REPORT

ASSESSING THE CERTIFICATE OF PHARMACEUTICAL PRODUCT (CPP) REQUIREMENTS FOR THE DRUG REGISTRATION PROCESSES IN THE REGION OF THE AMERICAS, TOWARDS A MORE TIMELY ACCESS TO MEDICINES AND MORE CONVERGENT REGULATORY APPROACHES

2020

Project of the Pan American Network for Drug Regulatory Harmonization (PANDRH Network) jointly coordinated by CECMED and FIFARMA

PANDRH
Pan American Network for Drug Regulatory Harmonization

CECMED
Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos

FIFARMA

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The group would like to dedicate the work to an esteemed colleague who is no longer with us, Dr. Rafael Pérez Cristiá, former director of CECMED, a great enthusiast of regulatory cooperation, who would undoubtedly be very satisfied with the work done.

The project team

LIST OF ABBREVIATIONS, ACRONYMS AND CODES

A

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines and Medical Devices)

APRaD: Association of Pharmaceutical Research and Development Laboratories (APRaD) (Colombia).

AGEMED: Agencia Estatal de Medicamentos y Tecnologías en Salud (State Agency for Drugs and Health Technologies) (Bolivia).

AGES: Austrian Agency for Health and Food Safety.

AIFA: Agenzia Italiana del Farmaco (Italian Medicines Agency).

ALAFARPE: Asociación Nacional de Laboratorios Farmacéuticos (National Association of Pharmaceutical Laboratories) (Peru).

ALIFAR: Asociación Latinoamericana de Industrias Farmacéuticas (Latin American Association of Pharmaceutical Industries).

AMIIF: Asociación Mexicana de Industrias de Investigación Farmacéutica (Mexican Association of Pharmaceutical Research Industries).

ANMAT: Agencia Nacional de Medicamentos, Alimentos y Tecnología Médica (National Administration of Drugs, Foods and Medical Devices) (Argentina).

ANSM: Agence Nationale de Sécurité du Médicament et des Produits de Santé (National Agency for the Safety of Medicines and Healthcare Products) (France).

ANVISA: Agencia Nacional de Vigilancia Sanitaria (Brazilian Health Regulatory Agency) (Brazil).

AR: Argentina.

ARCSA: Agencia Nacional de Regulación, Control y Vigilancia Sanitaria (Regulatory Control and Surveillance National Agency) (Ecuador).

ARSA: Agencia de Regulación Sanitaria (Sanitary Regulation Agency) (Honduras).

AT: Austria.

AU: Australia.

B

BB: Barbados.

BE: Belgium.

BFARM: Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices) (Germany).

BO: Bolivia.

BR: Brazil.

BZ: Belize.

C

CA: Canada.

CAEME: Cámara Argentina de Especialidades Medicinales (Argentine Chamber of Medical Specialties).

CARICOM: Caribbean Community.

CAVEME: Cámara Venezolana del Medicamento (Venezuelan Chamber of Medicine).

CECMED: Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (Centre for State Control of Medicines and Medical Devices) (Cuba).

CEFA: Cámara de Especialidades Farmacéuticas y Afines (Chamber of Pharmaceutical Specialties and Related Products) (Uruguay).

CIF: Cámara de la Innovación Farmacéutica (Chamber of Pharmaceutical Innovation) (Chile).

CL: Chile.

CFS: Certificate of Free Sale.

CO: Colombia.

COFEPRIS: Comisión Federal para la Protección contra Riesgos Sanitarios (Federal Commission for Protection against Sanitary Risk) (Mexico).

CPP: Certificate of Pharmaceutical Product.

CR: Costa Rica.

CRS: Caribbean Regulatory System.

CU: Cuba.

D

DE: Germany.

DIGEMID: Dirección General de Medicamentos, Insumos y Drogas (General Directorate of Medicines, Supplies and Drugs) (Peru).

DK: Denmark.

DMA: Danish Medicines Agency.

DO: Dominican Republic.

DPM/MT-MSPP: Direction de la Pharmacie, du Médicament et de la Médecine Traditionnelle du Ministère de la Santé Publique et de la Population (Directorate of Pharmacy, Medicines and Traditional Medicine of the Ministry of Public Health and Population) (Haiti).

E

EC: Ecuador.

EMA: European Medicines Agency.

EPAR: European Public Assessment Report.

ES: Spain.

EU: European Union.

F

FAMHP: Federal Agency for Medicines and Health Products (FAMHP) (Belgium).

FDA: Food and Drug Administration (United States).

FEDEFARMA: Federación Centroamericana de Laboratorios Farmacéuticos (Central American Federation of Pharmaceutical Laboratories) (regional chapter of the IFPMA).

FI: Finland.

FIFARMA: Federación Latinoamericana de la Industria Farmacéutica. (Latin American Federation of Pharmaceutical Industry).

FIMEA: Finnish Medicines Agency (Agencia Finlandesa de Medicamentos).

FR: France.

G

GMP: Good Manufacturing Practices.

GT: Guatemala.

H

HC: Health Canada.

Health: Ministry of Health (Israel).

HN: Honduras.

HPRA: Health Products Regulatory Authority (Ireland).

HT: Haiti.

HU: Hungary.

I

IE: Ireland.

IFI: Industria Farmacéutica de Investigación (Research and Innovation Pharmaceutical Industry Corporation) (Ecuador).

IFPMA: International Federation of Pharmaceutical Manufacturers & Associations.

IGZ: Inspectie Gezondheidszorg en Jeugd (Healthcare and Youth Care Inspectorate) (The Netherlands).

IL: Israel.

IL: Instruction leaflet.

IMA: Icelandic Medicines Agency.

IND: Industry.

INFARMED: Instituto Nacional da Farmácia e do Medicamento (National Authority of Medicines and Health Products) (Portugal).

INN: International Non-proprietary Name.

INTERFARMA: Associação da Indústria Farmacêutica de Pesquisa (Pharmaceutical Research Industry Association) (Brazil).

INVIMA: Instituto Nacional de Vigilancia de Medicamentos y Alimentos (National Institute of Food and Drug Monitoring) (Colombia).

IS: Iceland.

ISP: Instituto de Salud Pública (Institute of Public Health) (Chile).

IT: Italy.

J

JM: Jamaica.

JP: Japan.

K

KR: Korea.

L

LATAM: Latin America.

LI: Liechtenstein.

LLV: Oficina de Salud - Departamento de Farmacia (Health Office - Pharmacy Department) (Liechtenstein).

M

MEDSAFE: New Zealand Medicines and Medical Devices Safety Authority (New Zealand).

MFDS: Ministry of Food and Drug Safety (Korea).

MHRA: Medicines and Healthcare Products Regulatory Agency (United Kingdom).

MINSA: Ministerio de Salud (Ministry of Health). Dirección General de Regulación Sanitaria (General Directorate of Health Regulation) (Nicaragua).

MINSA: Ministerio de Salud (Ministry of Health). Dirección Nacional de Farmacia y Drogas (National Directorate of Pharmacy and Drugs (Panama).

MISALUD: Ministerio de Salud (Ministry of Health) (Costa Rica).

MOH: Ministry of Health (Suriname).

MPA: Medical Products Agency (Sweden).

MSPAS: Ministerio de Salud Pública y Asistencia Social (Ministry of Public Health and Social Assistance) (Guatemala).

MX: Mexico.

N

n: Sample size of the survey.

N/A: Not applicable.

NDM: Dirección Nacional de Medicamentos (National Directorate of Medicines) (El Salvador).

NI: Nicaragua.

NL: The Netherlands.

NMA: Norwegian Medicines Agency (Norway).

NO: Norway.

NRA: National Regulatory Authority.

NZ: New Zealand.

O

OGYEI: Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet (National Institute of Pharmacy and Nutrition) (Hungary).

P

PA: Panama.

PAHO: Pan American Health Organization.

PANDRH: Pan American Network for Drug Regulatory Harmonization (PANDRH Network).

PDF: Portable Document Format.

PE: Peru.

PIL: Patient Information Leaflet.

PMDA: Pharmaceuticals and Medical Devices Agency (Japan).

PRAIS: Plataforma Regional de Acceso e Innovación para Tecnologías Sanitarias. (Regional Platform on Access and Innovation for Health Technologies).

PY: Paraguay.

R

Resolución CD50.R9: 50.th Resolution of the Steering Committee of the Pan American Health Organization/World Health Organization, 9/27 to 10/1/2010 "Strengthening National Regulatory Authorities for Medicines and Biologicals."

rNRA: National Regulatory Authority of Regional Reference.

RTCA: Reglamento Técnico Centroamericano (Central American Technical Regulations).

S

SC: Confederación Helvética (Swiss Confederation).

SE: Sweden.

SINDUSFARMA: Sindicato da Indústria de Produtos Farmacêuticos (Pharmaceutical Products Industry Union) (Brazil).

SPC: Summary of Product Characteristics.

SR: Suriname.

SV: El Salvador.

SWISSMEDIC: Swiss Agency for Therapeutic Products.

T

TGA: Therapeutic Goods Administration (Australia).

TT: Trinidad and Tobago.

U

UK: United Kingdom.

US: United States.

UY: Uruguay.

V

VE: Venezuela.

W

WHO: World Health Organization.

I. INTRODUCTION

1. Background

This document presents a summary of the analysis of the results for the assessment of the requirements and practices for the acceptance, use and issuance of the Certificate of Pharmaceutical Product (CPP) as a key document in the regulatory processes of medicine registration in the region of the Americas, and in the legal basis supporting its use.

The aim is to summarize the impact of the CPP in the registration of the pharmaceutical products in the region in order to identify convergences and divergences, to generate points of consensus and to promote good practices and actions that allow for mitigating the time gaps in the availability of the medicines between the countries of the regions and those which are more technologically developed.

1.A THE WHO CERTIFICATION SCHEME

The World Health Organization (WHO) scheme for the certification of the pharmaceutical products subject to international commerce —is referred to as "Scheme" or "Certification Scheme" in this text— is an international voluntary agreement to provide information among the Regulatory Authorities (NRAs) of all countries participating on the pharmaceutical products that are exported and imported.

The Scheme was agreed upon by the Member States of the WHO as from the Resolution WHA22.50 (1969)[1] of the World Health Assembly. It corresponds to an administrative instrument that is intended to extend and unify several agreements among health authorities of the Member States, importers and exporters of medicines, aiming at ensuring the quality, safety and efficacy required for the pharmaceutical products commercialized globally. The Scheme was revised and later extended by means of Resolutions WHA28.65 (1975)[2], WHA41.18 (1988)[3], WHA45.29 (1992)[4], and WHA50.3 (1997)[5].

The Certificate of Pharmaceutical Product (CPP) is the main document in the Scheme. It represents a tool that allows the NRAs to share information and to avoid the duplication of efforts. The CPP, introduced in 1975, has been widely used in the submission processes of registration applications for the import of medicines around the world. The main purpose is to be an instrument that enables to contribute to the assurance of the standards expected in the quality of the medicines, communicating key information regarding the imported/exported medicines, mainly for the benefit of those NRAs which are less developed, and with limited resources, located in medicine importing countries.

After years of experience, the concept of CPP has faced challenges and distinctions resulting from the evolution of science, regulations and the international pharmaceutical markets. Because of this, discrepancies have arisen based on the different interpretations and uses of the CPP, triggered by the increasing complexity of the supply and manufacturing chains, the new types of products, the diversity related to regulations, legislations and others, which cause differences in the application of the document in different countries.

Some of the main challenges currently identified that do not allow for the efficient global implementation of the CPP are:

- Inconsistency in the implementation of the requirements established in the WHO guidelines for the CPP, which shows a variability for different countries, due to the information that was added or omitted, which results in an inconsistency of the procedures against the Scheme standardization purposes.
- Requirement of the CPP as a requirement to submit a registration application, which delays the access to the medicine instead of being provided at any moment before its approval.
- Limitation from some NRAs in issuing a CPP exclusively for exported products that are manufactured within the territory of the issuing NRA, which does not correspond to the globalization of the manufacturing of a product that is already manufactured locally.
- Interpretation of the CPP as an ¨export certificate¨, which does not have the scope of the CPP, but a more limited one.
- Limitations of the NRAs in issuing the CPP, which causes long delays in issuing CPP, which generates delays in the registration processes.
- Setting of short validity for the CPP, which causes the repetition of the requirements.
- Non-acknowledgement in the receiving country of the Good Manufacturing Practices (GMP) status stated by the issuing country in the CPP, which denies (or distorts) the principle with which it was created.
- Use of the WHO symbol or logo in the Certificate, gives the wrong impression that the document is authenticated by this organization.
- Lack of harmonization in the way of requesting a CPP.
- Lack of understanding of the fact that the CPP reflects the status of approval of a product only in the certifying country.
- Lack of support of the CPP concerning the different trade names of the same product.
- Falsified CPP.
- Requirements of consular legalization, or certification by Apostille, which generate a bureaucratic burden that delays the registration process involving a CPP.

To face the challenges, the WHO has led several draft revisions of its Certification Scheme and, more specifically, of the aspects related to the CPP.

In 2010, the WHO started a survey among its Member States on the use of the Scheme[6]. The answers provided indicated that the Scheme is considered to be a valuable tool for the exchange of regulatory information, but needs a higher adaptation and a more active participation by several Member States so that its application is truly useful to achieve the objectives that originated its creation.

In 2016, the WHO published an updated document of questions and answers on the Scheme[7], trying to complement aspects less clear in the Scheme. In 2018, this publication was followed by a recommendation from the WHO Expert Committee on Specifications for Pharmaceutical Preparations[8] so that the Scheme be revised by the WHO. This recommendation gave rise to a public consultation in 2018[9] that is currently under discussion.

1.B THE PAN AMERICAN NETWORK FOR DRUG REGULATORY HARMONIZATION (PANDRH NETWORK)

The PANDRH Network is an initiative by the NRAs in the region of the Americas, created in 1999 by the Pan American Health Organization (PAHO), to support the pharmaceutical regulation processes in the region. The members of the PANDRH Network are the Pan American Conference on Harmonization of Drug Regulatory Authorities, the Steering Committee and the Secretariat[10].

The founding members of the Network are the NRAs, the trade associations and other health technologies in the region, the Latin American Federation of Pharmaceutical Industry (FIFARMA) and the Latin American Association of Pharmaceutical Industries (ALIFAR). Part of the members are chosen to participate in the Steering Committee, a body that supports the Network in the decision-making process and the follow-up of projects during the periods between Conferences. The Conference is an open debate forum for discussion of common interest topics in the area of the regulation that provides the Network, in all of its structures, with the guidelines and general terms for the development of internal projects. The Pan American Health Organization (PAHO) acts as the Secretariat of the Network.

Considering priority areas and the objectives of the Strategic Development Plan, based on proposals that may arise from different interested parties, the Network Steering Committee assesses and approves the execution of projects, according to their potential contribution, to improve the regulatory convergence and to strengthen the regulatory capacities of the countries in the region.

The projects approved are led by a NRA of regional reference (defined according to the criteria of Resolution 50.R9 by the PAHO Steering Committee[11]) and their monitoring is carried out by the PANDRH Network Steering Committee that, on behalf of the NRAs in the region, verifies the adequate implementation of the activities in the work schedule, provides guidance in relation to difficulties and next steps, and provides support in any matter that may be necessary to ensure the execution of the activities initially planned in each project.

2. The project

In order to contribute to the revision initiatives of the WHO Certification Scheme, the industry representatives identified the need for generating information, related to the CPP, concerning the region of the Americas. Therefore, through FIFARMA, the proposal of the "Assessment of the CPP requirements for registration processes of medicines in the region of the Americas, towards a more timely access to medicines and more convergent regulatory approaches" project was submitted to be assessed by the PANDRH Network members.

This Project was approved by the PAHO Steering Committee in December 2017. The joint coordination of the project was in charge of FIFARMA, as the sponsor, and the Centre for State Control of Medicines, Medical Equipment and Medical Devices (CECMED) from Cuba, as a NRA of regional reference.

The purposes of the project approved were mapping the regulatory requirements related to the submission of a CPP for the registration of medicines in the region, by assessing their health value and considering the national needs and perspectives, as well as contributing to identify the opportunities of improvement for a more timely access to medicines and more convergent approaches for the regulation.

The project is based on the principle that the regular assessment and the update of the regulatory frameworks are key steps in responding to changing health needs. The timely access of patients to new health technologies is widely known as an important foundation of health protection policies, as well as the demand for said technologies to comply with technical and scientific guidelines to ensure their safety, efficacy and quality.

The regulatory systems and the NRAs in the region of the Americas have been developed for decades by means of the adoption of a series of measures to improve their capacity to ensure the quality of products and services under their jurisdiction. This implies the update of technical guidelines, the improvement of the authorities' structure and the rationalization-modernization of the administrative procedures for the submission and revision of new technologies, particularly medicine applications. The industry and the NRAs may and must collaborate, in this regard, by preserving their missions and legitimate objectives and by taking into account the patient as the main reason for their activities.

Having a permanent dialog for the assessment and update of the regulatory frameworks is one of the specific measures that may contribute to the purpose of ensuring a timely access to medicines and to treatments in general for patients. Most of the regulatory frameworks in the region require the submission of documentation that shows that an imported medicine was previously approved which, in most cases, corresponds to the CPP.

The CPP requirement varies in the region and is not exempt from the global problems and challenges we have already mentioned and that prevent Latin American countries from participating in the so-called "first wave" of submissions. This increases the time gap between the first submissions at a global level and those in the region, which seriously affects health systems, since it delays the availability of the treatment in the region.

However, there are also beneficial factors in the area, such as the maturity achieved by several regulatory systems, which may contribute to achieving transformations to eliminate or mitigate the gap without any damage or limitation for the decision-making process of the NRAs. Undoubtedly, they might have a positive impact on the management activities of the industry and of the NRA when reducing their administrative burden.

The project is aligned with the purposes of the PANDRH Network Strategic Development Plan 2014-2020[12], since it promotes the exchange of information and experiences among its members and generates information so that the NRA may revise the national regulatory requirements, in view of the changing health needs, thus contributing to the efficient performance of the essential regulatory function of medicines registration at a national level.

The diversity of the CPP forms and the need for prior approval requirements established in the region creates a noticeable opportunity for the exchange of information, in this regard, among the PANDRH Network members and, in the near future, the official approval in the shaping of criteria and decision-making regarding the agreed use of the CPP in the region of the Americas.

The project approved by the PANDRH Network does not represent the first initiative of information compilation related to the requirements and the use of the CPP in the region. One of the most recent ones corresponds to a study published in November 2017 by the Pharmaceutical Products Industry Union (SINDUSFARMA), a trade association that brings together national and multinational pharmaceutical industries in Brazil.

In the document "Comparison of concepts and rules for the CPP, country of origin and country of reference in Latin America"[13], an analysis of the situation in 23 countries in the region was submitted, which indicated the differences between the countries in Latin America in the CPP concept, country of origin and country of reference, as well as in the rules on when the CPP must be submitted. The results registered in this study correspond to the compilation of information provided by the companies associated to Sindusfarma.

The previous revision performed by SINDUSFARMA is one of the motivations for this project, which provides the opportunity to extend the universe of countries evaluated, gathering information from official sources and expanding the scope. Therefore, this allows for a more specific characterization of the regulations and the practices related to the CPP in the region of the Americas.

This project represents a relevant collaborative work by regulators and industry to enable the timely access to medicines in the region thanks both to the information provided by the health authorities and by industry representatives and the joint coordination effort of CECMED and FIFARMA, and the support offered by the PAHO.

3. Terms and definitions

To enable a better understanding of this report, a glossary with the main terms and definitions used throughout the study was included in this section.

