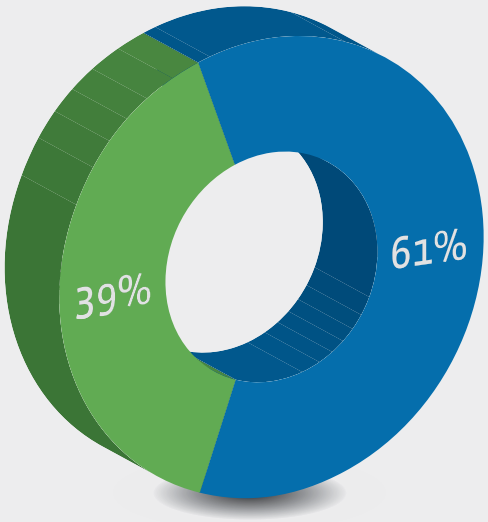
In 14 out of 23 markets, for a new marketing application, it is not mandatory that the product is approved in the reference country. These markets are Chile, Bolivia, Peru, Mexico, Uruguay, Argentina, Paraguay, Costa Rica, Honduras, Nicaragua, Panama, Colombia, Venezuela and Dominican Republic.

Nevertheless, this is mandatory for 9 out of 23 markets involved in this assessment. These 9 markets are Brazil, El Salvador, Guatemala, Aruba, Curacao, Jamaica, Saint Maarten, Trinidad & Tobago and Ecuador.

During this evaluation, some market particularities were found such as in Brazil where it is mandatory to present a proof that the product is registered in any country. Additionally, for Ecuador it is mandatory to have the product approved in a CoR just in cases of Homologation processes (a type of new marketing authorization application with simplified requirements which is based on official recognition of the registration granted by a COR).

For Colombia, although it is not mandatory that the product is approved in a reference country, it is desirable and for Guatemala, although it is not mandatory that the product is approved in the COR, the CPP from another country where the product is marketed must be submitted to the Health Authority.

IS IT MANDATORY TO HAVE THE PRODUCT APPROVED IN THE REFERENCE COUNTRY TO HAVE APPROVAL OF A NEW MARKETING AUTHORIZATION?



- Yes (9/23) : Brazil, El Salvador, Guatemala, Aruba, Curacao, Jamaica, Saint Maarten, Trinidad & Tobago and Ecuador
- No (14/23) : Chile, Bolivia, Peru, Mexico, Uruguay, Argentina, Paraguay, Costa Rica, Honduras, Nicaragua, Panama, Colombia, Venezuela and Dominican Republic

In conclusion, for 61% (14/23) of the markets it is not mandatory to have the product approved in the COR to submit a new marketing application and for 39% (9/23) of the markets it is mandatory that the product is approved in the COR to submit a new marketing application.

4. DOCUMENTS REQUIRED FOR NEW MARKETING APPLICATION IN LATAM COUNTRIES TO SHOW REGISTRATION STATUS IN THE COO OR COR

In the new marketing application package, the CPP issued by the COO could be submitted in all 23 Latin America markets assessed on this evaluation, this means that this approach is accepted by Brazil, Chile, Bolivia, Peru, Mexico, Uruguay, Argentina, Paraguay, Costa Rica, El Salvador, Honduras, Nicaragua, Guatemala, Panama, Aruba, Curacao, Jamaica, Saint Maarten, Trinidad & Tobago, Colombia, Venezuela, Ecuador and Dominican Republic markets.

Additionally, CPP issued by the COR is accepted in 8 out of 23 markets: Brazil, Chile, Uruguay, Argentina, El Salvador, Guatemala, Colombia and Ecuador. There are some particularities for Argentina in which this condition could be accepted if the country is listed in the Annex I or Annex II and the manufacturer is mentioned in this CPP.

The Exporting Certificate issued by a country involved in another step (such as exportation, release) is accepted by 9 out of 23 markets: Brazil, Mexico, El Salvador, Aruba, Curacao, Jamaica, Saint Maarten, Trinidad & Tobago and Ecuador.

The Approval Letter issued by the COO is accepted by a few markets (4 out of 23 markets): Brazil, El Salvador, Colombia and Ecuador.