National Regulatory Authority (NRA): Governmental entity, duly authorized, generally incorporated to the Ministry of Health or its equivalent body, which is intended to execute laws regulating the manufacturing and use of health products used in humans and, sometimes, also in animals, such as medicines —including biological and biotechnical products—, vaccines, medicines of natural origin, radiopharmaceutical products and diagnostic agents. In many cases, they also control dietary, cosmetic and cleaning products, equipment and medical devices. In general, they assess the safety, efficacy and effectiveness of the products within their scope, and they authorize and supervise the research, manufacturing, distribution and use processes during their entire lifecycle.

Trade associations: Associations of local pharmaceutical industries or national pharmaceutical companies.

Reference Regulatory Authority for the region of the Americas (rNRA): Competent authority, efficient when carrying out the health regulation functions evaluated by the PAHO with the maximum IV category, according to the assessment system used by said organization. Until 2020, eight NRAs are included in this category, namely: Food and Drug Administration (FDA), General Office of Medicines of the Ministry of Health of Canada (Health Canada), National Sanitary Surveillance Agency of Brazil (ANVISA), National Administration of Drugs, Foods and Medical Devices of Argentina (ANMAT), Public Health Institute of Chile (ISP), National Institute of Food and Drug Monitoring of Colombia (INVIMA), State Control of Medicines, Medical Equipment and Medical Devices of Cuba (CECMED) and Federal Commission for Protection against Sanitary Risk of Mexico (COFEPRIS).

Legal or technical references: It is the information about the legal and technical support that refers to the implementation of a certain requirement by a NRA. These bases were requested for each question in the survey applied in this project.

Good Manufacturing Practices (GMP): It is the set of requirements and activities related among themselves ensuring that the products are consistently produced and controlled according to the quality standards adequate to the intended use and in accordance with the conditions required for their commercialization.

Export Certificate: Document issued by the NRA of the country of export, at the request of the interested party, in which the following is stated: a) That the product has been registered and marketed in the country that was authorized. It is not related to the Scheme.

Certificate of Free Sale (CFS): Document issued by the NRA of the country of export, at the request of the interested party, in which the following is stated: a) That the product has been registered and marketed in the country that was authorized. b) That the manufacturer is subject to regular inspections and its production complies with the requirements set forth in the country for the production of medicine.

Certificate of Pharmaceutical Product (CPP): Document issued by the NRA of the country of export, at the request of the interested party, as established in the **WHO certification scheme on the quality of pharmaceutical products moving in international commerce** and in which the following is stated: a) whether the manufacturing facility complies with the Good Manufacturing Practices in relation to the basic rules that must be complied with in the processing of pharmaceutical products, recommended by the WHO; b) whether it has the authorization or not to manufacture and distribute in that country the medicine intended for export; c) whether its sale is subject to any restrictive rules or special control; and d) whether the product is in the market of the certifying country or not and, in case it is not, which are the reasons for this.

WHO certification scheme on the quality of pharmaceutical products moving in international commerce: It is a WHO activity to promote the quality and potentially of the safety and efficacy of pharmaceutical products moving in the international commerce. It consists of an administrative procedure arising from a voluntary agreement of participation by means of which guarantee is provided to participating countries regarding the quality of these products, since it allows countries of import to obtain information about the certifying country by means of certain documents, such as the **Certificate of Pharmaceutical Product (CPP)**. It was developed by the WHO in response to the request of the Member States to enable international trade of pharmaceutical products and it implies a guide both for the requesting NRA and the issuing authorities.

Marketing status of a product: Statement of a NRA of the market placement and commercialization of a medicine within the territory of its jurisdiction.

Abbreviated dossier: Application or dossier, submitted as requested in registration procedures, which contain less information, documentation or data in relation to those regularly required.

National Legislation: It refers to the legislation of a country, such as laws, regulations, decree-laws, resolutions and any other establishing the requirements for the registration of medicines and for the application and use of the CPP in said country.

Country of origin: Country where a certain product is manufactured, packed, released, distributed and exported. The criterion varies according to the country but, in general, it refers to the one intervening in some or all the stages in the manufacturing process.

CPP validity period: Time period during which the CPP validity is certified, generally as from its issuance date.

Finished product: Product that has been subject to all the production stages, presented in its final packaging, and ready to be distributed and commercialized.

Patient information leaflet/instruction leaflet/package leaflet: Written information accompanying the medicine intended for the patient or user. It offers basic and clear information, with simple language, to provide guidance on the administration, use and precautions, and also on the situations in which the patient or user must see a doctor.

PANDRH Network: Pan American Network for Drug Regulatory Harmonization. It is an initiative by the NRA in the region of the Americas and PAHO. Its purpose is to provide support on the harmonization processes of the drug regulatory authorities in this area.

Registration (Marketing Authorization): The Marketing Authorization is issued by the NRA of the certifying country by means of which the commercialization of the medicine is approved, once its quality, safety and efficacy have been deemed satisfactory, as well as the characteristics and practices followed by its manufacturer.

NRA rules or practices: These are procedures developed by the NRA to carry out the implementation of local or regional legislations. It also refers to the behaviors usually shown by them before a certain situation, even though there is no specific legislation in relation to it.

Summary of Product Characteristics (SPC) or Product data sheet: Specialized information published for health professionals so that the product is prescribed, dispensed and used in a rational, safe and effective manner. It widely describes the main administrative, technical and pharmacological characteristics of a product, for example: name, dosage form, strength, registration holder, presentation, registration number, composition, validity period, storage conditions, indications, contraindications, interactions, precautions and warnings, method of administration.

Package/packing site: Place where the package/packing is made during the manufacturing of a product. The packaging material is classified as primary and secondary, depending whether or not it is in direct contact with the product.

Manufacturing site: Place where the operations involved in the purchase of raw materials and products, production, quality control, approval, storage, distribution of the finished product and any related controls are carried out.

Submission of applications for new drugs or new pharmaceutical products: Procedure by means of which the documentation required to apply for the registration of a medicine is submitted before the NRA according to the current provisions set forth.

Submission of applications for variations: Procedure by means of which the documentation required to apply for variations in the registration of a medicine is submitted before the NRA.

Submission of applications for renewals: Procedure by means of which the documentation required to apply for the renewal of the registration of a medicine is submitted before the NRA, once the validity period granted to the product has expired.

Marketing authorization (Registration) holder: Individual or legal entity on behalf of which the registration of a medicine for human use is granted.

Fast track/accelerated/simplified pathways to register a medicine: Expedited processes of registration, generally with lower response times than the regular ones. It may include or not the submission of all usual requirements. It may include abbreviated/simplified files.

II. MATERIALS AND METHODS

This chapter summarizes the steps and methodology of the study.

The methodological main ideas were as follows:

A • Establishing the method of interaction between the coordinators;

B • Development of the instrument for collecting the data to be processed;

C • Distribution of the survey to the NRAs and the industry;

D • Processing and organizing the data from the responses received to ensure their subsequent evaluation;

E • Evaluation of the compiled information by matching and comparing the data, and looking more closely at the references mentioned;

F • Preparation of the report;

G • Providing the mechanisms to ensure transparency of project information;

H • Establishing the stages and deadlines for the development of the study and the elaboration of the report.

A · Interaction between the coordinators of the project

Language. The languages chosen for the exchange were Spanish and English.

E-mail. The communication between the coordinators was based on e-mail exchange for most of the activities.

Virtual meetings. Virtual meetings were considered necessary communication tools for jointly reviewing critical aspects, making decisions, planning the next steps, and sharing interim conclusions and agreements. Each session required summaries in the two languages containing the issues discussed and the arrangements made. The use of private platforms was not a common practice due to CECMED's telephone access limitations. For this reason, we used the virtual meeting room in the WebEx system of the PANDRH Network's Secretariat of the PAHO as appropriate.

Periodic reports. Spontaneous and free format periodic reports were another mechanism to update the results and the project's historical memory. The reports presented followed the official form provided by the PAHO to monitor projects and show the status of our own project at the meetings of the PANDRH Network's Steering Committee and in compliance with PAHO requests.

Allocation of Focal Points. The allocation of Focal Points, one for FIFARMA and another for CECMED, was a necessary organizational measure to expedite the analyses and attempt a consensus policy agreed upon by both parties before involving the remaining coordinators.

Public information. The public information on the steps taken was entered in both languages in the Regional Platform on Access and Innovation for Health Technologies (PRAIS) of the PAHO. FIFARMA was in charge of entering the information produced by both parties into the PRAIS. Besides, the news on the project's progress was published on the CECMED Intranet.

Face-to-face meetings. No face-to-face meetings between the project coordinators were planned.

B · Collection of the information required for characterization

B.1 Participants. The participants identified to provide information for the study were the following:

a • The NRAs of the countries of the region of the Americas that voluntarily agreed to participate in response to the project coordinators' formal invitation.

b • Industry associations from the countries with such an organization, under the same conditions as above.

c • The participation of private companies was not initially considered since the associations representing them were considered to have identical points of view. However, their participation was deemed appropriate in certain justified cases and the absence of local associations.

B . 2 Instrument for data collection

Questionnaire. A questionnaire was prepared, including topics and questions derived from aspects in the use of the CPP identified as controversial by the WHO, and in published studies and approved by consensus between CECMED and FIFARMA.

Survey. The questionnaire questions were subsequently consulted with some NRAs to elaborate a survey, based on their recommendations and using the SurveyMonkey tool. This tool facilitates collecting, processing, and turning the answers into practical perceptions to better visualize and understand the different respondents' data.

The conditions required for the questions/survey and to lay the basis for the design are the following:

a • Identification of respondents with at least the name of the institution and the name and contact details of the person responsible for the responses.

b • Inclusion of as many questions as possible with predetermined or closed-ended responses to reduce respondent effort and time, and standardization of responses to simplify their evaluation.

c • Inclusion of some questions with open response options to enter justifications or additional information, which is necessary to further examine the characterization items. Also, there was an "open response" section at the end, inviting respondents to express any comments on aspects not covered in previous questions.

d • Inclusion of references to the supporting legal and methodological documents for each response provided and their application level, either national, regional, or the NRA in itself, as appropriate. Similarly, NRA practices that guide the usual way the NRA deals with a given issue should be included, even if it is not covered in any legal provision, but rather reflects a standard behavior.

C · Administration of the survey to the NRAs and the industry

An introductory message with filling instructions, delivery deadlines, and links to access the survey was sent via e-mail. FIFARMA was responsible for locating the associations and their e-mail addresses, and CECMED was responsible for those of the NRAs. The PAHO collaborated in the support for the localization of the NRAs.

D · Processing of responses received

This stage was carried out with the support of a team of consultants hired by FIFARMA (IPRAT SRL - Intellectual Property, Regulatory Affairs, Translations) to compile and classify the initial data received from the survey participants. This consultancy work helped generate an initial raw database for project coordinators to work on during the following stages. The necessary steps were programmed as described below:

D.1 Identification of valid responses

This identification was aimed to eliminate test responses, those originated by errors in the system and, in general, those not evaluable due to any other situation, as long as both CECMED and FIFARMA agreed. Valid responses were identified with the support of the consulting company that worked on the consolidation of data, the generation of informative tables, and the recording of the results for later use in the mapping report.

D.2 Organization of the data collected in the survey

Excel worksheets were created to load the information obtained from the survey responses. The coordinators decided to present the results sorted by country rather than by category of the respondent (NRA or industry) to reach unique conclusions. This organization would ensure achieving the objective of mapping CPP regulations and practices in the region at this stage of the project, instead of obtaining a map of the individual experiences and perceptions of regulators and industry.

The data consolidation tables included different columns for each country and each question: the NRA's response, the industry association's response, CECMED's criteria, FIFARMA's opinion, and, finally, the consensus response.

E. Evaluation of responses to produce the database

The Excel worksheet was reviewed to ensure the quality of the data needed for the diagnostic or mapping report, considering the following aspects:

- Treatment of possible omitted responses.
- Level of adherence to the survey's instructions and design, i.e., consistency between the responses whose precedent question conditioned the need to respond to the following question. For example, "If the above response is Yes, please explain..." Therefore, if the previous response was No (interdependent or chained questions), there was nothing to respond to that question.
- Level of consistency between the NRA and the industry association responses (divergent responses).

The guidelines for resolving inconsistencies were agreed upon based on proposals of CECMED and FIFARMA and settled in virtual meetings.

E.1 Evaluation of responses from groups of countries with particular characteristics

During the discussions to reach an agreement on the report's development, the project coordinators identified two groups of countries whose results could provide valuable specific information of the characterization of practices in the region.

The first group included the regulatory authorities of regional reference (rNRA). Given the frontline role of these NRAs, the coordinators considered it appropriate to evaluate their practices to identify possible trends and allow, whenever possible, to compare the practices of the remaining countries in the area. The PAHO considered eight countries as having NRAs with the highest performance level (level 4), thus reaching the rNRA category: Argentina, Brazil, Canada, Chile, Colombia, Cuba, Mexico, and the United States.

The second group included the six countries that signed the Central American Technical Regulations (RTCA), namely: Costa Rica, El Salvador, Guatemala, Honduras, and Nicaragua. The authorities of these countries agree that there is a common legal and technical basis for the registration of medicines. Therefore, a relevant alignment in relation to the use of CPP can be expected. They represent the only example of a regional harmonization initiative, impacting on the marketing of their products across borders.

F · Report preparation

Based on the agreements reached by the coordinators, a general outline was defined for the study report consisting of the following chapters:

Chapter I. Introduction.
Chapter II. Materials and methods.
Chapter III. Results and discussion.
Chapter IV. Legal basis.
Chapter V. Conclusions.

F. Particular features of Chapter III. Results and discussion

Given the relevance and complexity of this chapter, the consolidated data of the questions as well as the analysis of their meaning were presented as detailed below:

- Total numerical data, percentages, and graphics, as obtained from survey analysis.
- Description and discussion of this data showing trends and key elements for the characterization of the regulations and practices regarding the use of CPPs in the region.
- Inclusion of any relevant remarks from the respondents. (Any information representing a context or an explanation for the response to the survey is considered relevant).
- Inclusion of possible divergences observed between the NRA and the industry responses.
- Summary of the policies or trends identified for the subgroups of rNRAs and NRAs in Central American countries.
- A brief reference to the conclusions of the comparison between the results observed in this study and the one carried out by SINDUSFARMA in 2017, provided that there was a coincidence in the subject matter.

G · Transparency in the development of the project

G.1 PRAIS community

To ensure that the information about the project is clear and transparent, a dedicated community was created in the PAHO's Regional Platform on Access and Innovation for Health Technologies (PRAIS), the same procedure used in other current projects. This community is periodically updated to include new information as it appears.

The PRAIS is a virtual resource integrated by a series of tools supported by the PAHO designed to facilitate the interaction between stakeholders in the health area beyond the institutional, country, and sector barriers. It is a channel to promote transparency and information flow in communities of practice, including stakeholders on a specific topic.

The information recorded takes the structure predefined on the platform and uses the following options:

- About the project. Explanation of the project, name, objectives, and stages.
- Participants. Name, association, and photograph of the participants.
- Discussions. Circulating documents, such as the survey.
- Agenda. List of events and meeting agenda.
- Library. Section for cumulative historical information: memories of meetings, reports, and presentations at events.

G.2 Publications

Actions are carried out to give visibility to the project work and its results in the different programmed stages. The coordinators share knowledge and provide information at scientific platforms and events for the regulatory community in the Americas and globally.

H · Stages and deadlines for the development of the study and the elaboration of the report

The general plan and work stages approved in December 2017 for the project by the PANDRH Network Steering Committee were used as a guide to carry out the study, including the modifications required during the development.

Phase I: developing an online survey, with the participation of the NRAs and industry members, to gather information on the way that regulatory framewoks regard CPP and its role in the regulatory pre-requirements, including the relevant standards supporting them. Due date: six months after project approval.

Phase II: developing a report on the current scenario about CPP registration pre-requirements in the region of the Americas, and the opinion of the NRAs, the industry, and, eventually, other stakeholders with appropriate expertise on the current sanitary roles of such requirements. Due date: three months after completion of Phase I.

Phase III: based on the report, identification by the participating NRA and the industry of opportunities for updating and improving the current CPP-related regulatory requirements; and the prior registration by the country of origin/exporter/holder of the marketing authorization in the drug registration processes. Due date: three months after completion of Phase II.

Phase IV: report preparation with suggested updates and improvement opportunities and, if appropriate, the views on such opportunities from other stakeholders. Due date: three months after completion of Phase III.

Fase V: submit the report to the PANDRH Network Steering Committee for the discussion of updating and improving opportunities for the current regulatory CPP-related requirements, and registration pre-requirements. If appropriate, decide future steps and submit such opportunities to the PANDRH Network Conference. Due date: immediate PANDRH Network Steering Committee meeting after completion of Phase IV.

The complete records of the changes in the project's stage schedules are included in the Steering Committee meeting minutes. They are available for consultation at the PANDRH Network Community in the PRAIS platform.

III. RESULTS AND DISCUSSION

1. Results

A · Interaction between the coordinators of the project

Virtual meetings

During the project stages and until completing the draft of this report, the coordinators held ten discussion meetings from February 2018 to January 2020. Nine were virtual meetings, as scheduled, and one was a face-to-face meeting with a representative of FIFARMA at CECMED. It was not considered as a common-practice communication approach but it was necessary due to the change of coordinator in FIFARMA.

The minutes of the meetings, agreements, results, and follow-up activities established in the referred meetings were recorded in the Library of the project community, in the PRAIS Platform, in English and Spanish versions, to make them visible and available for consultation.

For many meetings, the project coordinators used the virtual meeting room in the WebEx system of the PANDRH Network Secretariat. For the remaining sessions, FIFARMA provided its resources.

B · Collection of the information required for characterization

B.1 Participants

The call for research data sent to authorities and industry associations in the region yielded responses from 24 NRAs and one regulatory system, the Caribbean Regulatory System (CRS).

FIFARMA members were in charge of surveying the industry associations. The strategy used to generate the industry response was to maintain frequent interactions between the members of the FIFARMA Regulatory Working Group, specifically, the existing Working Sub-Group for PANDRH Network issues.

The contributions and their sources are listed in the table below.

Table I • Study participants

COUNTRY	NATIONAL REGULATORY AUTHORITY	INDUSTRY ASSOCIATION
ARGENTINA	Agencia Nacional de Medicamentos, Alimentos y Tecnología Médica (National Administration of Drugs, Foods and Medical Devices) (ANMAT).	CAEME
BARBADOS	Ministry of Health and Wellness - Barbados Drug Service.	
BELIZE	Ministry of Health.	
BOLIVIA	Agencia Estatal de Medicamentos y Tecnologías en Salud (State Agency for Drugs and Health Technologies) (AGEMED).	BAYER
BRAZIL	Agencia Nacional de Vigilancia Sanitaria (Brazilian Health Regulatory Agency) (ANVISA).	INTERFARMA
CANADA	Health Canada (HC).	
CHILE	Instituto de Salud Pública (Institute of Public Health) (ISP).	
COLOMBIA	Instituto Nacional de Vigilancia de Medicamentos y Alimentos (National Institute of Food and Drug Monitoring) (INVIMA).	APRaD
COSTA RICA	Dirección de Regulación de Productos de Interés Sanitario (Directorate for the Regulation of Products of Health Interest).	FEDEFARMA
CUBA	Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (Centre for State Control of Medicines and Medical Devices) (CECMED).	
DOMINICAN REPUBLIC		FEDEFARMA
ECUADOR	Agencia Nacional de Regulación, Control y Vigilancia Sanitaria (Regulatory Control and Surveillance National Agency) (ARCSA).	IFI
EL SALVADOR	Dirección Nacional de Medicamentos (National Directorate of Medicines).	FEDEFARMA
GUATEMALA	Departamento de Regulación y Control de Productos Farmacéuticos y Afines (Department of Regulation and Control of Pharmaceutical and Related Products).	FEDEFARMA
HAITI	Direction de la Pharmacie, du Médicament et de la Médecine Traditionnelle du Ministère de la Santé Publique et de la Population (Directorate of Pharmacy, Medicines and Traditional Medicine of the Ministry of Public Health and Population).	
HONDURAS	Agencia de Regulación Sanitaria (Sanitary Regulation Agency) (ARSA).	FEDEFARMA
JAMAICA	Ministry of Health.	ROCHE
MEXICO	Comisión Federal para la Protección contra Riesgos Sanitarios (Federal Commission for Protection against Sanitary Risk) (COFEPRIS).	AMIIF
NICARAGUA		BAYER
PANAMA	Dirección Nacional de Farmacia y Drogas (National Directorate of Pharmacy and Drugs).	FEDEFARMA
PARAGUAY		BAYER

COUNTRY	NATIONAL REGULATORY AUTHORITY	INDUSTRY ASSOCIATION
PERU	Dirección General de Medicamentos, Insumos y Drogas (General Directorate of Medicines, Supplies and Drugs) (DIGEMID).	ALAFARPE
SURINAME	Ministry of Health.	
THE CARIBBEAN	Caribbean Regulatory System (CRS).	
TRINIDAD AND TOBAGO	Chemistry/Food and Drugs Division.	ROCHE
UNITED STATES	Food and Drug Administration (FDA).	
URUGUAY	Ministry of Public Health.	CEFA
VENEZUELA	Instituto Nacional de Higiene “Rafael Rangel” (National Institute of Hygiene “Rafael Rangel”).	
27 COUNTRIES	24 ARN 1 REGULATORY SYSTEM	18 responses from countries provided by 8 pharmaceutical associations and 2 companies

B.2 Instrument for data collection

B.2.1 Questionnaire

According to the proposed methodology, a questionnaire was designed to gather the necessary data to carry out the characterization study. It included the topics and questions selected according to the focal problems identified as the main ideas of the research stated in the Introduction.

The questionnaire consisted of 10 topics and 53 questions, which, in general, referred to the central regulatory stages of the life cycle of medicines and the difficulties in using the Scheme published by the WHO in "WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce: Questions and Answers (Q&A)." The content of this document was deemed appropriate for the project.

Table II • Initial design of the questionnaire

	TOPICS	QUESTIONS
1	Submission of applications for new drugs/new pharmaceutical products.	**16**
2	Submission of renewal applications.	**3**
3	Submission of post-approval changes/variations.	**4**
4	CPP form/document content.	**4**
5	Evaluation of the CPP by the NRA.	**6**
6	Assessment of the previous registration in the country of origin.	**3**
7	Effects of registration/marketing authorization cancelation or suspension in the CPP-issuing country.	**4**
8	CPP and marketing status of the product.	**4**
9	Other relevant information.	**3**
10	NRAs that issue CPP (only for NRAs issuing CPPs).	**6**
	Total: 10 topics	**53**

B.2.2 Validation of the proposed questionnaire

The proposed questionnaire was submitted to the NRAs members of the PANDRH Network from April and May 2018 for subsequent adjustments.

The initial deadline for comments was May 15 and was extended until the end of that month. This process was considered the validation of the survey. During the period destined to comments, the project coordinators held a webinar to clarify the doubts of the stakeholders and to socialize the questionnaire. Eight NRAs sent comments on the questionnaire, and these are described in the table below.

Table III • Validation of the questionnaire on the CPP: NRAs participating and their contributions

NRA	CONTRIBUTION
Ecuador (ARCSA)	May 4, 2018. Completed the questionnaire. No remarks or recommendations.
Brazil (ANVISA)	May 18, 2018. No suggestions.
Peru (DIGEMID)	April 27, 2018. Completed the questionnaire and included questions and recommendations: "Cases of medicines accompanied by solvents and/or devices for their administration have not been considered, likewise, medicines supplied in co-packing have not been considered either, i.e., the CPP form shall contain information on the solvent, device or co-packing and their manufacturer. It does not include mandatory information required by the form either; e.g., in our country, the complete qualitative/quantitative formulation is required".
Venezuela (National Institute of Hygiene "Rafael Rangel")	May 10, 2018. Completed and validated the questionnaire, and considered that it would allow obtaining the information corresponding to the CPP Practices in the region of the Americas when gathering the data during the registration and post-approval of a Pharmaceutical Product.
Cuba (CECMED)	May 22, 2018. Completed the questionnaire and considered that its content is clear and understandable, "... it will allow the evaluation of future information on the management of CPP practices and uses in our region."
Mexico (COFEPRIS)	May 22, 2018. Completed the questionnaire, no remarks or recommendations.
El Salvador (DNM)	May 8, 2018. Completed the questionnaire and included its opinion: "El Salvador agrees that the survey shall be applied as is, since it is considered adequate for the proposed purposes."
Panama (DFD)	May 16, 2018. Completed the questionnaire, no remarks or recommendations.

Therefore, in general, NRAs completed the questionnaire, and, in this regard, their interpretation of each question was considered satisfactory. The NRAs expressed their agreement with the proposal, so they validated it and made recommendations in very few cases. The remarks made by DIGEMID were considered in the final version of the questionnaire and the development of the survey. Based on these favorable results, the questionnaire was approved.

B.3 Preparation of the survey based on the validated questionnaire

To make the validated questionnaire into a survey, the online tool SurveyMonkey was chosen. This procedure incorporated a degree of difficulty since, unlike the questionnaire, the survey showed only one page at a time. This demanded a great deal of concentration on the part of the respondent and made it uncomfortable to go back and review previous responses.

In addition, the survey seemed to be longer than the questionnaire. The questionnaire included a column for *Additional remarks - Complementary information required for each question: Is this specific requirement implemented following national legislation or NRA requirements?* The survey had no columns. This problem was solved by adding a question with answer options included. This addition extended the length of the questionnaire, as shown by the first question from both forms in the figures below.

Questionnaire

REQUIRED INFORMATION	ANSWERS	SURVEY INSTRUCTIONS	ADDITIONAL REMARKS
National Regulatory Authorities (NRAs) requiring or receiving CPPs 1. Submission of applications for new drugs/new pharmaceutical products			
1.1 Is a CPP required for the submission/ registration of a new pharmaceutical product/ new registration in the country?	Yes	If the response is NO, go to questions: 1.11 to 1.15; 3.4 to 3.7; 6.1 to 6.3; 7.1 to 7.4 and sections 9 and 10	Complementary information required for each question: Is this specific requirement implemented following national legislation or NRA requirements?

Survey

1.1 Is a CPP required for the submission/registration of a new pharmaceutical product/new registration in the country?

- ○ Yes
- ○ No
- ○ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

The number of topics remained at 10, while the total number of questions increased from 53 to 58 due to the addition of questions in topics 4, 9, and 10. The survey was diagrammed as detailed in the table below.

Table IV • Composition of the revised survey

	TOPICS	QUESTIONS
1	Submission of applications for new drugs/new pharmaceutical products.	16
2	Submission of renewal applications.	3
3	Submission of post-approval changes/variations.	4
4	Form/content of the CPP document.	5
5	NRA assessment of the CPP.	6
6	Assessment of the previous registration in the country of origin.	3
7	Effects of registration/marketing authorization cancelation or suspension in the CPP's issuer-country.	4
8	CPP and marketing status of the product.	4
9	Other relevant information.	9
10	NRAs issuing CPP (only for NRAs issuing CPPs).	4
	Total: 10 topics	58

A particular characteristic of the design of the questionnaire/survey were the interdependent topics and questions. These are the topics and questions with responses depending on the specific characteristics of the country's CPP regulations and practices and the responses to previous questions. In general, the response to the first question of a topic conditioned the need to respond to the following questions since subsequent questions usually seek to obtain more details about the topic. Therefore, if the response to the first question is *No*, the interdependent questions are not applicable.

To illustrate this, see the example of question 1.1. Is a CPP required for the submission registration of a new pharmaceutical product/new registration in the country? In this case, if the response is *No*, the 15 following questions of this topic are not applicable, neither are the questions corresponding to topics 2, 3, 4, 5, and 6.

The survey included other cases with more particular characteristics as explained below, and it always clarified where the interdependent questions were not applicable.

Table V • Interdependent questions due to the design of the survey

	TOPICS	QUESTIONS
1	Submission of applications for new drugs/pharmaceutical products.	(3) 1.13; 1.14; 1.16
2	Submission of applications for renewals.	(3) 2.1; 2.2; 2.3
3	Submission of changes/variations after the approval.	(3) 3.1; 3.2; 3.3
4	Form/content of the CPP document.	
5	NRA assessment of the CPP.	(5) 5.1; 5.2; 5.3; 5.5; 5.6
6	Evaluation of prior registration in the country of origin.	
7	Effects of registration/marketing authorization cancelation or suspension in the CPP's issuer-country.	(3) 7.1; 7.2; 7.3;
8	CPP and status of product commercialization.	(2) 8.1 y 8.4
9	Other relevant information.	(6) 9.1; 9.2; 9.3; 9.4; 9.7; 9.8
10	NRAs issuing CPP (only for NRAs issuing CPPs).	(3) 10.1; 10.2; 10.3

For these cases, it would have been most convenient that these questions were automatically blocked from being answered. However, the architecture of the SurveyMonkey tool did not allow it. Therefore, although the instructions were self-explanatory, for example: *If your response is Yes ...* , *In the event that ...* , it was each respondent's responsibility to answer according to the logic and instructions provided. Topic 10 was included to be answered only by NRAs issuing CPP, and this condition was clearly stated.

The surveys and their instructions were prepared in Spanish and English and distributed by e-mail to the contact persons identified. They included information on the project's respective focal points regarding possible doubts and consultations. The survey was distributed to all NRAs in the region of the Americas and the pharmaceutical industry associations members of FIFARMA.

PDF files of the surveys in English and Spanish are attached as Annex No. 1. The PAHO appointed a staff member to support the management of the project. This entity also collaborated extensively in the communication with the countries of the Caribbean Regulatory System. These countries were: Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Belize, Bermuda, the BES Islands (Bonaire, St. Eustatius, Saba), British Virgin Islands, Cayman Islands, Curaçao, Dominica, Grenada, Guyana, Haiti, Jamaica, Montserrat, St. Christopher and Nevis, St. Lucia, St. Martin, St. Vincent and the Grenadines, Suriname, Trinidad and Tobago, Turks and Caicos Islands.

The start date for the survey distribution was July 10, 2018, and the end date for responding was August 24, 2018. Since a minimal number of countries in the region responded by this date, the deadline was extended to October 31, 2018.

This considerable delay in responses also caused a delay in the implementation schedule. The delay was reported as a challenge of the stage under *C - Difficulties in project implementation of the standardized project evaluation form with the following text: "So far, project implementation has posed two main challenges for coordinators: (i) the commitment and mobilization of the NRAs and local associations."*

During the period to respond to the online questionnaire, the coordinators carried out actions to promote the project and the survey to obtain greater participation from NRAs and industry representatives. These actions included virtual meetings of FIFARMA representatives with the participation of industry associations from different countries and presentations at the following events:

- "XIX Mexican Convention of Sanitary Officers of the Chemical-Pharmaceutical Industry," organized by the National College of Pharmaceutical Chemists and Biologists of Mexico (August 22-24, 2018).

- "18th International Conference of Drug Regulatory Authorities (ICDRA)," organized by the WHO, held in Dublin, Ireland (September 3-4, 2018), as part of the program of the Pre-ICDRA meeting, in a workshop dedicated to CPPs.

- "IX Pan American Network for Drug Regulatory Harmonization Conference," organized by PAHO and the regulatory authority of El Salvador (October 24-26, 2018), for the presentation of the project status and the preliminary outcomes.

C. Processing of responses received

Below are the activities carried out by the project coordinators to obtain, process, and compile all the responses received from the different respondents. The original responses considered valid from the survey participants who authorized the publication of their data are available for consultation in the project's community library on the PRAIS platform.

C.1 Identification of valid responses

Responses were obtained from both NRAs and pharmaceutical industry associations from the countries of the region. Responses needed to be refined due to errors in the system, incomplete questionnaires, multiple answers from a single institution (NRA or local association), and other causes that generated invalid documents.

The refinement was performed to eliminate test responses, those originated by errors in the system and, in general, those not evaluable due to any other issue. This was done after consultation and agreement between CECMED and FIFARMA. The breakdown of the validated and canceled responses is shown in the table below.

Table VI • Identification of valid responses and responses canceled by cause

SITUATION	QUANTITY
Total forms received	**63**
Forms considered valid	**43**
Incomplete forms considered "tests" (Ind. + NRA)	**4**
Complete forms considered invalid for duplication	**1**
Forms considered invalid for being system tests only	**15**

After an exchange between the project coordinators and, in some cases, after the necessary consultations with the respondents, 43 surveys were accepted as valid, covering 27 countries and 1 regulatory system. The information from the Caribbean Regulatory System was used to interpret the regulatory context in its countries, considering that it is a regional mechanism to facilitate registration in the member states of the CARICOM, but that it is not a NRA, it does not issue marketing authorizations or registrations, and it does not require a CPP for its abbreviated reviews.

Three of the questionnaires considered valid received responses from the country's industry and not from the RNA. The information submitted by the industry was considered as an official response for the country in order to expand the universe of information recorded in the report. For the Dominican Republic, the response of the country was based on the information submitted by the industry association. As there were no available responses from the industry associations from Nicaragua and Paraguay, the information submitted by companies was considered as the country's data.

The NRA of Panama was the only one sending an incomplete survey form. For a comparative analysis of the questions, the coordinators assumed the NRA's information as the country's response, and the areas not completed by the NRA were complemented with the response of the industry association.

Companies' responses were considered the industry responses for the countries that did not provide responses from industry associations (Bolivia, Jamaica, Trinidad and Tobago). In these cases, when the NRA response was available, the companies' data was used for comparison with the authority's response.

C.2 Consolidation of responses to produce the initial database

Although the survey required responses from NRAs and local industry associations in several countries, the project coordinators decided to present the results sorted by country rather than by respondent category. This decision responded to the fact that the project was not intended to show individual experiences and perceptions.

Considering that each country's responses had to be unique in the mapping and that, in some cases, two or more responses per country were received —from the NRA and industry associations— the parties' information was reviewed and compared. The questions were included in data consolidation tables developed for this purpose. For the analysis, a column for "final answers to be considered" was added. The basis for the decision making regarding final responses is detailed in the following section.

C.3 Evaluation of responses to elaborate the database

The consolidation of responses helped identify some situations that the project coordinators needed to resolve so as to facilitate the preparation of a report based on each question's valid responses by country. This led to the need to define parameters to decide such responses. Situations were as follows:

(i) Lack of responses from some NRAs: this means lack of response for the entire survey of three countries (Nicaragua, Paraguay, and the Dominican Republic); lack of response for a considerable part of the survey in one case (Panama); and lack of response for isolated questions (blank responses).

The coordinators decided to consider the whole industry information as an official response for the country, once the NRA's response possibilities were exhausted. However, since some questions in the questionnaire corresponded to experiences exclusive to NRAs, it was agreed to record these specific responses as blank because the industry does not have the authority to answer questions specific for NRAs.

Blank responses are a particularity and occurred mainly in the general case of "lack of response." In the evaluation of the responses, it was noted that, in some cases, the NRAs stopped responding, and, in others, the industry associations stopped responding. The project coordinators discussed the potential causes for this behavior. The main one identified was the lack of possible response, both for questions not applicable to the country's situation and not applicable interdependent questions based on responses to previous questions. In the latter situation, the *Not applicable (N/A)* option was not always available, and respondents did not consign it either as *Other*. Thus, they simply did not respond and left the response blank. The coordinators agreed to create the *blank* response category to reflect in the report the questions not answered and committed to describing relevant observations on what could have led to such behavior. In cases of missing answers from NRAs, the answers provided by the industry for specific questions were considered, except for the questions that were to be answered exclusively by NRAs. All the problems solved using this solution were detailed in the mapping report.

(ii) Divergent answers between NRAs and the industry for the same question, in different degrees of discrepancy, either total or partial.

For opposite responses to the same question from the NRAs and the industry, the coordinators assumed the NRA responses as valid, provided that a response was available. This solution was called the "golden rule."

The rationale for the golden rule comes from different reasons. In principle, NRAs are official bodies of the local governments and are assumed as the competent institutions to submit official information. Also, regarding national regulations, the coordinators are not specialists in the laws and regulations of the respondent countries. Therefore, although the coordinators may have some information to make adjustments or corrections on some divergent responses, their level of knowledge for all countries is not the same. Additionally, they do not have the authority to choose the most appropriate response regarding national regulations.

For the necessary transparency on this situation in the report, all relevant divergences were recorded and commented on.

Questions that required a descriptive response, i.e., open-ended questions, were excepted from the golden rule. Some of these questions included a section for expanding the information, and others were not responded to by respondents. Therefore, information was not always available. For the open-ended questions, when the descriptions between the NRAs and the industry were not comparable, all responses were considered adequate, and, to the extent that they showed relevant content, they were recorded as an observation in the report.

(iii) Apparent inconsistencies in interdependent questions in the same survey.

For apparent inconsistencies in interdependent questions in the same survey, extensive work was required to refine responses and evaluate the possible causes that might have led to such inconsistencies. For making the best decisions and obtaining clearer and more consistent data, a case by case analysis was carefully conducted to interpret the problems observed in the responses to the interdependent questions. However, there are errors do occur. Such inconsistencies are deemed to decrease the quality of the data obtained.

Regarding the acceptance of the Good Manufacturing Practices (GMP) stated in the CPP, many cases showed that the NRA claims acceptance of GMP status and requires the Certificate of GMP in addition to the CPP, which is an inconsistency. This situation posed additional divergences between the NRA and the industry because the latter considers that the NRA does not accept the GMP's statement in the CPP, and the NRA claims that it does.

A particular situation was identified in Central America. Several requirements on the CPP are established by the Central American Technical Regulations (RTCA), so a certain degree of uniformity in all signatory countries was expected, but that was not always the case. This situation was analyzed in the case-by-case report.

(iv) Limitations for the comparison of information on the legal basis adopted by each country.

Many complementary questions associated with the legal terms required in the primary question were answered differently by respondents in the same country. In response to the description section (open-ended questions) regarding the applicable regulations, the interpretation of the level of detail expected for the responses and, in some cases, the omission of such description made it impossible to contrast the information presented by the NRA and the industry.

Therefore, the coordinators decided to present the information on the legal level of the CPP requirement in a separate chapter. Following the golden rule, the NRA response was assumed as valid, provided that a response was available. It was also agreed to include an annex with a table, sorted by country, with a compilation of all responses (NRA and industry) received for the open-ended questions. This annex contains a description of all legislative and regulatory references mentioned in the survey. It is considered the bibliography of the legal basis applicable to CPP requirements in each country.

(v) Doubts generated by selecting the option *Other.*

Some questions do not include the option *Not applicable (N/A)* available as a possible answer. This condition distorts the response and prevents respondents from clearly stating a response. Therefore, to avoid false interpretations and approaches, in this report, the coordinators decided to consider the option *Other* in the questionnaire to generate graphs and figures on the survey. However, during the analysis, the cases in which *Other* means *N/A* were specified as an observation, according to the specific comment.

Considering the situations and rules defined in each of the above-mentioned groups, and considering the project coordinators' decisions, it was possible to consolidate a final database to prepare this report. To allow a critical evaluation of the final data, the coordinators chose to record in a general way any data limitations or inconsistencies observed, without changing or interpreting the original responses received from the respondents.

2. Discussion

The results of the survey are detailed below. These were obtained from the responses of the participating countries in the region of the Americas, according to their varying CPP-related regulatory practices.

The final database used for the graphics in this section is available for consultation by the interested parties in the project's community library on the PRAIS platform.