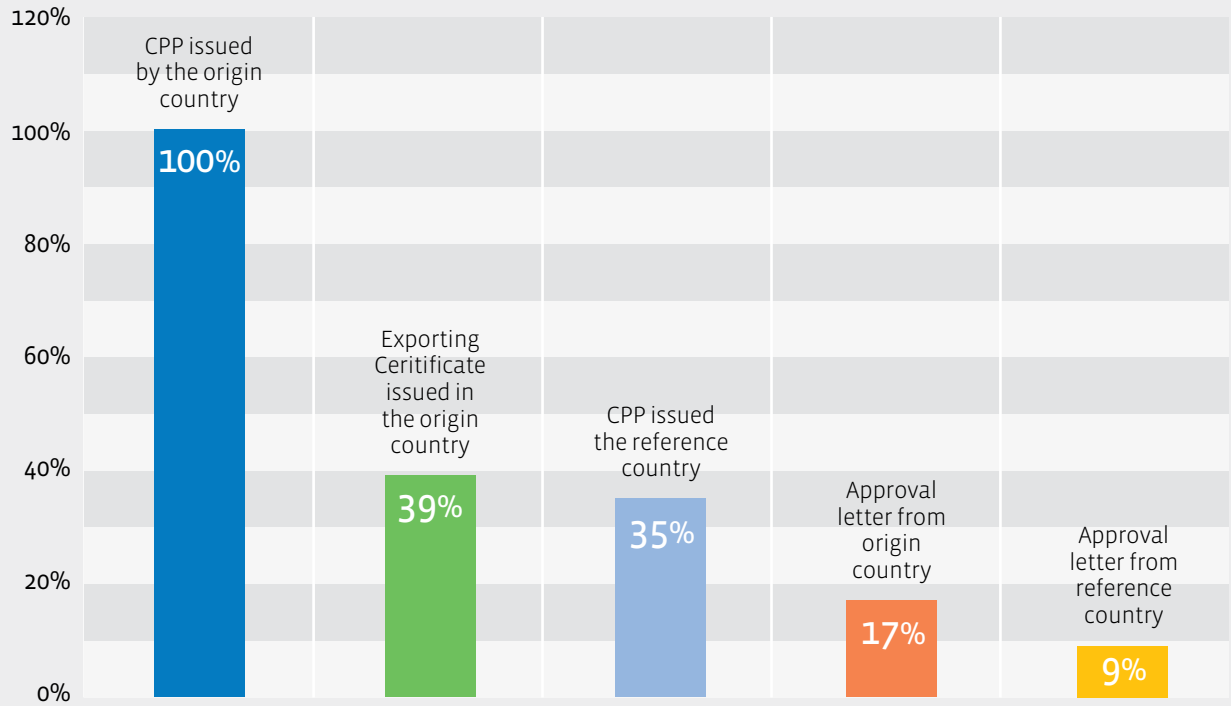
Only 2 out of 23 markets accept the Approval Letter issued by the COR. These markets are Brazil and Ecuador. In Ecuador, this document is mandatory for the procedures of Homologation.

Additionally, in the new marketing application, specifically for Mexico, it is possible to present the Free Sale Certificate or Clinical Study Report with Mexican patients.

To summarize, 100% (23/23) of the markets accept the CPP issued by the origin country.

- 35% (8/23) of the markets accept the CPP issued by the reference country.
- 39% (9/23) of the markets accept the exporting certificate issued by the origin country.
- 17% (4/23) of the markets accept the approval letter from the origin country.
- 9% (2/23) of the markets accept the approval letter from the reference country.

DOCUMENTATION ACCEPTED IN THE NEW MARKETING APPLICATION



Brazil is the only market in LATAM that accepts all the options presented here: CPP from the origin country, CPP from the reference country, exporting certificate, approval letter from the origin country, approval letter from the reference country.