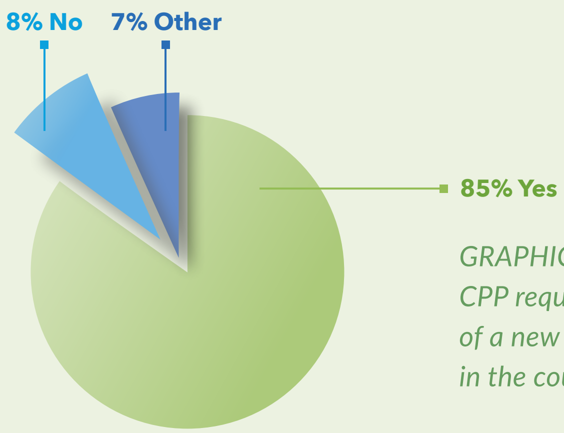
This section records the results observed after the consolidation of responses in the final database according to the methodology and methods described in the previous chapter. For each question, the following is presented: the country responses, an explanation of the data, any relevant comments from the respondents, any divergences observed between the NRA and the industry responses, the identification of the practices of the reference authorities and the NRAs of the RTCA member states.

Section 1

Submission of applications for new drugs/new pharmaceutical products

QUESTION 1.1

Is a CPP required for the submission/registration of a new pharmaceutical product/new registration in the country?



GRAPHIC 1.1
CPP requirement for the submission/registration of a new pharmaceutical product/new registration in the country.

Yes: *(23) AR, BB, BO, BZ, CO, CR, CU, EC, SV, GT, HT, HN, JM, MX, NI, PA, PY, PE, DO, SR, TT, UY, VE.*	
No: *(2) CA, US.*	
Other: *(2) BR, CL.*	

The CPP requirement for registration applications by the NRAs in the region of the Americas is generalized, i.e., all NRAs require it. Although two countries (BR, CL) answered Other, the explanatory comments explicitly state that the CPP is a requirement. This result is entirely consistent with the study conducted by SINDUSFARMA, in agreement with the scope and the participating countries.

Only two countries surveyed (US, CA) do not require CPP at all for drug registration. Thus, no response to the additional questions in this section is expected from these countries' authorities (these NRAs correspond to the blank answer option). It means that the CPP is required by 75% of the National Regulatory Authorities of Regional Reference (rNRA).

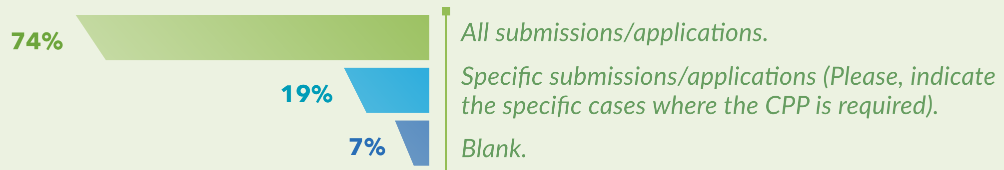
Based on the countries' observations, some particularities in their practice are detailed in the discussion of question 1.2, specifically formulated for this purpose.

For this question, divergences between the responses submitted by the NRAs and the industry members (IND) from the same country were not significant.

All the NRAs from the states signatory to the Central American Technical Regulations (RTCA) require a CPP for the submission/registration of a new pharmaceutical product/new registration in the country*.

QUESTION 1.2

What are the cases requiring CPP for the submissions of applications for new drugs or new pharmaceutical products?



GRAPHIC 1.2
CPP requirement according to the submission/application of new drug/new pharmaceutical product.

All submissions/applications: *(20) AR, BB, BO, BZ, CL, CR, CU, SV, GT, HT, HN, JM, MX, NI, PA, DO, SR, TT, UY, VE.*
Specific submissions/applications: *(5) BR, CO, EC, PY, PE.*
Blank: *(2) CA, US.*

*For additional information on the RTCA, see chapter "Legal basis".

Most countries require a CPP for all submissions. Among those countries requiring the document only for specific submissions/applications, one country (PE) clarifies that it is required for all imported products, except custom manufacturing abroad. Another country (CO) mentions that the CPP is needed in new registrations, renewals, or modification procedures. Therefore, both responses can be interpreted as *All submissions/applications*.

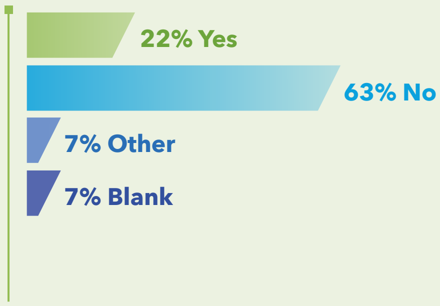
In this question, when the NRAs and the IND from the same country responded, there were divergent opinions in six countries (AR, BO, CO, MX, PA, SV): five NRAs responded All submissions/applications, and one responded *Specific submissions/applications* (CO).

All countries signatory to the RTCA request the CPP for all submissions.

In assessing the rNRAs situation, six of the eight countries require the CPP, and most of them require the CPP for all submissions.

QUESTION 1.3

Is the CPP required to be issued by a NRA recognized by local legislation as a reference/strict/supervisory authority?



GRAPHIC 1.3
CPP is required to be issued by a NRA recognized by local legislation as a reference authority.

Yes: *(5) AR, CO, HT, HN, PY, TT.*
No: *(18) BZ, BO, BR, CL, CO, CR, CU, EC, SV, GT, JM, MX, NI, PA, PE, SR, UY, VE.*
Other: *(2) BB, DO.*
Blank: *(2) CA, US.*

More than half of the responding countries indicate that the CPP does not need to be issued by a NRA recognized as a reference, strict or supervisory authority. However, the CPP must be issued by the regulatory authority of the product's country of origin or country of consignment. While all NRAs in this group share the answer that it is not necessary, there are some differences. One country (SV) specifies that the CPP must be issued by the manufacturing country. Another (CO) comments that the CPP issued by the health authority of the exporter's country of origin is accepted and, if the product is not used in the country of origin or exporter, the CPP of the manufacturing country or any of the reference countries is accepted. A third country (BR) responds that it is accepted, provided that the product is marketed in the exporting country, and it is demonstrated that the product is duly registered. In addition, one NRA (PE) indicates that they keep an updated list of the competent authorities to issue the CPP by country. If the authority is not included in the list, the legalization of the consulate or embassy of the exporting country must be obtained.

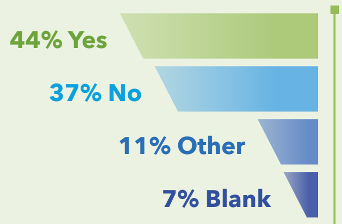
In this question, divergent responses between the NRA and the IND of the same country occurred mostly in No responses from the NRA and Other responses from the IND, indicating which new submissions can be issued by the reference authority or by that of the country of origin.

For the RTCA member states, the trend is no to require a CPP issued by a NRA recognized by local legislation as a reference authority.

Regarding the eight rNRAs situations, five out of the six requiring the document responded that the CPP doesn't need to be issued by a supervisory NRA.

QUESTION 1.4

Is prior registration of a product in the country of origin mandatory?



GRAPHIC 1.4
Mandatory prior registration of a product in the country of origin.

Yes: *(12) AR, CO, CR, EC, GT, HT, JM, PA, PE, DO, SR, UY.*
No: *(10) BZ, BO, CL, CU, SV, HN, NI, PY, TT, VE.*
Other: *(3) BB, BR, MX.*
Blank: *(2) CA, US*

It can be concluded that there is no harmonized approach in the region on the mandatory prior registration of a product in the country of origin. The differences observed in the responses may derive from different interpretations of this question by the respondents. The question refers solely to the need for registration in the country of origin and does not clarify the definition of "origin," the topic of the next question in the survey.

For the countries responding that it is mandatory, two NRAs (CO, EC) state as a requirement of the CPP, the authorization for the product to be marketed in the territory of the exporting country, while the countries that do not consider it mandatory, one (CU) indicates that a product not registered in the country of origin may be accepted as long as there is justification for this. For the countries responding Other, the response could be interpreted as Yes, since they consider it mandatory for the drug to have a previous registration, except for justifiable exceptions.

The different comments from the countries (AR, BO, BR, GT, HN, JM, MX, PA) mention cases such as: (a) (AR IND) need for registration by an authority from a pre-established list of countries, and authorities vary according to whether the product is manufactured locally or imported; (b) (GT, JM, PA) differences between the texts of the legal framework and the regulations in force; (c) the CPP is accepted when a product is registered and marketed in a country or when it does not correspond to the country of origin (manufacturing country) of the product. Based on the comments received, it is possible to say that for at least two of the countries responding Other, the registration in the exporting country is a condition for the CPP. Considering this data, it can be inferred that the trend in the region is to require as mandatory the previous registration of a product in the country of origin.

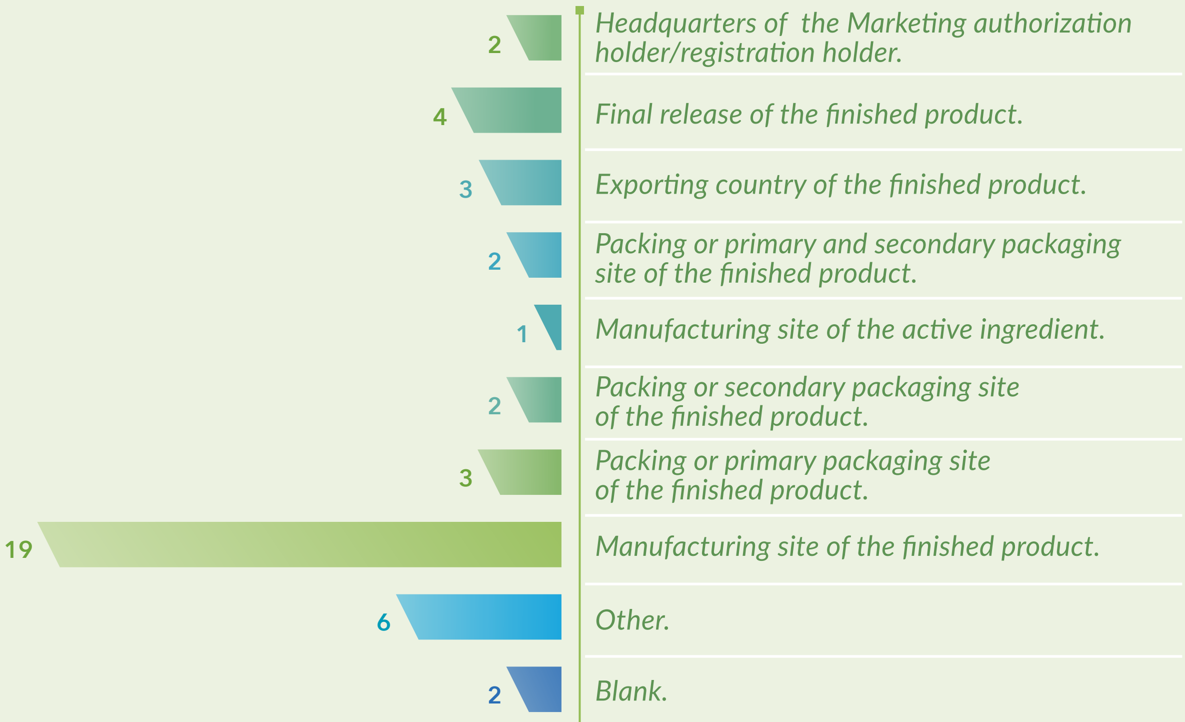
The practices of the RTCA member states in this requirement are diverse: prior registration of a product in the country of origin is not always mandatory. This is reasonable, considering that the registration holder can issue the CPP, so it may not always coincide with the manufacturing country.

The rNRAs responses show a pattern similar to that of the countries included in the survey. Thus, rNRAs responses are distributed in equal percentages for each of the possible ones: Yes, No, Other (and Blank for CA and US, because the question is not applicable to their practices).

QUESTION 1.5

Which country is considered the country of origin?

In this question, the questionnaire offered nine options to describe the concept of "country of origin." Additionally, it included the option Other, and it required an explanation in the additional observations.



GRAPHIC 1.5
Options for the concept of "country of origin."

Options describing the concept of "country of origin":
Headquarters of the Marketing authorization holder/registration holder: *(2) JM, TT.*
Final release of the finished product: *(4) CO, NI, SR, TT.*
Exporting country of the finished product: *(3) CO, CU, EC.*
Packing or primary and secondary packaging site of the finished product: *(2) GT, DO.*
Manufacturing site of the active ingredient: *(1) PY.*
Quality control testing site of the finished product: *(0).*
Packing or secondary packaging site of the finished product: *(2) DO, TT.*
Packing or primary packaging site of the finished product: *(3) GT, SV, DO.*
Manufacturing site of the finished product: *(19) BB, BZ, BO, BR, CO, CR, SV, GT, HT, JM, MX, NI, PA, PY, PE, DO, SR, TT, VE.*
Other: *(6) AR, CL, CR, HN, SR, UY.*
Blank: *(2) CA, US.*

Table VII • Details on the concept of "country of origin" by country

COUNTRY	NUMBER OF RESPONSES PER COUNTRY	HEADQUARTERS OF THE MARKETING AUTHORIZATION HOLDER/REGISTRATION HOLDER	FINAL RELEASE OF THE FINISHED PRODUCT	EXPORTING COUNTRY OF THE FINISHED PRODUCT	PACKING OR PRIMARY AND SECONDARY PACKAGING SITE OF THE FINISHED PRODUCT	MANUFACTURING SITE OF THE ACTIVE INGREDIENT	QUALITY CONTROL TESTING SITE OF THE FINISHED PRODUCT	PACKING OR SECONDARY PACKAGING SITE OF THE FINISHED PRODUCT	PACKING OR PRIMARY PACKAGING SITE OF THE FINISHED PRODUCT	MANUFACTURING SITE OF THE FINISHED PRODUCT	OTHER	BLANK
AR	1										●	
BB	1									●		
BZ	1									●		
BO	1									●		
BR	1									●		
CA	0											●
CL	1										●	
CO	3		●	●						●		
CR	2									●	●	
CU	1			●								
EC	1			●								
SV	2								●	●		
GT	3				●				●	●		
HT	1									●		
HN	1										●	
JM	2	●								●		
MX	1									●		
NI	2		●							●		
PA	1									●		
PY	2					●				●		
PE	1									●		
DO	4				●			●	●	●		
SR	3		●							●	●	
TT	4	●	●					●		●		
US	0											●
UY	1										●	
VE	1									●		
TOTAL	42	2	4	3	2	1	0	2	3	19	6	2

The interpretation of the concept “country of origin” differs based on the different operations associated with manufacturing, analysis, packaging, and even the location of the authorization holder's offices. However, it is worth noting that the vast majority of countries coincide in considering the finished product's manufacturing site as the country of origin.

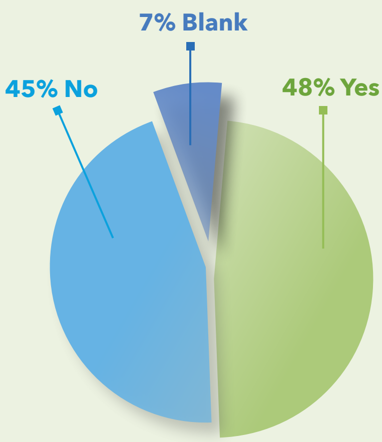
Some crucial comments made by the respondents are: some countries state that the CPP should detail the participation of all the manufacturing companies (active ingredient, bulk product, finished product, packers), and the control and export companies (consignment); other countries state that if more than one manufacturing laboratory is involved in the manufacture, the country of origin is considered to be the one where at least the bulk product is manufactured. Additionally, some comments indicate that step-wise manufacturing and custom manufacturing are considered.

The practices of the RTCA member states vary in relation to this requirement, but most agree to recognize the manufacturing site of the finished product as the country of origin.

In general, the six rNRAs requesting CPPs interpret the manufacturing site or the country of export of the finished product as the country of origin.

QUESTION 1.6

Is a statement of prior registration status in the country of origin required to submit a new drug/new pharmaceutical product/new registration in the country?



GRAPHIC 1.6
Need of a statement of prior registration status in the country of origin required to submit a new drug/pharmaceutical product/registration in the country.

Yes: *(13) AR, BO, BR, CO, CR, EC, HT, JM, MX, PA, DO, TT, UY.*
No: *(12) BB, BZ, CL, CU, SV, GT, HN, NI, PY, PE, SR, VE.*
Blank: *(2) CA, US.*

This question is interdependent with question 1.4 regarding the mandatory requirement of prior registration in the country of origin. When cross-checking the data from these two questions, the trend in the region showed that most countries requiring the mandatory prior registration of a product in the country of origin also request a statement of this registration status.

Due to the already explained interdependence of the questions, it was expected that countries requiring a statement of the prior registration status in the country of origin would also have responded Yes to question 1.4. However, two cases (BO, TT) showed inconsistencies: there were countries claiming to require a statement of prior registration status in the country of origin that responded that they do not consider prior registration in the country of origin mandatory. It is understood that inconsistencies may result from misinterpretation or misresponse by the NRAs.

For those countries that do not consider mandatory prior registration of a product in the country of origin (responded No to question 1.4), question 1.6 should not be applicable. But since there was no option for *Not applicable*, most of them answered *No*. Among the countries claiming not to require a statement of prior registration status in the country of origin, three countries (GT, PE, SR) require prior registration in the country of origin (according to question 1.4). This apparent inconsistency may derive from their interpretation of the meaning of the “statement” mentioned in question 1.6.

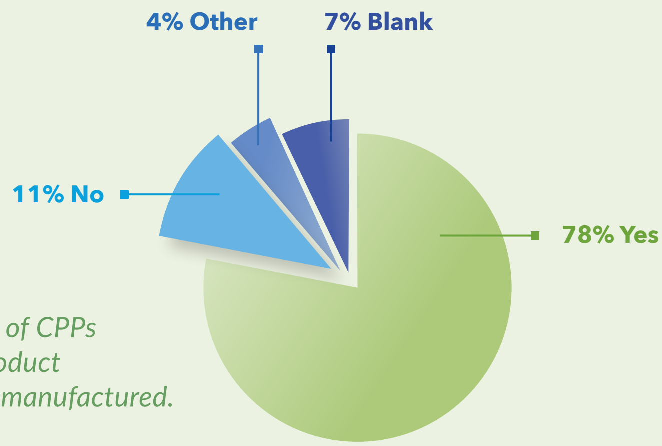
Regarding the countries where the NRA and the IND responded to the question, there were divergences of opinion in one-third of the cases (AR, HN, JA, MX, TT). These occurred mostly in the *Yes* responses from the NRA and the *No* responses from the IND. The discrepancies observed may derive from the interpretation of the question.

Only one NRA from the RTCA member states claims to require a statement of prior registration status in the country of origin to submit new registrations in their country.

The rNRAs responses to the question are consistent with the responses recorded for question 1.4.

QUESTION 1.7

Does the recipient NRA accept CPPs issued by a country where the product is registered/approved but not manufactured?



GRAPHIC 1.7
Acceptance by the recipient NRA of CPPs issued by a country where the product is registered or approved but not manufactured.

Yes: *(21) AR, BO, BR, BZ, CL, CO, CR, CU, SV, HT, HN, JM, MX, NI, PA, PY, PE, DO, SR, TT, UY.*
No: *(3) BB, GT, VE.*
Other: *(1) EC.*
Blank: *(2) CA, US.*

There is high consistency in the positive response to this question since most countries accept CPPs issued by authorities other than those of the manufacturing country.

Some NRAs mention that, at the time of initiating the application, they accept CPPs issued by a NRA other than that of the manufacturing country, as long as it is issued by the holder country's authority. However, at the time of approval, they do request the CPP of the country of origin or the holder.

There were divergences of opinion in the responses of eight countries (BO, CO, EC, GT, MX PA, PE, UY) out of fifteen where the NRA and the IND responded to the question. Most IND responses do not coincide with the opinion of the NRAs, which claim that they accept CPPs issued by a country where the product is registered/approved but not manufactured. For two cases (EC, GT), the opposite is observed: the NRAs responded No, and the IND responded Yes.

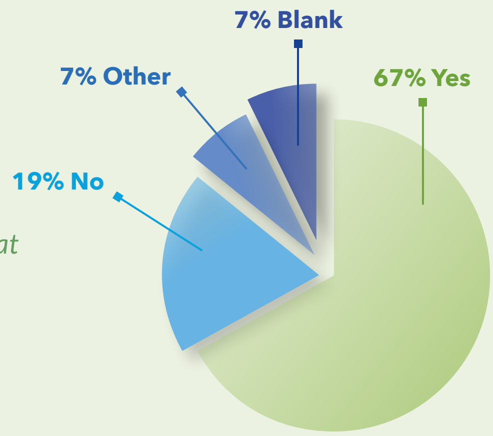
Only one NRA from the RTCA member states claims not to accept CPPs issued by a country where the product is registered but not manufactured.

As with the responses from the rest of the countries, there is also high consistency in the rNRAs responses: all six rNRAs said they accept CPPs issued by a country where the product is registered/approved but not manufactured.

QUESTION 1.8

Does the recipient NRA accept CPPs issued by a country that granted product registration/approval based on the assessment and the inspection of the Good Manufacturing Practices (GMP) conducted by another NRA (a third party)?

GRAPHIC 1.8
Acceptance of CPPs issued by a country that granted product registration based on the assessment and the inspection of the Good Manufacturing Practices (GMP) conducted by another NRA.



Yes: *(18) AR, BZ, BR, CL, CO, CU, SV, HT, JM, MX, NI, PA, PY, PE, DO, SR, TT, VE.*
No: *(5) BO, CR, GT, HN, UY.*
Other: *(2) BB, EC.*
Blank: *(2) CA, US.*

Most respondents (67%) stated that the recipient NRA accept CPPs issued by a country that granted product registration/approval based on the assessment and the inspection of the Good Manufacturing Practices (GMP) conducted by another NRA (a third party).

There were divergent opinions in eleven (BO, CO, CR, EC, GT, HN, JM, MX, PA, PE, TT) of the fifteen countries in which the NRA and the IND responded: six NRA responded Yes, four, No, and one, Other, clarifying that the CPP must indicate that the manufacturing laboratory complies with the GMP, with the corresponding periodic supervision by health authorities.

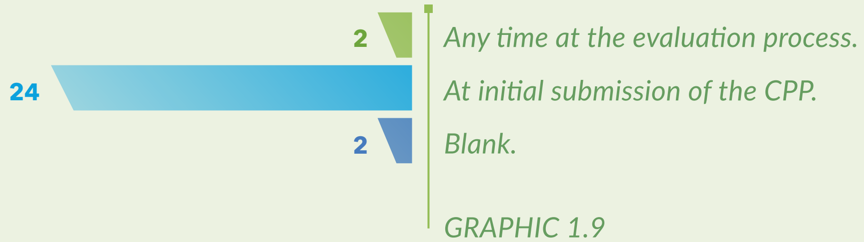
Based on the comments for this question recorded by respondents, the divergences between industry and regulators probably occurred due to different interpretations of the question's wording.

The practices of the RTCA member states vary in this requirement. Still, most countries report not accepting CPPs issued by the country that granted product registration/approval based on the GMPs evaluation and the inspection by another NRA.

In assessing the rNRAs situation, all those requiring a CPP (six out of eight) accept CPPs issued by the country that granted the registration based on the assessment carried out by a third party.

QUESTION 1.9

At what stage/time of the application process is the CPP required?



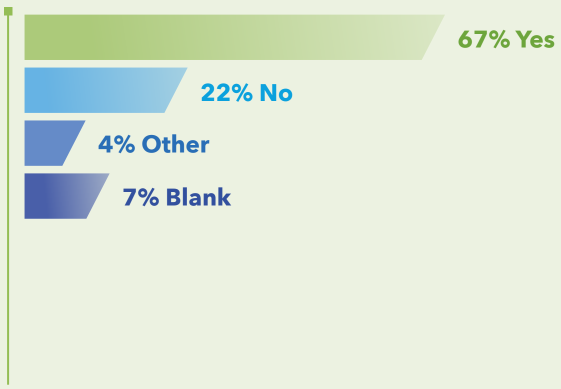
GRAPHIC 1.9
Time of the application process when the CPP is required.

Of the twenty-five countries whose authorities require the CPP, twenty-four responded that the CPP must be submitted at the time of the initial submission of the registration. Two NRAs mention that the CPP can be attached at another time in the process but before the final decision.

Concerning the rNRAs situation, five (AR, CL, CO, CU, MX) of the six rNRAs indicated that the application is required for submitting the file (with the initial submission). Only one rNRA (BR) said that it must be submitted at any time during the process/evaluation, but before the final decision of the application process.

QUESTION 1.10

Can the CPP be substituted by another document(s) in the application process?



GRAPHIC 1.10
Acceptance of the substitution of the CPP by another document in the application process.

Yes: *(18) AR, BO, BZ, BR, CL, CR, CU, SV, GT, HT, HN, MX, NI, PA, PE, DO, TT, VE.*
No: *(6) BB, CO, JM, PY, SR, UY.*
Other: *(1) EC.*
Blank: *(2) CA, US.*

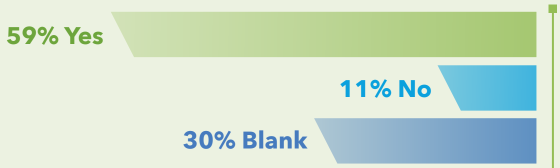
Most countries (18) responded Yes to the option of using another document to substitute the CPP. In one particular case (EC) the response was Other, clarifying that it can be substituted for synthetic drugs and not for biological products. The results obtained are consistent with those previously published in the SINDUSFARMA study.

The NRAs of the RTCA member states allow for the substitution of the CPP by another document.

For the rNRAs that require CPPs submission (6/8), only one reports that it does not allow the CPP's substitution by other documents. The remaining rNRAs accept the CPP's substitution by equivalent pharmaceutical records in the country (letter of approval, certificate of GMP and manufacturing agreement, CFS).

QUESTION 1.11

Are there any conditions for replacing a CPP with a different document?



GRAPHIC 1.11
There are conditions for replacing a CPP with a different document.

Yes: *(16) AR, BZ, BO, BR, CR, CU, EC, SV, GT, HT, HN, NI, PE, DO, TT, VE.*
No: *(3) CL, MX, PA.*
Blank: *(8) BB, CA, CO, JM, PY, SR, US, UY.*

Question 1.11 of the survey is complementary to 1.10. Therefore, countries responding No or Blank in item 1.10 were not expected to respond, which is consistent with the results observed, since eight countries did not respond.

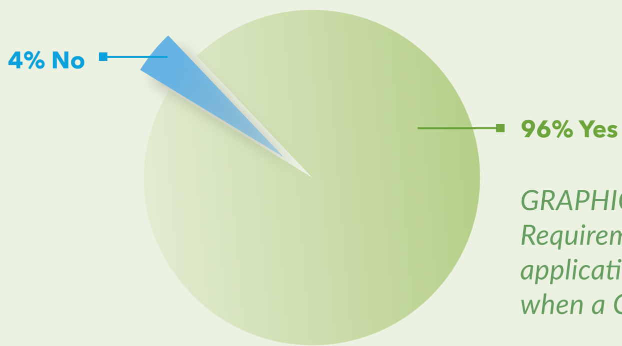
Most of the countries accepting the substitution of the CPP with other documents (question 1.10) state that there are conditions for this substitution. Only three countries responded that there are no specific conditions for such substitution (CL, MX, PA).

All NRAs from the RTCA member states state that there are conditions for replacing a CPP with a different document.

Five of the eight rNRAs that require the CPP and allow its substitution by other documents were expected to respond to this question. Only the NRAs from three countries (AR, BR, CU) claim that there are conditions for replacing a CPP with a different document. Two NRAs did not show the expected consistency.

QUESTION 1.12

Whenever a CPP is provided, either as a requirement or voluntarily, does the application for drug registration go through a full NRA evaluation?



GRAPHIC 1.12
Requirement for a full evaluation of the application for registration by the NRA when a CPP is provided.

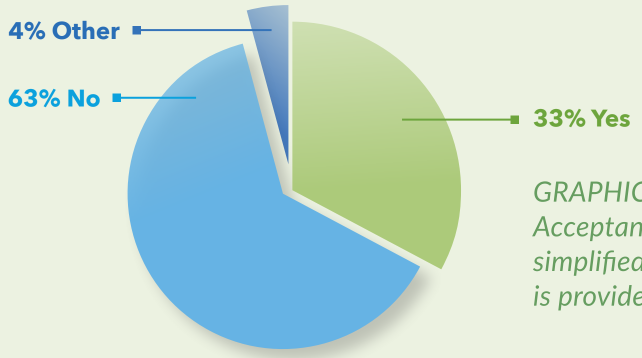
Yes: *(26) AR, BB, BZ, BO, BR, CA, CL, CO, CR, CU, EC, SV, GT, HT, HN, JM, MX, NI, PA, PY, PE, DO, SR, US, UY, VE.*	
No: *(1) TT.*	

Almost all respondent countries (26/27) agree that the NRA thoroughly assess the submission of applications for drug registrations, including all the rNRAs and the RTCA member states.

Only one country (TT) responded No, stating that full evaluations correspond to specific cases. The only discrepant response between the NRA and the industry corresponds to this same country: the IND responded Other without specifying its response.

QUESTION 1.13

Whenever the CPP is provided, as a requirement or voluntarily, is the use of fast track/accelerated/simplified procedures allowed?



GRAPHIC 1.13
Acceptance of fast track/accelerated/ simplified procedures whenever a CPP is provided.

Yes: *(9) AR, CR, GT, HT, HN, MX, PA, DO, TT.*
No: *(17) BB, BZ, BO, BR, CA, CL, CO, CU, EC, SV, JM, NI, PY, SR, US, UY, VE.*
Other: *(1) PE.*

According to the percentages obtained from the responses of the countries consulted, it is evident that the majority (63%) do not allow the use of fast track procedures after the submission of a CPP. However, it is worth remembering that the country's response is independent of the CPP. In the absence of fast track registration procedures in the country, the NRA can only respond No to this question. The country responding Other explained that, for medicines, evaluation by categories (1 and 2) with differentiated requirements is contemplated.

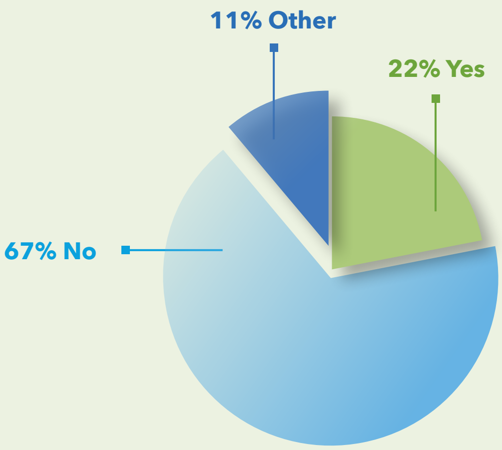
Out of the fifteen cases in which NRAs and the IND from the same country responded to this question, in five, the NRAs state that the use of fast track procedures is possible in disagreement with the industry's opinion. The divergence may derive from differences in the interpretation of the concept "fast track."

The practices of the RTCA members vary regarding this issue.

Among the six rNRAs requesting a CPP, two respond that fast track procedures are allowed, as long as the CPP is provided, and clarify that medicines must be authorized for consumption in reference countries.

QUESTION 1.14

Whenever a CPP is provided, as a requirement or voluntarily, are abbreviated files accepted? Comment: Consider as abbreviated files any file with less documentation, information, or data needed.



GRAPHIC 1.14
Acceptance of abbreviated files whenever a CPP is provided.

Yes: *(6) AR, BZ, HT, JM, PA, PY.*
No: *(18) BO, BR, CA, CL, CO, CR, CU, EC, SV, GT, HN, MX, NI, DO, TT, US, UY, VE.*
Other: *(3) BB, PE, SR.*

Sixty-seven percent of the countries responded No. However, as mentioned in the previous question, this value is not associated with whether a CPP is submitted or not, but with the possibility that the NRA of a country does not accept abbreviated files.

The NRAs of the RTCA member states agree that they do not accept abbreviated files.

Among the six rNRAs requesting a CPP, only one (AR) responded that abbreviated files are allowed, as long as the CPP is provided. For this NRA, the acceptance of abbreviated files is a particularity of the fast track procedure for medicines authorized in reference countries.

QUESTION 1.15

In the case of fast track/accelerated/simplified procedures or abbreviated files, from which NRAs are CPPs accepted?

Table VIII • NRAs whose CPPs are accepted for simplified processes or abbreviated files

NRA OF WHICH CPP IS ACCEPTED	AR	BB	BZ	BO	BR	CA	CL	CO	CR	CU	EC	SV	GT	HT	HN	JM	MX	NI	PA	PY	PE	DO	SR	TT	US	UY	VE
EMA - EU		•									•	•	•			•	•		•			•	•	•		•	
FDA - US	•	•									•	•	•			•	•		•		•	•	•	•		•	
COFEPRIS - MX		•									•	•	•									•		•			
ANVISA - BR		•									•	•	•									•		•			
INVIMA - CO		•									•	•	•									•		•			
CECMED - CU		•									•	•	•									•		•			
ISP - CL		•									•	•	•									•					
ANMAT - AR		•									•	•	•									•		•			
HC - CA	•	•									•	•	•			•	•		•		•	•	•	•			
TGA - AU											•	•					•		•		•	•		•			
SWISSMEDIC - CH	•											•					•		•		•	•		•			
MHRA - UK	•																		•		•	•		•			
PMDA - JP	•										•	•							•		•		•				
MPA - SE	•																		•		•	•					
HEALTH - IL	•																										
AGES - AT	•																		•								
BFARM - DE	•																		•		•	•					
ANSM - FR	•																		•		•	•					
IGZ - NL	•																		•		•	•					
AFMPS - BE	•																		•		•						
DMA - DK	•																		•		•	•					
AEMPS - ES	•																		•		•	•					
AIFA - IT	•																		•		•						
CRS		•																									
MFDS - KR											•										•						
MSPAS - GT															•												
MOH - BZ															•												
ARSA - HN																											
DNM - SV															•												
MINSA - NI															•												
MISALUD - CR															•												
MINSA - PA															•												
IMA - IS																			•			•					
NMA - NO																			•		•	•					
FIMEA - FI																			•								
MEDSAFE -NZ																			•								
HPRA - IE																			•		•						
INFARMED - PT																			•		•						
OGYEI - HU																					•						
LLV - LI																						•					
NOT APPLICABLE			•	•	•	•	•	•	•	•																	

This question is complementary to 1.13 and 1.14. Respondents had two choices: Not applicable or Indicate the NRAs from which you accept a CPP to be used in fast track/accelerated/ simplified procedures or abbreviated files. Therefore, descriptive responses were expected from the 15 countries responding Yes or Other with explanations for the above questions; for example, from the country that responded that they adopt differentiated practices depending on the product (question 1.13).

Twelve countries indicated NRAs from which CPPs are accepted for simplified procedures or abbreviated files. One country (UY) responded inconsistently with negative responses to questions 1.13 and 1.14.

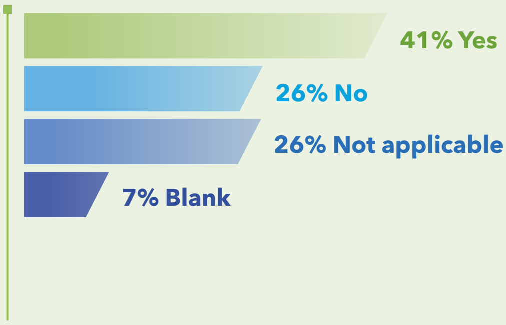
Four countries (BZ, CR, HT, PY) mentioned allowing the use of simplified procedures or abbreviated files; however, they do not include any NRA from which they accept the CPP. However, two countries (CR, HT) responded that they allow fast track/accelerated procedures for specific vaccination programs or endemic diseases.

The two NRAs from the RTCA member states that claim that the CPP allows the use of fast track procedures (question 1.13) responded to this question but show inconsistency with the list of countries.

As expected, based on the verified rNRA responses for questions 1.13 and 1.14, only two rNRAs (AR, MX) report that they accept the CPP for simplified procedures or abbreviated files.

QUESTION 1.16

Does the CPP have to meet specific conditions to assess the drug submission according to the fast track/accelerated/simplified procedures or for an abbreviated file to be accepted?



GRAPHIC 1.16
Mandatory compliance of the CPP with specific conditions for fast track procedures or abbreviated files.

Yes: *(11) AR, HT, HN, JM, MX, PA, PE, DO, SR, TT, UY.*
No: *(7) BB, BZ, CR, CU, SV, GT, PY.*
Not applicable: *(7) BO, BR, CL, CO, EC, NI, VE.*
Blank: *(2) US, CA.*

Due to interdependence with previous questions, NRAs accepting fast track procedures or abbreviated files when a CPP is submitted, should only have responded to question 1.16, according to the responses to questions 1.13 or 1.14. That is, fifteen countries were expected to respond Yes or No to question 1.16, and the others were expected to choose *No*.

This premise is inconsistent with the data obtained. Seventeen countries responded to this question. Eleven indicated that the CPP must comply with specific conditions to be assessed in fast track procedures or abbreviated files. One country (UY) responded inconsistently with negative responses to questions 1.13 and 1.14. Of the six countries that responded that the CPP does not require specific conditions, two (CU, SV) included apparent inconsistencies in their responses. Their response to this question was not that expected.

Such inconsistencies may derive from the fact that fast-track or abbreviated files is governed by requirements other than those of the CPP. Therefore, their interpretation was different according to national practices.

In this question, of the fifteen cases in which NRAs and IND from the same country responded, ten countries showed divergences of opinion between the NRAs and IND. The NRAs of six countries responded that the CPP must comply with specific conditions (AR, JM, MX, PE, TT, and UY). Still, the IND's responses indicate other situations: three NRAs claimed that the question was not applicable to their situation (BR, SV, HN), and the industry understands it differently. Finally, one NRA (GT) responded not having specific conditions for the CPP, although the IND believes the opposite.

Some apparent inconsistencies in the NRAs responses —as compared to previous questions—, and the divergences observed in some of the responses of the NRAs —as compared to those of the IND—, may be the result of different interpretations of the *No* and *Not applicable* options. Some respondents may have responded No for situations in which they should have used the *Not applicable* option. Another potential confusion is the interpretation of "specific conditions." The question was intended to identify special situations applicable to CPPs precisely when fast track procedures or abbreviated files are used. However, some responses suggest that respondents have interpreted the "specific conditions" in a general way.

Of the two NRAs from the RTCA member states that claim that the CPP allows the use of fast track procedures (question 1.13), only one (HN) claims to require specific conditions for the document.

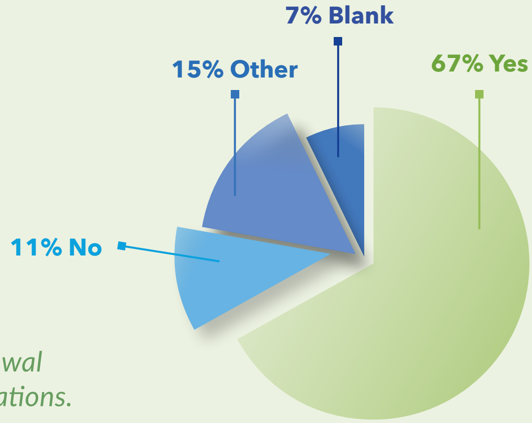
Two of the eight rNRAs were expected to respond to this question. Both (AR, MX) responded that the CPP must comply with specific conditions to be assessed in fast track procedures or abbreviated files, including validity period, translation, and apostille/legalization. Such conditions seem to apply to all submitted CPPs and not specific for the use of fast track procedures or abbreviated files.