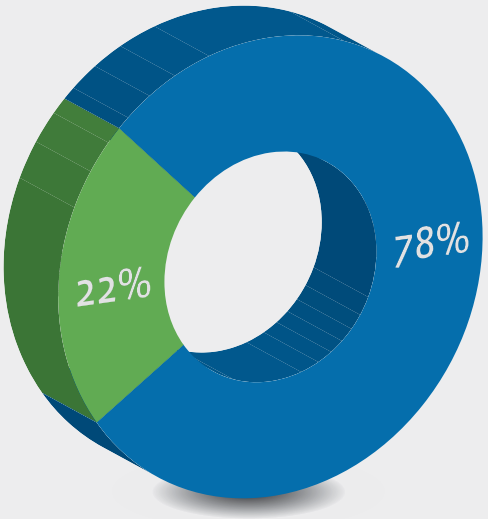
Regarding the possibility to submit a new marketing application without the approval in the origin/reference country but amend it during the review process by the Health Authority, this approach could be accepted by Brazil, Chile, Bolivia, Peru and Mexico. Specifically for Peru it would be required to submit the Manufacturing Agreement for the marketing application and then present the CPP afterwards during the dossier review.

Additionally, in Mexico, although it is possible to submit the new marketing application without the approval in the origin country, in the submission it is required to provide at least the Exporting Certificate and it is not possible to amend the filing.

On the other hand, this approach is not accepted for many of Latin America markets. 18 out of 23 markets do not accept the submission of a new marketing application without the approval in the origin/reference country. These markets are Uruguay, Argentina, Paraguay, Costa Rica, El Salvador, Honduras, Nicaragua, Guatemala, Panama, Aruba, Curacao, Jamaica, Saint Marteen, Trinidad & Tobago, Colombia, Venezuela, Ecuador and Dominican Republic.

To sum up, in 22% (5/23) of the markets it is possible to submit a new marketing application without the approval in the origin/reference country but amend it during the process review and 78% (18/23) of the markets do not accept this approach.

SUBMISSION OF A NEW MARKETING APPLICATION WITHOUT THE APPROVAL IN COO/COR



Yes (5/23) :
Brazil, Chile, Bolivia, Peru, Mexico

No (18/23) :
Uruguay, Argentina, Paraguay, Costa Rica, El Salvador, Honduras, Nicaragua, Guatemala, Panama, Aruba, Curacao, Jamaica, Saint Maarten, Trinidad & Tobago, Colombia, Venezuela, Ecuador and Dominican Republic

5. IMPLICATIONS OF MARKETING AUTHORIZATION CANCELLATION IN THE COO OR COR

Another important issue raised was the evaluation of the implications in case the company requests the marketing authorization cancellation in the country that issued the Certificate of Pharmaceutical Product (hereafter referred to as “CPP”) or any other Certificate used for submission in a country of Latin America region.

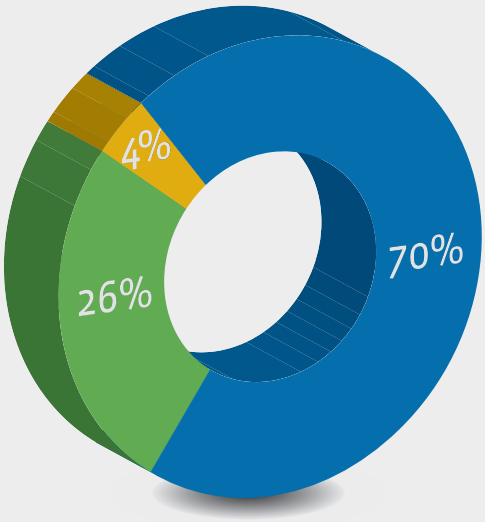
For this evaluation, three main aspects were considered: the first was if the Health Authority of the respective Latin America country that holds the license registration should be communicated about the cancelation, the second was if the marketing authorization in the respective country is cancelled as well, and the third is if another CPP or similar document (as per the options described on item 4 of this article) from a reference country should be submitted to the Health Authority of the respective country.

Based on the results evaluation for the first aspect it was possible to conclude that for 16 out of 23 of the countries assessed (70% – Uruguay, Argentina, El Salvador, Honduras, Nicaragua, Guatemala, Panama, Aruba, Curacao, Jamaica, St. Maarten, Trinidad, Colombia, Venezuela, Dominican Republic and Ecuador) it is required to communicate the Health Authority. Specifically for Ecuador the communication is required only when the marketing authorization has been granted through Homologation process.

For 1 out of 23 markets (4% – Brazil) the communication of cancellation to the Health Authority is determined based on the Marketing Authorization status: if it is still ongoing it is required to communicate the Health Authority, but if approval has already been granted, communication is not required.

For the remaining countries, 6 out of 23 (26% – Chile, Bolivia, Peru, Mexico, Paraguay and Costa Rica), the Health Authority does not need to be communicated about the Marketing Authorization cancellation.

COMMUNICATION OF MA CANCELATION IN THE COO OR COR TO LATIN AMERICA COUNTRIES



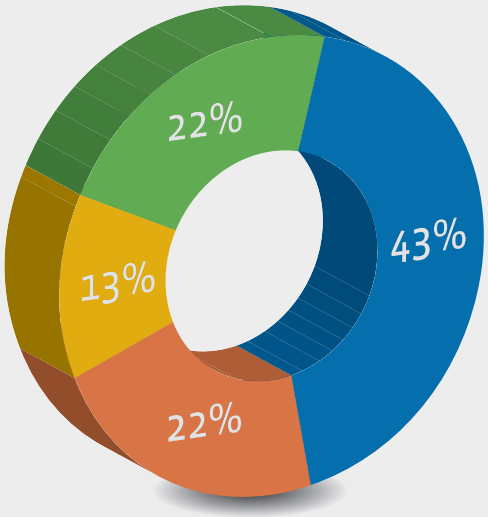
- NOT REQUIRED (6/23): Chile, Bolivia, Peru, Mexico, Paraguay and Costa Rica.
- REQUIRED (16/23): Uruguay, Argentina, El Salvador, Honduras, Nicaragua, Guatemala, Panama, Aruba, Curacao, Jamaica, St. Maarten, Trinidad & Tobago, Colombia, Venezuela, Dom. Republic, Ecuador* (*when MA has been granted through homologation process).
- DEPENDS ON THE STAGE OF THE MA (1/23): Brazil

As for the second aspect, it was evaluated if the marketing authorization cancellation in the country that issued the CPP or any other Certificate would also lead to the cancellation of the marketing authorization of that specific country.

The conclusion was that the Marketing Authorization is not cancelled in most of the countries, 18 out of 23, however there are a few relevant aspects that should be taken into account. First is that for 5 countries (22% – Brazil, Chile, Bolivia, Mexico and Ecuador) the Marketing Authorization is not cancelled. Second, for 10 countries (43% – Uruguay, Argentina, Honduras, Nicaragua, Guatemala, Panama, Dominican Republic, Colombia, Venezuela and El Salvador) the registration is kept as long as a CPP or Approval Letter from another reference country is submitted to the Health Authority. And for 3 countries (13% – Paraguay, Costa Rica and Peru), even though cancellation is not an immediate result, the consequence may be quite significant: the marketing authorization renewal would be difficult in Paraguay and in Costa Rica, and it would not be possible in Peru.

For the remaining countries, 5 out of 23 (22% – Aruba, Curacao, Jamaica, Saint Maarten and Trinidad & Tobago), the marketing authorization is cancelled as well.

IMPLICATION OF MA CANCELATION IN THE COO OR COR TO LATIN AMERICA COUNTRIES



- MA IS CANCELLED (5 /23) : Aruba, Curacao, Jamaica, St. Maarten and Trinidad & Tobago.
- MA IS NOT CANCELLED BUT ANOTHER CPP/ APPROVAL LETTER SHOULD BE SUBMITTED: Uruguay, Argentina, Honduras, Nicaragua, Guatemala, Panama, Dom. Republic, Colombia, Venezuela and El Salvador.
- MA IS NOT CANCELLED (5 /23): Brazil, Chile, Bolivia, Mexico and Ecuador.
- MA IS NOT CANCELLED BUT RENEWAL WILL BE IMPACTED (3/23): Peru, Paraguay and Costa Rica.

The third aspect evaluated was the need to submit to the Health Authority in the respective country a CPP or an Approval Letter from another reference country in order to maintain the Marketing Authorization.