Section 2

Submission of renewal applications

QUESTION 2.1

Is a CPP required for the renewal of pharmaceutical product registrations?



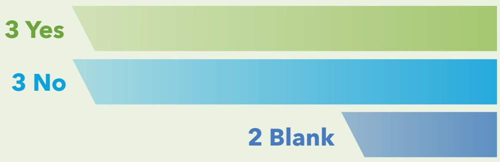
GRAPHIC 2.1a
Requirement of a CPP for the renewal of pharmaceutical product registrations.

Yes: *(18) BZ, BO, CL, CO, CR, CU, SV, GT, HT, HN, JM, NI, PA, PY, PE, DO, UY, VE.*
No: *(3) AR, BR, MX.*
Other: *(4) BB, EC, SR, TT.*
Blank: *(2) US, CA.*

Most countries (67 %) responded that a CPP is required for the renewal of pharmaceutical product registrations. One of the countries responding Other (EC) mentions that a CPP is needed to register chemically synthesized drugs and not for biological products unless these have had any modification or suspension. For the remaining three countries responding *Other*, similar alternatives were expected in their responses for registration renewals. However, they claimed that they do not use registration renewals yet and that registered products keep such a state (BB), or simply that they do not use registration renewals (SR), or that the registration covers the entire shelf-life of the drug only with supplementary changes without renewal procedures (TT). So, these countries' responses can be interpreted as *No* instead of *Other*, since registration renewals do not apply at all.

Of the fourteen cases in which NRAs and IND from the same country responded to this question, three countries showed divergences of opinion (CO, EC, JM). The differences do not derive from opposite responses. While the three NRAs responded Yes, the three IND responded *Other*, including clarifications or specifications, rather than opposing considerations.

The NRAs from all RTCA members require a CPP for drug registration renewals.



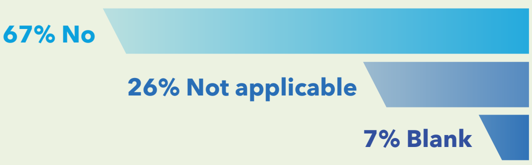
GRAPHIC 2.1b
Responses from the rNRAs.

Yes: *(3) CL, CO, CU.*
No: *(3) AR, BR, MX.*
Blank: *(2) US, CA.*

From the six responding rNRAs, three claimed to require a CPP for registration renewal of pharmaceutical products (CL, CO, and CU), and three that they do not need this document at the time of processing the registration renewals in their country (AR, BR, MX).

QUESTION 2.2

Are the requirements/conditions applicable to the CPP for registration renewals different from those required for the submission of application for new drugs/new pharmaceutical products?



GRAPHIC 2.2
Differences in the requirements applicable to CPPs for registration renewals and the submission of applications for new drugs.

No: *(18) BO, BZ, CL, CO, CR, EC, SV, GT, HT, HN, JM, NI, PA, PY, PE, DO, UY, VE.*
Not applicable: *(7) AR, BB, BR, CU, MX, SR, TT.*
Blank: *(2) CA, US.*
Yes: *(0).*

Due to the interdependence with questions 1.1 and 2.1, responses to this question were expected from those countries requiring a CPP to register a pharmaceutical product and for the renewal of such registration.

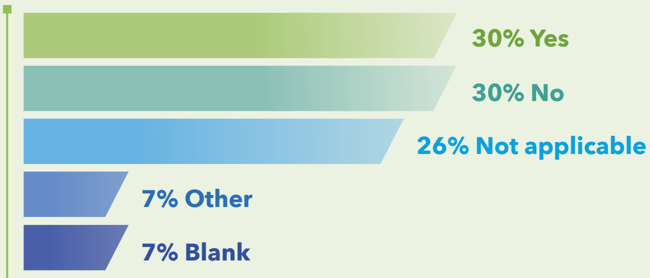
For the NRAs responding *No* to question 2.1, responses to question 2.2 were consistent, indicating that it is *Not applicable* for their countries (AR, BR, MX). Other NRAs (BB, SR, TT), who had responded *Other* to the previous question, indicated that the situation is *Not applicable*. (See reference paragraph in the last question).

No NRAs of the RTCA members treat documents issued for pharmaceutical products registration or renewals differently. The same goes for rNRAs requiring a CPP.

Considering the universe of countries from which responses were expected, even when there are inconsistencies, the conditions applicable to CPPs submitted for the renewal of drug registrations in the region tend not to be different from those required for the initial registration of the product.

QUESTION 2.3

If the CPP is required for renewals, is it mandatory that the CPP be issued by the same regulatory authority that issued the CPP for the initial registration?



GRAPHIC 2.3
Mandatory requirement that the CPP for renewals be issued by the same regulatory authority that issued the CPP for the initial registration.

Yes: *(8) BZ, CL, CR, EC, GT, HN, UY, VE.*
No: *(8) BO, CU, SV, JM, NI, PY, PE, DO.*
Not applicable: *(7) AR, BB, BR, HT, MX, SR, TT.*
Other: *(2) CO, PA.*
Blank: *(2) CA, US.*

Only countries that have reported requiring a CPP for drug registration renewal should have answered this question. From the countries responding *Yes* to question 2.1 (18), less than half (8) consider it mandatory that the CPP for the renewal be issued by the same authority that issued the CPP for the initial registration.

For the NRAs responding *No* to question 1.1 (CA, US) and 2.1 (AR, BR, MX), responses to question 2.3 were consistent since the situation does not exist in their countries. Similarly to question 2.2, other NRAs (BB, SR, TT), who had responded *Other* to question 2.1, indicated that the current situation is *Not applicable* for their countries. One NRA requiring a CPP for registration renewals (HT) responded *Not applicable*, which may mean that the CPP doesn't need to be issued by the same regulatory authority that issued the CPP for the initial registration.

One NRA that responded *Other* (OC) clarifies that they accept the CPP issued by the health authority of the exporting country, the manufacturing country, or the reference country (the latter if the product is not marketed in the exporting country). The second NRA (PA) explained that it could be issued by another NRA, as long as it is duly justified. Therefore, in both cases, it is derived that it is not mandatory that the CPP be issued by the same regulatory authority that issued the CPP for the initial registration.

For the fifteen cases in which NRAs and IND from the same country responded to this question, there were divergent opinions in five countries (EC, HN, JM, PE). In one country (EC), the difference may derive from NRA practices (requiring a CPP for renewals only in specific cases).

The practices of the NRAs of the RTCA member states vary on this subject.

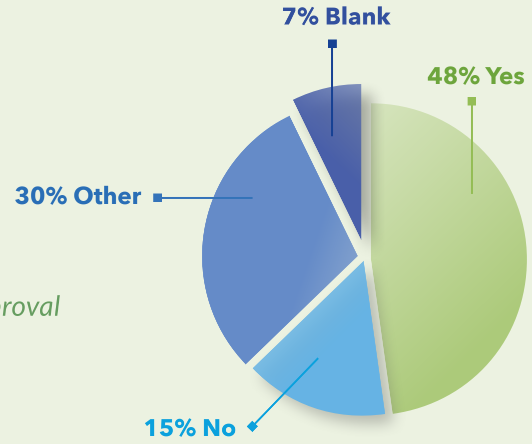
Of the eight rNRAs, the three countries requiring a CPP for registration renewal of pharmaceutical products were expected to respond. One rNRA (CL) requires that the CPP for renewals be issued by the same regulatory authority that issued the CPP for the initial registration.

Section 3

Submission of post-approval changes/variations

QUESTION 3.1

Is a CPP required for post-approval change/variation applications of pharmaceutical products?



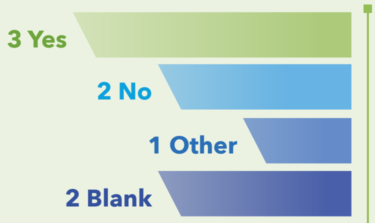
GRAPHIC 3.1a
Requirement of a CPP for post-approval change or variation applications of pharmaceutical products.

Yes: *(13) AR, BZ, CO, CR, HT, HN, MX, NI, PY, PE, DO, SR, TT.*
No: *(4) BO, BR, CL, JM.*
Other: *(8) BB, CU, EC, SV, GT, PA, UY, VE.*
Blank: *(2) CA, US.*

There is a trend to require a CPP for post-approval change submissions. In addition to this group of countries responding *Yes*, almost all countries responding *Other* stated that some post-approval variations do not require a new CPP. Therefore, only a CPP is needed for specific variations. One country (BB) reports not receiving post-approval changes submissions, so the question does not apply to their situation. This trend is consistent with the findings described in the SINDUSFARMA study.

Seven countries showed divergences of opinion between the NRAs and the IND (BR, CO, SV, HN, JM, MX, UY) out of the fifteen cases in which the NRAs and the IND from the same country that responded to this question. Divergences are mainly based on the different interpretations caused by the diversity of variations or changes after the product was approved. Therefore, responses were understood as *Yes*, *No*, or *Other* regarding the CPP requirement.

NRAs from all RTCA members claim that they require a CPP for post-approval changes of a drug, although two require it only for specific changes.



GRAPHIC 3.1b
Responses from the rNRAs.

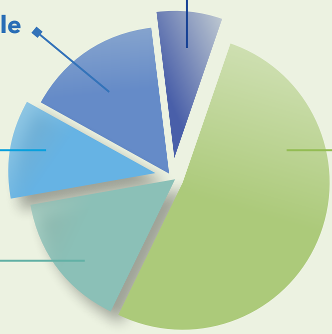
Yes: *(3) AR, CO, MX.*
No: *(2) BR, CL.*
Other: *(1) CU.*
Blank: *(2) CA, US.*

Responses from the rNRAs indicate that most of those requiring the CPP for registrations eventually require such a document for post-approval variations (AR, CO, CU, MX). Still, the cases vary: for all variations or for specific variations/changes (CU).

In the filed for additional remarks for this question, many countries anticipated their response and mentioned the types of changes requiring a CPP. The following question of the survey required such description.

QUESTION 3.2

Which post-approval changes/variations require the CPP?



GRAPHIC 3.2
Post-approval changes/variations requiring a CPP.

Specific changes/variations: *(14) CO, CR, CU, EC, SV, HN, MX, NI, PA, PY, PE, DO, SR, VE.*
Requirement depending on the case: *(4) GT, HT, JM, UY.*
All changes/variations: *(3) AR, BZ, TT.*
Not applicable: *(4) BB, BO, BR, CL.*
Blank: *(2) CA, US.*

For question 3.2, responses were expected only from those countries requiring a CPP for all or part of post-approval variations or changes applications of pharmaceutical products registration (21 countries, according to question 3.1.) This trend is consistent with the findings described in the SINDUSFARMA study. However, there are apparent contradictions in the responses of two of the countries (BB, JM).

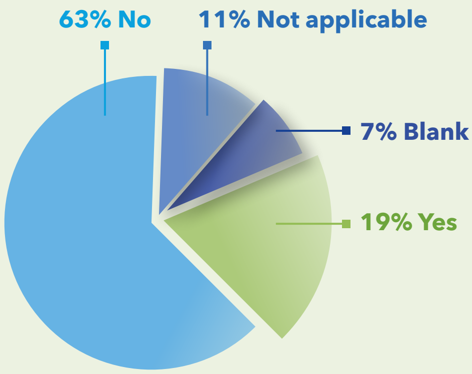
They indicate a trend in the region for CPPs to be required for specific changes or variations. Some countries mention that this is the case for variations in the site, in the manufacturing process or later additions in the formulation of the product, extensions in the expiration period, and changes in the manufacturer or the country of origin (CO, CR, EC, HN, MX, PE).

Most RTCA member states respond that CPPs are required for specific changes or variations.

Four of the eight rNRAs were expected to respond to this question. Only one rNRA requires a CPP for all post-approval change or variation applications.

QUESTION 3.3

Are the requirements/conditions applicable to the CPP for post-approval changes/variations different from those required for the submission of applications for new drug/new pharmaceutical product?



GRAPHIC 3.3
Differences in the requirements applicable to CPPs for post-approval changes and the submission of applications for new drugs.

Yes: *(5) CR, GT, HN, NI, SR.*
No: *(17) AR, BZ, BO, CO, CU, EC, SV, HT, JM, MX, PA, PY, PE, DO, TT, UY, VE.*
Not applicable: *(3) BB, BR, CL.*
Blank: *(2) CA, US.*

For question 3.3, responses were also expected only from those countries requiring a CPP for all or part of post-approval variations or changes applications of pharmaceutical products registrations (21 countries, according to question 3.1.) In the case of the two countries (BO, JM) responding *No* to question 3.1, the *Not applicable* response was expected. But, considering that they may have misinterpreted the question, in the analysis, their *No* response is considered equivalent to *Not applicable*.

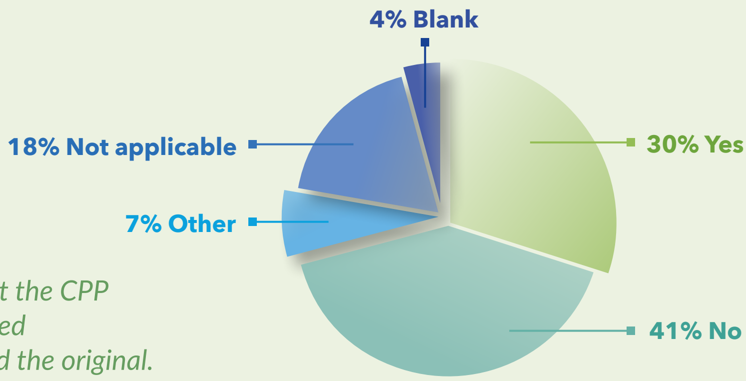
Seventeen of the twenty-two countries with this requirement agree that the requirements for changes are the same as those for new registrations.

Most RTCA member states claim that there are differentiated CPP requirements for post-approval changes.

In relation to the rNRAs responses, four respondents were expected. All responded that the CPP requirements for post-approval changes are the same as the those for the submission of applications for new drugs or new pharmaceutical products.

QUESTION 3.4

In the case of post-approval changes/variations requiring a CPP, is it mandatory that the CPP be issued by the same regulatory authority that issued the CPP for the initial registration?



GRAPHIC 3.4
Mandatory requirement that the CPP required for changes be issued by the same NRA that issued the original.

Yes: *(8) BZ, EC, GT, HN, PE, TT, UY, VE.*
No: *(12) AR, CO, CU, SV, HT, JM, MX, NI, PA, PY, DO.*
Other: *(2) CR, SR.*
Not applicable: *(4) BB, BO, BR, CL, US.*
Blank: *(1) CA.*

For this question, responses were expected only from those countries requiring a CPP for all or part of post-approval variations or changes applications of the pharmaceutical products registration (21 countries, according to question 3.1.) For changes, the usual practice of the authorities is not to require that the submitted CPP be issued by the same NRA that issued the original CPP.

There were divergences of opinions in six out of the fifteen cases in which the NRAs and the IND responded. Most of these divergences were found in the IND responses. They were conditioned to different variables, such as the amount of variations or changes in the pharmaceutical product, the manufacturer's nationality, and that of the agency issuing the CPP. In contrast, the NRAs responses are specific as to whether or not this condition is mandatory.

Practices vary for the NRAs of the RTCA member states, which is to be expected since the RTCA Regulation does not mention this aspect.

All rNRAs that report requiring a CPP for post-approval change or variation applications in the registration (AR, CO, CU, MX) agreed that it is not mandatory that the CPP be issued by the same regulatory NRA that issued the original CPP.

Section 4

CPP form/document content

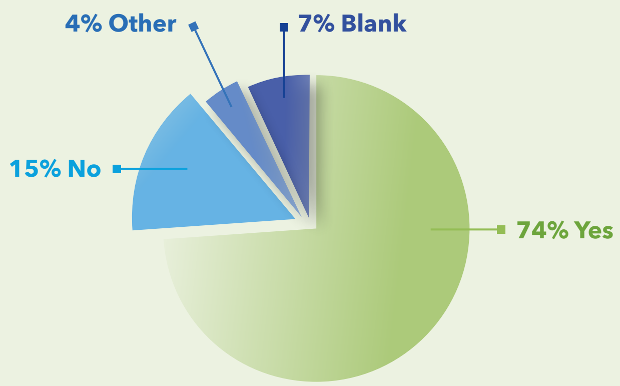
Section 4 of the survey refers to the following:

QUESTION 4.1

Load/provide a copy of the standard CPP form/document/template required by the local regulation, and attach the file if any.

QUESTION 4.2

Is the CPP required to include information on the marketing status of the product?

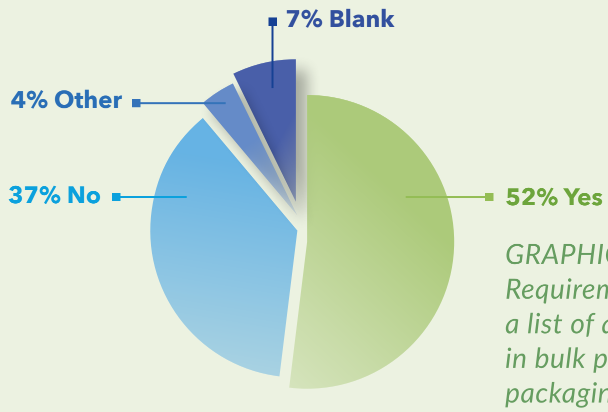


GRAPHIC 4.2
Requirement that the CPP include information on the marketing status of the product.

Yes: *(20) AR, BO, CO, CU, EC, SV, GT, HT, HN, JM, MX, NI, PA, PY, PE, DO, SR, TT, UR, VZ.*
No: *(4) BB, BZ, CL, CR.*
Other: *(1) BR.*
Blank: *(2) CA, US.*

QUESTION 4.3

Is the CPP required to include a list of all manufacturing sites involved in bulk production, packing or primary packaging, and final release?

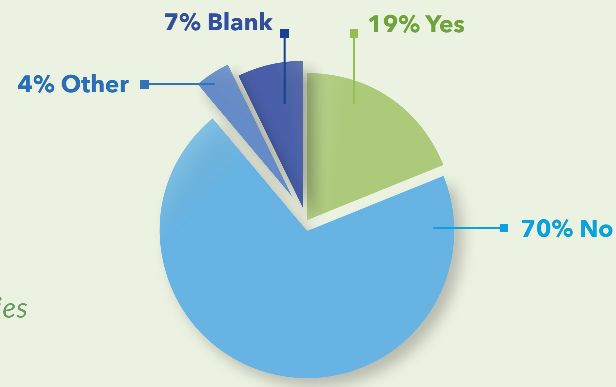


GRAPHIC 4.3
Requirement that the CPP includes a list of all manufacturing sites involved in bulk production, packing or primary packaging, and final release.

Yes: *(14) AR, CR, CU, EC, SV, GT, MX, PA, PY, PE, SR, TT, UY, VZ.*
No: *(10) BB, BZ, BO, BR, CL, HT, HN, JM, NI, DO.*
Other: *(1) CO.*
Blank: *(2) CA, US.*

QUESTION 4.4

Is the patient information leaflet/instruction leaflet (IL) or the summaries of product characteristics (SPC) required to be attached to the CPP?