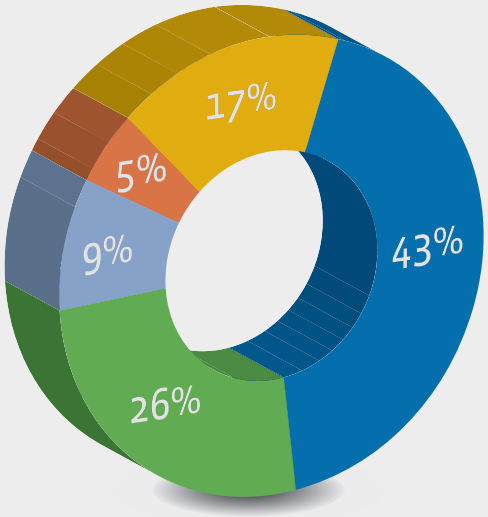
For 10 out of 23 countries (43% – Uruguay, Argentina, Honduras, Nicaragua, Guatemala, Panama, Dominican Republic, Colombia, Venezuela and El Salvador) this aspect is directly related to the previous one, as it was evidenced it is possible to keep a marketing authorization in a determined country if a CPP or an Approval Letter from another reference country is submitted.

For 2 out of 23 countries (9% – Paraguay and Costa Rica) a CPP or an Approval Letter from another reference country may be submitted at the time of renewal but there is a significant risk involved, and for 1 out of 23 (5% – Brazil) it should be submitted to support a marketing authorization only when the registration is still ongoing.

Submission of a CPP or an Approval Letter from another reference country is not required for 4 out of 23 countries (17% – Chile, Bolivia, Mexico and Ecuador).

It was also evidenced that for 6 out of 23 countries (26% – Peru, Aruba, Curacao, Jamaica, Saint Maarten and Trinidad & Tobago) the submission of a CPP or an Approval Letter from another reference country is not supportive to keep the existing marketing authorization, instead it would just enable a new application to be submitted.

DOCUMENTS (CPP/APPROVAL LETTER) REQUIRED BY LATIN AMERICA COUNTRIES WHEN MA IN COO OR COR IS CANCELLED



- NO OTHER CPP / APPROVAL LETTER IS REQUIRED (4/23) : Chile, Bolivia, Mexico and Ecuador.
- OTHER CPP / APPROVAL LETTER IS REQUIRED (10/23) : Uruguay, Argentina, El Salvador, Honduras, Nicaragua, Guatemala, Panama, Dominican Republic, Colombia (country for which there is Mutual Recognition) and Venezuela.
- ANOTHER CPP / APPROVAL LETTER IS REQUIRED BUT IT WILL BE A NEW APPLICATION (6/23) : Peru, Aruba, Curacao, Jamaica, St. Maarten and Trinidad & Tobago.
- ANOTHER CPP / APPROVAL LETTER MAY BE AN OPTION FOR RENEWAL (2/23) : Paraguay and Costa Rica.
- ANOTHER CPP / APPROVAL LETTER IS REQUIRED WHEN REGISTRATION IS STILL ON GOING (1/23) : Brazil.

6. POST-APPROVAL CHANGES

Post-approval variation is a very complex and extensive subject, and the requirements may vary depending on the country where the change is intended to be submitted, so this was another matter evaluated within the markets.

The evaluation comprised the assessment of the impact of post-approval changes in that specific market, that means to identify the ones that require prior approval before submission, and when required, the country that should be considered.

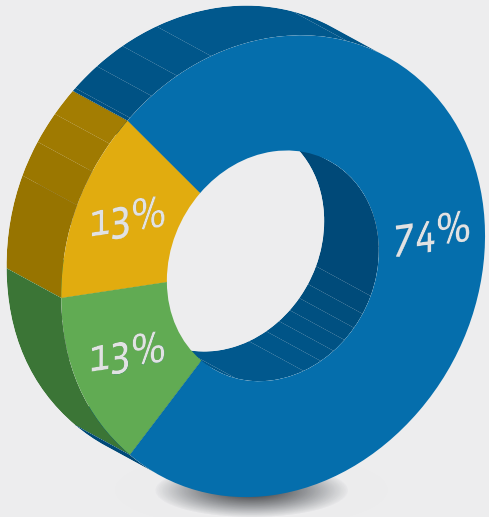
The results demonstrated that prior approval of the variations in another country is not required for 3 out of 23 markets (13% – Brazil, Guatemala and Dominican Republic), and it is required for 20 out of 23 countries assessed.

Within the countries that require the prior approval of the variations inanother country , only 3 (13% – Uruguay, Argentina and Venezuela) need prior approval for all changes, and for 17 (74% – El Salvador, Costa Rica, Chile, Bolivia, Mexico, Paraguay, Honduras, Nicaragua, Panama, Jamaica, Trinidad & Tobago, Aruba, Curacao, Saint Maarten, Ecuador, Paraguay and Colombia) prior approval is required for specific changes, which are indicated as follows:

a) Prior approval required for the changes in the registered information: El Salvador.
b) Prior approval required for the changes which impact in the CPP: Costa Rica.
c) Prior approval required for change in:
   - Bulk manufacturer & Primary packaging: Chile.
   - Manufacturer: Bolivia, Mexico, Paraguay (name of manufacturer), Honduras, Nicaragua, Panama, Jamaica, Trinidad & Tobago, Ecuador (addition or elimination of alternative manufacturer).
   - Packager: Paraguay (name of manufacturer), Aruba, Curacao, Jamaica, Saint Maarten, Trinidad & Tobago.
   - Formulation: Chile, Bolivia, Mexico, Paraguay, Honduras, Nicaragua, Panama, Ecuador (excipients only).
   - New indications: Chile, Honduras, Nicaragua, Panama.
   - Legal changes: Bolivia, Mexico.
   - Labeling: Peru
   - Shelf-life: Mexico, Paraguay, Ecuador.
   - Pharmaceutical Form: Honduras, Nicaragua, Panama.
   - Marketing Authorization Holder: Honduras, Nicaragua, Panama.
   - Address of Marketing Authorization Holder: Honduras, Nicaragua, Panama.
   - Name of Marketing Authorization Holder: Ecuador.
   - Name of drug product: Aruba, Curacao, Jamaica, Saint Maarten, Trinidad & Tobago, Ecuador.
   - Name of legal entity: Jamaica, Trinidad & Tobago.
   - Pack size: Jamaica.
   - Address / Name of manufacturing site, release site, packaging site: Colombia, Ecuador (name of manufacturer).

Moreover there are a few other specific variation requirements in Ecuador, for which it is also needed that the variation is previously approved in the COO. These variations are: change in nature of packaging material, change in name of the applicant, change in manufacturing site location within the same city, change in presentation, change in size or color of the capsules, and change of city or country of alternate manufacturer.

REQUIREMENT OF PRIOR APPROVAL OF CHANGES IN ANOTHER COUNTRY BEFORE SUBMISSION IN LATAM REGION



- PRIOR POST-APPROVAL IS NOT REQUIRED (3/23): Brazil, Guatemala and Dominican Republic.
- PRIOR POST-APPROVAL IS REQUIRED FOR ALL CHANGES IN ANOTHER COUNTRY (3/ 23): Uruguay, Argentina and Venezuela.
- PRIOR POST-APPROVAL IS REQUIRED FOR SPECIFIC CHANGES (17/23): El Salvador, Costa Rica, Chile, Bolivia, Mexico, Paraguay, Honduras, Nicaragua, Panama, Jamaica, Trinidad, Aruba, Curacao, St. Maarten, Ecuador, Paraguay and Colombia.

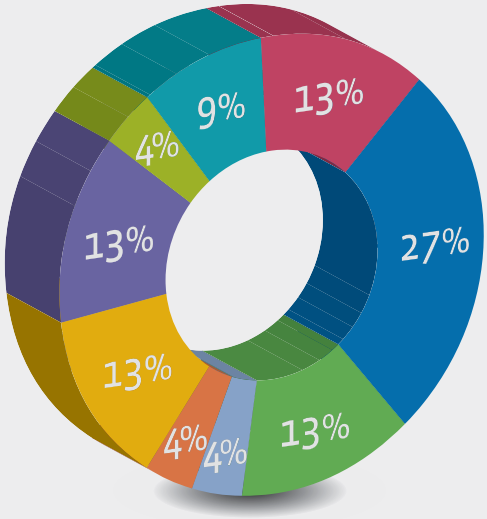
As previously indicated, for 3 out of 23 markets (13% – Brazil, Guatemala and Dominican Republic) it is not required that the variation is prior approved, and therefore for these countries it is not required that a CPP or Approval Letter is submitted either.