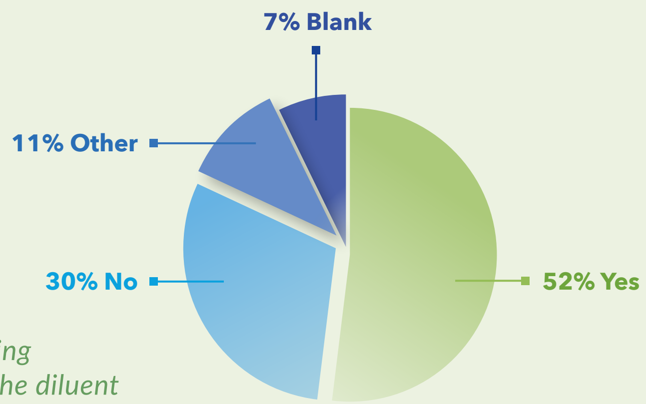


GRAPHIC 4.4
Requirement to attach to the CPP the leaflet or the summaries of product characteristics.

Yes: *(5) AR, BZ, HT, TT, VZ.*
No: *(19) BB, BO, BR, CO, CR, CU, EC, SV, GT, HN, JM, MX, NI, PA, PY, PE, DO, SR, UR.*
Other: *(1) CL.*
Blank: *(2) CA, US.*

QUESTION 4.5

Does the information on the diluent included in the submission, if applicable, have to be stated in the CPP?



GRAPHIC 4.5
Mandatory requirement of stating in the CPP the information on the diluent included in the submission.

Yes: *(14) AR, CL, CO, CU, EC, SV, GT, NI, PA, PE, SR, TT, UY, VE.*
No: *(8) BB, BZ, BO, CR, HT, HN, JM, PY.*
Other: *(3) BR, MX, DO.*
Blank: *(2) CA, US.*

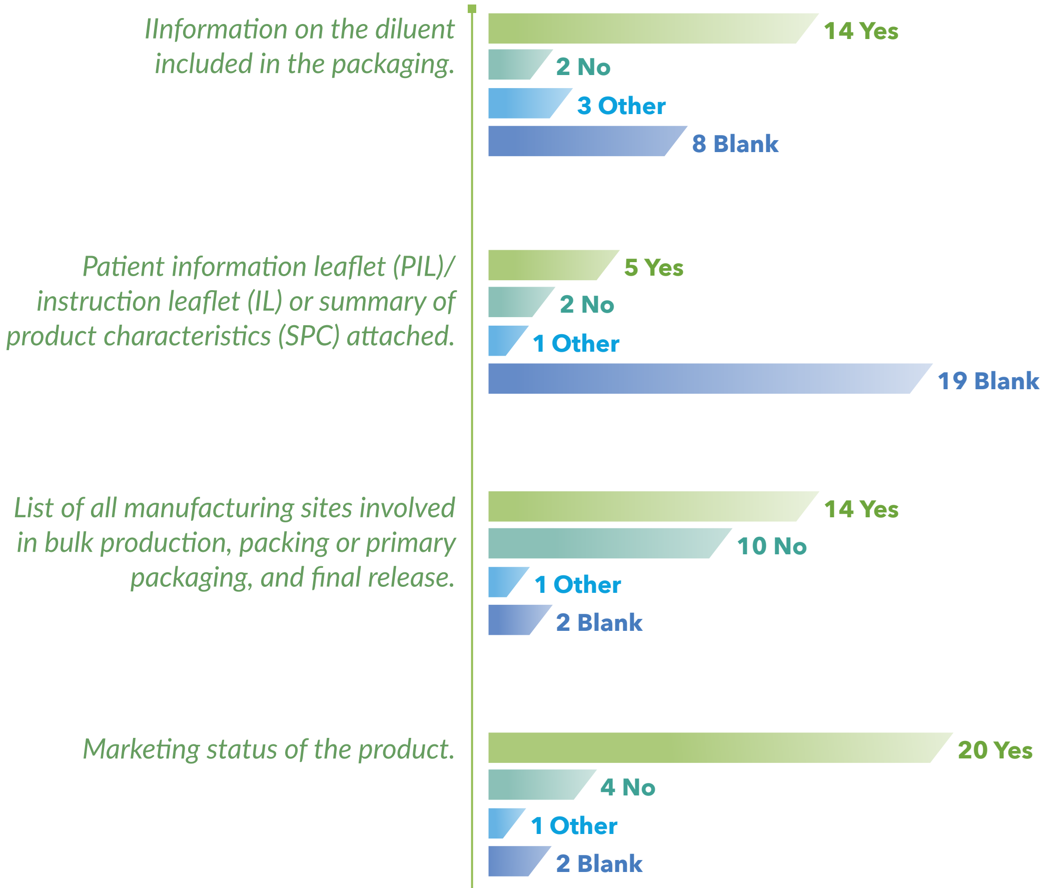
Question 4.1 asked for the submission of the CPP form required from the authorities. The documents received from the respondents were compared with the WHO Scheme CPP form. This analysis was performed together with the documents provided in question 10.2 of the questionnaire. The reasons for this joint evaluation and the results of the analysis of the documents provided are presented in the section “Comparison of the WHO CPP form and the characteristics of the CPPs issued and received by the NRAs of the Americas.”

Responses to questions 4.2, 4.3, 4.4, and 4.5 regarding the required CPP content information accepted by each NRA are summarized in the following graphic sorted by country.

Table IX • Summary of the information contained in the CPP by country

Information included in the CPP	Marketing status of the product	List of all manufacturing sites involved in bulk production, packing or primary packaging, and final release	Patient information leaflet (PIL)/ instruction leaflet (IL) or summary of product characteristics (SPC) attached.	Information on the diluent included in the packaging
AR	Yes	Yes	Yes	Yes
BB	No	No	No	No
BZ	No	No	Yes	No
BO	Yes	No	No	No
BR	Other	No	No	Other
CA	Blank	Blank	Blank	Blank
CL	No	No	Other	Yes
CO	Yes	Other	No	Yes
CR	No	Yes	No	No
CU	Yes	Yes	No	Yes
EC	Yes	Yes	No	Yes
SV	Yes	Yes	No	Yes
GT	Yes	Yes	No	Yes
HT	Yes	No	Sí	No
HN	Yes	No	No	No
JM	Yes	No	No	No
MX	Yes	Yes	No	Other
NI	Yes	No	No	Yes
PA	Yes	Yes	No	Yes
PY	Yes	Yes	No	No
PE	Yes	Yes	No	Yes
DO	Yes	No	No	Otro
SR	Yes	Yes	No	Yes
TT	Yes	Yes	Yes	Yes
US	Blank	Blank	Blank	Blank
UY	Yes	Yes	No	Yes
VE	Yes	Yes	Yes	Yes

The following graphic shows the distribution of the four categories consulted as necessary in the CPP content.



GRAPHIC 4.a
Distribution of responses among the four categories consulted as necessary in the CPP content.

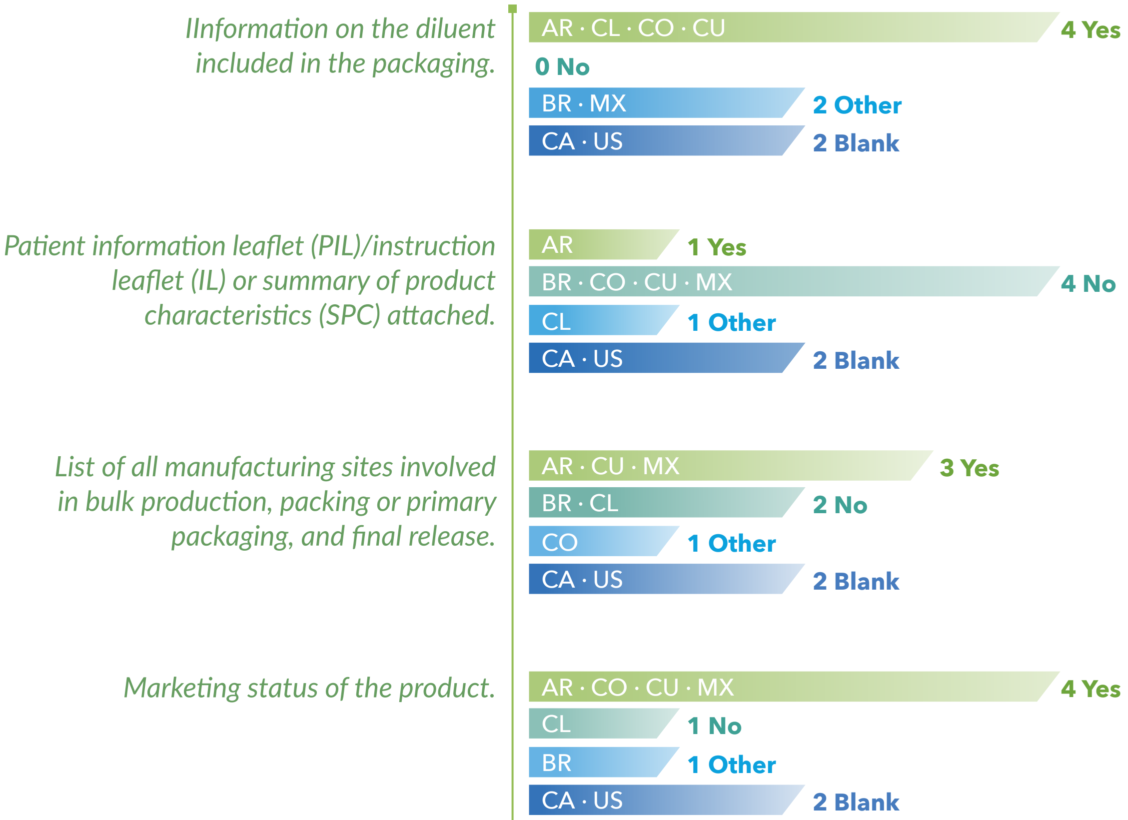
Most countries require that the CPP include information on the marketing status of the product (question 4.2).

For question 4.3, there is a trend to require that the CPP includes a list of all manufacturing sites involved in bulk production, packing or primary packaging, and final release. However, there were eight countries (AR, BO, CR, EC, SV, GT, HN, TT) with divergences of opinion between the NRA and the IND. Most NRAs (6) responded that they require a list of all the manufacturing sites. At the same time, the responses of the IND vary: some indicate that it is unnecessary, and others indicate *Other*, differentiating according to the type of products or the different manufacturing steps.

Most countries state that the patient information leaflet, the instruction leaflet, or the summaries of product characteristics do not need to be attached to the CPP (question 4.4). Thus, it is not generally mandatory to attach information about the product and its labeling.

Finally, for question 4.5, there is no marked difference, although requests for information on the diluent prevails. Also, there were seven countries (AR, BO, CO, CR, SV, GT, MX) with divergences of opinion between the NRA and the IND.

As can be observed, the practices of the RTCA member states vary in relation to the content of the CPP. This might be expected since the Regulations do not include information on this subject. Among these countries, there is total agreement on the non-mandatory nature of attaching the PIL/IL or the SPC to the CPP and a trend to request information on the diluent.



GRAPHIC 4.b
Distribution of the responses of the rNRA in the four categories consulted as necessary in the CPP content.

As regards the rNRAs, most of them require the CPP includes information on the marketing status of the product. Still, there are different approaches regarding the need to indicate all manufacturing sites involved in the bulk production, packing or primary packaging, and final release of the drugs. Only one rNRA reports that it is necessary to attach the PIL, the IL, or the SPC to the CPP. Regarding the diluent information in the CPP, although one rNRA (BR) has responded that it is not necessary, they comment that it is not mandatory because such a requirement is not stated in the national legislation. Instead, they recommend that the CPP includes the formula of the product since the one stated in the certificate must be the same as that of the product submitted. It can be concluded that the request for information on the diluent is a trend for rNRAs.

Section 5

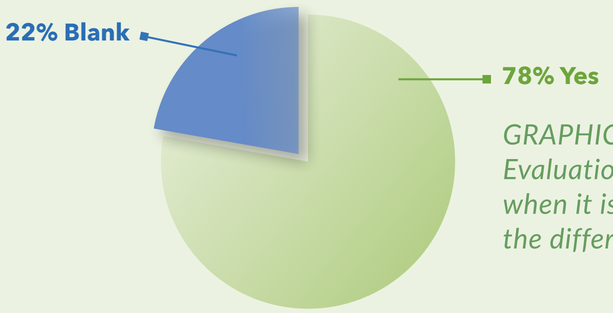
Evaluation of the CPP by the NRA

As an initial finding regarding the NRAs not requiring a CPP (CA, US), and considering the *N/A* option was not available as a response to the questions in this section of the survey, it is verified that they have not responded (blank option).

Other relevant information for this section is that four countries (NI, PA, PY, DO) did not respond to questions 5.1 to 5.5. These questions are associated with NRA practices, and, according to the methodology adopted, industry responses were excluded from the analysis. If there are no NRA responses for these countries, the response is considered as blank.

QUESTION 5.1

If the CPP is submitted during the regulatory processes (registration, renewal and/or post-approval changes), is it assessed by the NRA?



GRAPHIC 5.1
Evaluation of the CPP by the NRA when it is submitted during the different regulatory processes.

Yes: *(21) AR, BB, BZ, BO, BR, CL, CO, CR, CU, EC, SV, GT, HN, HT, JM, MX, PE, SR, TT, UY, VE.*
Blank: *(6) CA, NI, DO, PA, PY, US.*
No: *(0).*

The most relevant aspect of this question is that no countries stated that they do not conduct the CPP evaluation, thus defining the region's trend to conduct the CPP evaluation during registration processes.

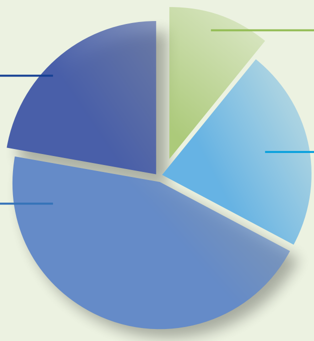
In this question, respondents were asked to indicate which aspects of the CPP are assessed. NRAs mentioned that they consider technical aspects associated with the pharmaceutical product, such as the manufacturing laboratory, the declared qualitative-quantitative composition, the product's validity period, and the specifications on specific legal information, such as information from the marketing license holder and information related to the issuing regulatory agency. They mention that the CPP is also proof of the GMP compliance status in the country of origin.

In all cases where there is a response from a NRA that is a RTCA member state the authority claims to assess the document.

All rNRAs requesting a CPP (6/8) claim to perform their evaluation. They point out that they consider the characteristics of the exporting country (certifying country) and the health registration holder's status; for example, consistency between the company's address and the manufacturer's address, between the formula stated in the certificate and the one stated in the pharmaceutical product, compliance with the GMPs recommended by the WHO, and the certification of periodic inspections.

QUESTION 5.2

If the CPP is not assessed, the reason for requiring the CPP is that it constitutes supporting information for the process and supports the drug approval decision?



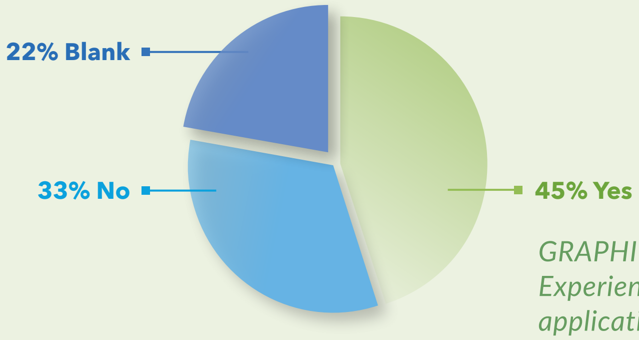
GRAPHIC 5.2
Requirement for the CPP to be used as supporting information for the drug approval process (CPPs not assessed by the NRA).

Yes: *(3) BZ, HT, TT.*
No: *(6) EC, CO, CR, CU, SV, HO.*
Other: *(12) AR, BB, BO, BR, CL, GT, JM, MX, PE, SR, UY, VE.*
Blank: *(6) CA, NI, DO, PA, PY, US.*

Based on the NRAs responses to question 5.1, no responses were expected from the NRA. As there is no *N/A* option available (which should be used in case the CPP is effectively assessed), most responses of the twenty NRAs that responded *No* or *Other* can be interpreted as *N/A*, considering that the countries responded that the CPP is effectively assessed

QUESTION 5.3

Does the NRA have experience with rejected applications because the CPP does not contain all the necessary information?



GRAPHIC 5.3
Experience of the NRA with rejected applications due to lack of the information necessary in the CPP.

Yes: *(12) AR, BO, CO, EC, SV, GT, HN, JM, MX, PE, SR, UY.*
No: *(9) BB, BZ, BR, CL, CR, CU, HT, TT, VE.*
Blank: *(6) CA, NI, DO, PA, PY, US.*

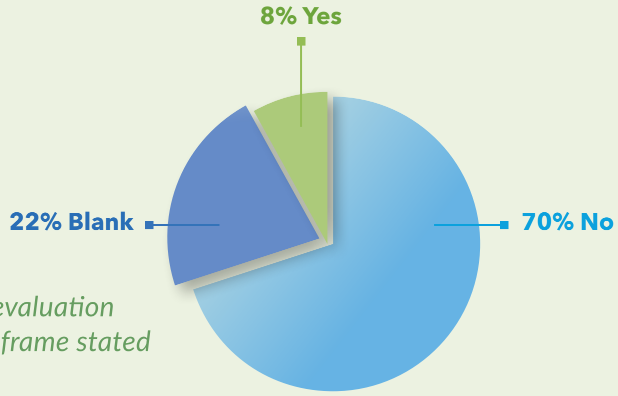
Countries report having experience with total or partial rejections, summary rejections or requests for additional information due to incomplete documents; rejections due to lack of product name or information regarding the marketing status, illegible information, or lack of the product's qualitative-quantitative formula.

The experiences of the RTCA member states with CPP rejections vary. As a trend, most of them claim to have it.

The rNRAs comments regarding the rejections of applications due to the characteristics of the CPP do not differ from the other countries' statements. Three of the six rNRAs that responded explained that they have experience with rejections (AR, CO, MX); the others (BR, CL, CU) responded *No*.

QUESTION 5.4

Are there particular considerations in the evaluation according to the marketing time frame stated in the CPP?



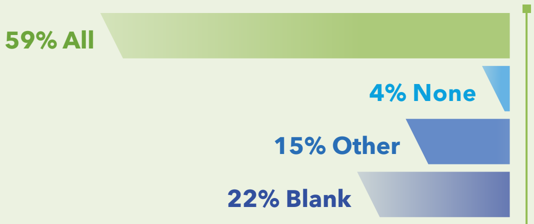
GRAPHIC 5.4
Particular considerations in the evaluation according to the marketing time frame stated in the CPP.

Yes: *(2) HT, TT.*
No: *(19) AR, BB, BZ, BO, BR, CL, CO, CR, CU, EC, SV, GT, HN, JM, MX, PE, SR, UY, VE.*
Blank: *(6) CA, US, NI, PA, PY, DO.*

The absolute majority of the countries requiring a CPP agree that they do not have particular considerations in the evaluation according to the marketing time frame stated in the document. Such is the opinion of all RTCA member states and all rNRAs responding to the question, except for the two rNRAs not requiring a CPP, which, as no *N/A* option was available, did not respond to this question.

QUESTION 5.5

What information in the CPP sections is relevant to determine the future characteristics of the drug's registration by the NRA of the receiving country?



GRAPHIC 5.5
Information considered relevant to determine the future characteristics of the drug's registration by the NRA of the receiving country.

All the information: *(16) AR, BZ, BO, CR, CU, EC, SV, GT, HT, HO, JM, MX, SR, TT, UY, VE.*
None information: *(1) BR.*
Other: *(4) BB, CL, CO, PE.*
Blank: *(6) CA, NI, DO, PA, PY, US.*

For this question, there is a trend in the countries of the region to consider all the information contained in the CPP sections as relevant to determine the future characteristics of the drug's registration.