For 1 out of 23 markets (4% – El Salvador) presenting a CPP or Approval Letter is a case by case evaluation, so the actual submission of this document is unpredictable.

For the other countries assessed, it is required that a CPP or Approval Letter is presented and the country that should issue this document may vary as follows:

a) 2/23 (9%) – CPP or Approval Letter does not need to be from the same country as the CPP initially submitted: Chile and Peru (both countries accept if it is issued by COR);
b) 3/23 (13%) – CPP or Approval Letter needs to be from the same country as the CPP initially submitted: Bolivia, Costa Rica and Venezuela;
c) 6/23 (27%) – CPP or Approval Letter needs to be from the COO: Uruguay, Paraguay, Aruba, Curacao, Colombia and Ecuador;
d) 3/23 (13%) – CPP or Approval Letter needs to be from the same country as the CPP initially submitted and also from the COO: Honduras, Nicaragua and Panama;
e) 1/23 (4%) – CPP or Approval Letter needs to be from the manufacturing country: Argentina;
f) 1/23 (4%) – Country that should issue the CPP is not specified: Mexico;
g) 3/23 (13%) – CPP depends on the type of post-approval variation:
   - Jamaica: CPP needs to be from the same country as the CPP initially submitted for change in pack size and CPP from the COO for change in manufacturer, packaging source, legal entity name;
   - Saint Maarten: CPP needs to be from the same country as the CPP initially submitted for change in name of the product and CPP from the country of origin for change in packaging source.
   - Trinidad & Tobago: CPP needs to be from the country of origin for change in manufacturer, packaging source, legal entity name.

REQUIREMENT OF CPP PRESENTATION FOR POST-APPROVAL CHANGE SUBMISSION IN LATAM COUNTRIES



- CPP IS NOT REQUIRED (3/23): Brazil, Guatemala and Dominican Republic.
- CPP MAY BE REQUIRED - CASE BY CASE EVALUATION (1/23) : El Salvador.
- CPP DOES NOT NEED TO BE FROM THE SAME COUNTRY AS THE CPP INITIALLY SUBMITIED (2/23) : Chile and Peru.
- CPP NEEDS TO BE FROM THE SAME COUNTRY AS THE CPP INITIALLY SUBMITIED (3/23): Bolivia, Costa Rica and Venezuela.
- CPP NEEDS TO BE FROM THE COUNTRY OF ORIGIN (6/23): Uruguay, Paraguay, Aruba, Curacao, Colombia and Ecuador.
- CPP NEEDS TO BE FROM THE SAME COUNTRY AS THE CPP INITIALLY CUBMITIED AND ALSO THE COUNTRY OF ORIGIN (3/23) : Honduras, Nicaragua and Panama.
- CPP NEEDS TO BE FROM THE MANUFACTURING COUNTRY (1/23): Argentina.
- NO INFORMATION PROVIDED ON THE COUNTRY THAT SHOULD ISSUE THE CPP (1/23) : Mexico.
- CPP DEPENDS ON THE TYPE OF POST-APPOVAL VARIATION (3/23): Jamaica, St . Maarten and Trinidad & Tobago.

7. CONCLUSION

As described in this position paper, there is a considerable variance in rules and concepts on CPP for Latin America markets. These differences tend to create a complex regulatory scenario for pharmaceutical industries.

Therefore the harmonization of the rules and concepts on documents from COR or COO (as CPP) required for submission in Latin America countries would make it easier and faster to obtain a marketing authorization and, as a consequence, there would also be a significant decrease in the delays on the delivery of safe and effective medicines to patients. Considering the lead-time for issuing, legalizing and notarizing a CPP in which also cause impact and delays in dossier submissions, this harmonization would also be relevant for the criteria in accepting another relevant document as an evidence of registration and approval in COO or COR.

MASTHEAD / EXPEDIENTE

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