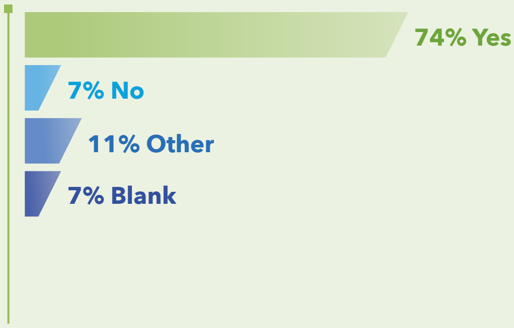
For all the cases where there is a response of a NRA that is a RTCA member state, the authority claims that all information is important.

Only one country (BR) states that no part of the CPP is relevant for this purpose and clarifies that the future characteristic of the registration will depend on the entire file submitted to the NRA. This policy is consistent because this country's NRA does not require the submission of the CPP with the initial application documentation.

The countries that responded *Other* indicate that the determining factors are: CPP validity period and characteristics, such as active ingredient, pharmaceutical formula, strength, manufacturer, registration and marketing status, and GMPs compliance status. Additionally, one country indicates that the lack of standardization of the form prevents the NRA from determining the relevance of the future registration characteristics based on the CPP received.

QUESTION 5.6

When the CPP includes information on the Good Manufacturing Practice (GMP) of the product's manufacturing site, does the NRA acknowledge this status?



GRAPHIC 5.6
Acknowledgement by the NRA of the GMP status certification when such information is included in the CPP.

Yes: *(20), AR, BB, BZ, BO, CL, CR, CU, SV, GT, HT, HN, JM, MX, NI, PA, PY, SR, TT, UY, VE.*
No: *(2) BR, DO.*
Other: *(3) CO, EC, PE.*
Blank: *(2) CA, US.*

The vast majority of the countries requiring the CPP use the document for the issuing authority to acknowledge the GMPs certification of the product's manufacturing site.

For countries responding *Other*, this acknowledgment is used for specific cases. In some countries, this status is only acknowledged for certificates from a country considered as a reference by the NRA (PE, CO). In another country (EC), the NRA only acknowledges this status for the registration of chemically synthesized drugs, and the GMPs certificate is an additional requirement for the registration of biological drugs.

NRAs of the RTCA are consistent as regards the acknowledgment of the GMP status reported in the CPP.

The rNRA practices indicate a trend (5/6) to a degree of acknowledgment of the GMP status from the CPP information. In one case (CO), there is limited acknowledgment only if the CPP comes from a reference country; in another case (MX), because the NRA, even if it is a supervisory agency, does not issue CPPs. It is noteworthy that one rNRA (BR) does not acknowledge the GMPs certification, and certification by ANVISA is mandatory.

Section 6

Assessment of the prior registration in the country of origin

QUESTION 6.1

Is the statement of prior registration status assessed in the country of origin?

GRAPHIC 6.1
Evaluation of the prior registration status in the country of origin.

Yes: *(11) AR, BR, CO, CR, EC, HT, JM, PA, DO, TT, UY*
No: *(4) BO, CA, MX, US.*
Blank: *(12) BB, BZ, CL, CU, SV, GT, HN, NI, PY, SR, VE, PE.*

For this question, responses were expected only from countries requiring the product to be registered in the country of origin (see question 1.4)**.

As expected, a substantial part of respondents did not respond because this situation does not apply to their practice. In turn, *No* responses from three NRAs can also be interpreted as *Not applicable*: Two NRAs (CA, US) do not consider the CPP in regulatory processes. The other NRA (BO) states that the prior registration of the product in the country of origin is not mandatory.

Thus, of all the countries from which responses were expected, there is a clear trend (10/15) to assess the statement of the status of prior registration in the country of origin. However, they do not represent the majority in absolute numbers.

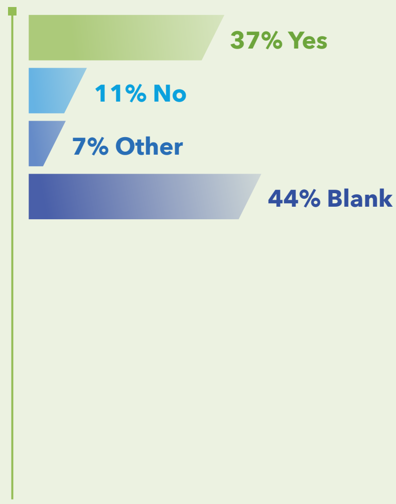
There is an apparent discrepancy for one NRA (TT) that had claimed that the prior registration of the product in the country of origin was not mandatory but claimed to assess prior registration status. The country's detailed response clarifies this situation: the NRA performs this evaluation based on other documents, not just the CPP.
Of the four rNRAs from which responses were expected, three claim to assess the statement of prior registration status in the country of origin.

**These are the twelve countries (AR, CO, CR, EC, GT, HT, JM, PA, PE, DO, SR, UY) that responded *Yes* to question 1.4, and the three countries (BR, MX, BB) that responded *Other* to the same question, as their response could be interpreted as *Yes* given that they consider it mandatory for the drug to have a prior registration, with justifiable exceptions.

Only one authority of the RTCA member states (CR) claims to assess the statement of prior registration status in the country of origin. However, no trends of non-evaluation can be claimed, as this response is blank for two countries (GT, SR) that were expected to respond.

QUESTION 6.2

If the product is registered/approved in the country of origin, but not marketed in that country, is additional information required for submissions of applications of new drugs/new pharmaceutical products?



GRAPHIC 6.2
Requirement of additional information for submissions of applications for new drugs/new pharmaceutical products when the product is registered/approved in the country of origin but not marketed in that country.

Yes: *(10) AR, BO, BR, CR, JM, MX, PA, DO, TT, UY.*
No: *(3) CO, HT, US.*
Other: *(2) CA, EC.*
Blank: *(12) BB, BZ, CL, CU, SV, GT, HO, NI, PY, PE, SR, VE.*

For this question, responses were expected only from the twelve countries (AR, CO, EC, GT, HT, JM, MX, PA, PE, DO, SR, UY) that had claimed to require information on the product's marketing status in the country of origin (question 4.2) and that, at the same time, considered it mandatory for the drug to have a prior registration (question 1.4).

However, responses were obtained from nine countries, as expected, and, from another six countries (BO, BR, CA, CR, TT, US). For some countries that were not expected to respond (BR, CA, US), the NRA explanations in the form show that the specific situation is not applicable to their practices, although they responded to the question. In one country (TT), the answer is explained by the fact that the NRA had already claimed to assess the prior registration status based on other documents, not just the CPP. For two other countries, there are apparent inconsistencies in their responses.

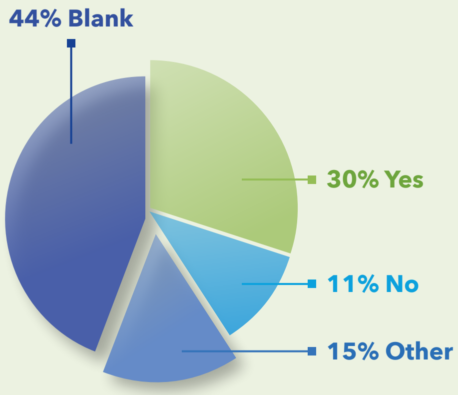
Of the nine countries from which a response was expected and responded to this question, only two claim not to request additional information for products registered that are not marketed in the country of origin.

For those countries requiring prior registration of the drug in the country of origin and that the marketing status be included in the CPP, there is a certain trend (7/12) to require additional information if the product is registered/approved but not marketed in the country of origin.

Of the three rNRAs from which a response was expected, two claim to require additional information. Considering the practices of the RTCA member states, no responses were expected from the majority of them in this question.

QUESTION 6.3

If the product is not registered/approved in the country of origin and not marketed in that country, is additional information required for the submission of applications for new drugs/new pharmaceutical products?



GRAPHIC 6.3
Requirement of additional information for submissions of applications for new drugs/new pharmaceutical product when the product is not registered/approved in the country of origin and not marketed in that country.

Yes: *(8) AR, BO, BR, JM, MX, PA, DO, TT.*
No: *(3) CR, HT, US.*
Other: *(4) CA, CO, EC, UY.*
Blank: *(12) BB, BZ, CL, CU, SV, GT, HO, NI, PY, PE, SR, VE.*

As in the previous question, responses were expected from the twelve countries requiring information on the prior registration status in the country of origin and marketing status.

However, responses were obtained from eight countries, as expected, and from the same six other ones (BO, BR, CA, CR, TT, US) that also responded to the previous question. For some of these countries from which no response was expected (CA, CR, US), the NRA explanations in the form show that the specific situation is not applicable to their practices, although they responded to the question. Again, the apparent contradictory situation in one country (TT) is explained by the fact that the authority performs the prior registration evaluation based on documents other than the CPP. The evaluation of the response of another country (BR) shows that the interpretation of “country of origin” as “manufacturing site of the finished product” explains the apparent contradiction: additional information for products not registered in the country where they are produced must verify that the product is registered and marketed in another country. In this respect, there are inconsistencies in only one country (BO). They claim to require additional information but not to require prior registration or assess this information in the CPP.

Of the eight countries from which responses were expected, two (EC, UY) state that the question does not apply to their country because they do not accept this situation, and another country (HT) does not require additional documentation.

Regarding the requirement of additional information for products not registered or marketed in the country of origin, there is no general trend for those countries requiring prior registration in the country of origin and request information on the product’s marketing status. However, at least three rNRAs (AR, BR, MX) do request additional information, accounting for half of the rNRAs using the CPP in the region. Considering the practices of the RTCA member states, no responses were expected from most of them in this question.

Section 7

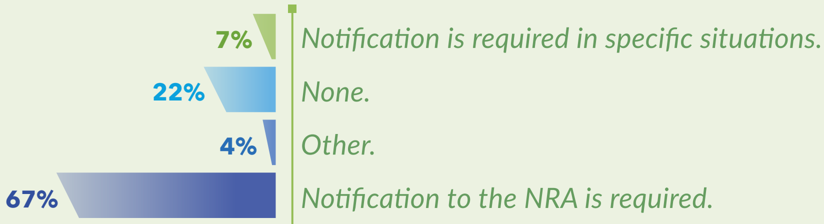
Effects of the registration/marketing authorization cancelation or suspension in the CPP-issuing country

Section 7 of the survey is intended to understand the impacts on the CPP-receiving country in the event of cancelation or suspension of the registration in the issuing country. Registrations can be canceled at the NRA's or the company's request, and this is a permanent decision. The suspension of a registration is a precautionary decision. During the suspension, the product is not available. The termination of this decision depends on the registration holder solving the problems that have caused the suspension.

Due to the survey design, the countries in the region not requiring a CPP (CA, US) could not interpret the response options in this section according to their practice. Thus, although they responded the questions, their responses should be interpreted as *Not applicable.*

QUESTION 7.1

Indicate the obligations of the product's registration holder before the NRA when its registration/marketing authorization is canceled in the CPP-issuing country.



GRAPHIC 7.1
Obligations of the product's registration holder before the NRA when the product's registration/marketing authorization is canceled in the CPP-issuing country.

Notification is required in specific situations: *(2) BZ, DO.*
None: *(6) BR, CA, CR, NI, PE, US.*
Other: *(1) BB.*
Notification to the NRA is required: *(18) AR, BO, CL, CO, CU, EC, SV, GT, HT, HN, JM, MX, PA, PY, SR, TT, UY, VE.*

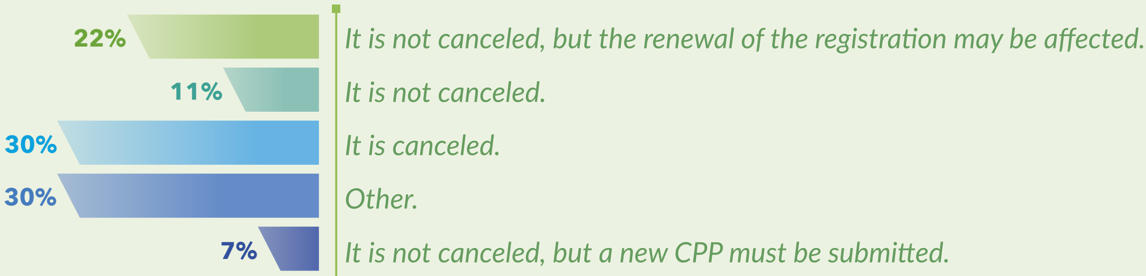
Most NRAs in the region require the product registration holder to notify them when the registration is canceled in the CPP-issuing country (20 of the 27 countries). Only six countries have no requirement for the CPP recipient NRA. The trend that leads to these results is consistent with that of the SINDUSFARMA study.

This general trend also occurs for Central American countries. For the rNRAs, notification is mostly required.

In four cases, the responses of the NRAs and the industry were divergent. The data from their responses were not relevant to the FDA and HC, due to varying interpretations of the question arising from their condition as CPP-issuing entities only.

QUESTION 7.2

Indicate the impact of the registration/marketing authorization cancelation in the CPP-issuing country on the registration/marketing authorization in the CPP-receiving country.



GRAPHIC 7.2
Impact of the registration/marketing authorization cancelation in the CPP-issuing country on the registration/marketing authorization in the CPP-receiving country.

It is not canceled, but the renewal of the registration may be affected: *(6) CO, CU, NI, PA, PY, PE.*
It is not canceled: *(3) BR, CA, CR.*
It is canceled: *(8) BO, HT, HN, JM; DO, TT, UY, GT.*
Other: *(8) AR, BB, EC, SV, US, MX, SR, VE.*
It is not canceled, but a new CPP must be submitted: *(2) BZ, CL.*

Mostly, registrations in the region are not canceled when there is a cancelation in the CPP-issuing country.

Of the countries that claim to cancel the registration/marketing authorization, it is worth noting that in five countries (AR, EC, BB, SV, VE), the cancelation occurs in specific situations, generally when there are safety and quality problems with the product.

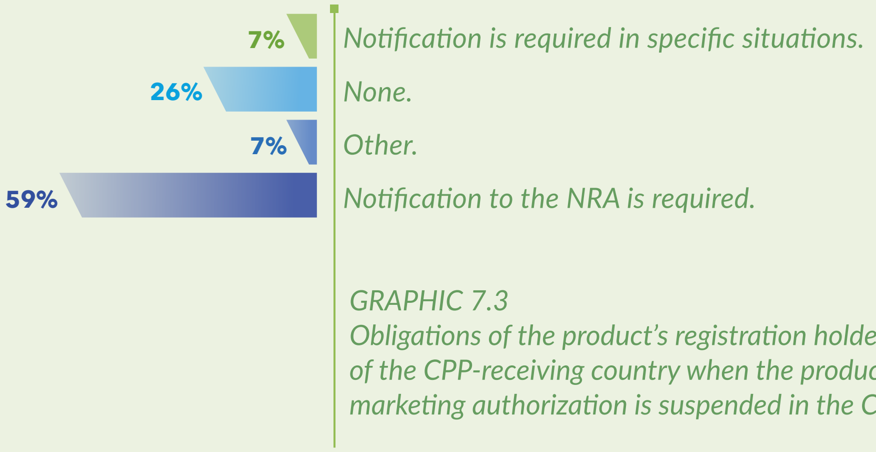
The trend not to cancel had already been identified in the SINDUSFARMA study, although the difference found was more evident in that study.

Central American countries express divergent opinions. The response of three countries (CR, NI, PA) coincide in not canceling the registration, and two of them explained that the renewal could be affected. The other three countries (CR, HN, GT) cancel the registration, though in one of them (SV), it can only be canceled under special conditions, i.e., when the causes are safety (pharmacovigilance) and quality problems. Therefore, it can be concluded that there is an impact on the registration processes after a cancelation (5/6) and that this affects not only the cancelation but also the renewal.

The rNRAs show a similar impact, i.e., the cancelation of the registration in the CPP-issuing country does not go unnoticed (4/6). However, the trend of the majority is not to cancel (7/8), and half of rNRAs (3/6) mention that the causes of cancelation are assessed, and the registration is adjusted when necessary.

QUESTION 7.3

Indicate the obligations of the product's registration holder before the NRA of the CPP-receiving country when the product's registration/marketing authorization is suspended in the CPP-issuing country.



GRAPHIC 7.3
Obligations of the product's registration holder before the NRA of the CPP-receiving country when the product's registration/marketing authorization is suspended in the CPP-issuing country.

Notification is required in specific situations: *(2) AR, DO.*
None: *(7) BR, CA, CL, CR, US, NI, PE.*
Other: *(2) CU, MX.*
Notification to the NRA is required: *(16) BB, BZ, BO, CO, EC, SV, GT, HT, HN, JM, PA, PY, SR, TT, UY, VE.*

Most NRAs report that the product's registration holder must notify the regulatory authority when the product's registration is suspended in the CPP-issuing country.

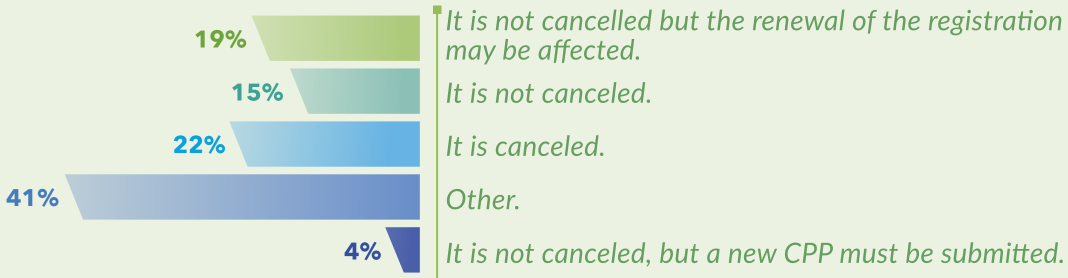
Bearing in mind that both cancelation and suspension are decisions of a similar nature, a significant correlation was found among the NRAs responding that there are no obligations as notification is concerned for the registration holder in the event of the cancelation (question 7.1) or the suspension of a registration (this question).

For the RTCA member states, there is no coincidence in the obligations of the registration holder in the event of the suspension in the CPP-issuing country. The rNRA practices vary, but at least in three out of five requiring a CPP in their processes, no actions are reported regarding suspensions. One of them does not consider the figure of the suspension, but only the cancelation.

Two cases (CR, MX) showed significant divergences of opinion between the IND and the NRA from the same country. In one case, although the NRA states that there are no obligations, the IND reports that notification is required in specific situations (if the suspension is associated with safety and quality issues). In the second case, the NRA responds *Other* and indicates that an international notification should be issued for marketing suspension due to a health alert or adverse reactions. Still, the IND indicates that there are no obligations required.

QUESTION 7.4

Please indicate the impact of the suspension of the registration/marketing authorization in the CPP-issuing country on the registration/marketing authorization in the CPP-receiving country.



GRAPHIC 7.4
Impact of the suspension of the registration/marketing authorization in the CPP-issuing country on the registration/marketing authorization in the CPP-receiving country.

It is not cancelled but the renewal of the registration may be affected: *(5) CO, DO, NI, PA, PE.*
It is not canceled: *(4) BR, CA, CL, CR.*
It is canceled: *(6) BO, HT, HN, JM, SR, TT.*
Other: *(11) AR, BB, CU, SV, EC, GT, MX, PY, US, UY, VE.*
It is not canceled, but a new CPP must be submitted: *(1) BZ.*

This question is closely related to the two previous ones. It is intended to specify the actions of the CPP recipient NRA after acknowledging the registration loss, either by cancelation or suspension. For this situation, both countries that consider it necessary to notify suspensions to the NRA, and those requiring so in specific situations, report different approaches. Most countries (7) responding *Other* explain that the impact depends on the particular situation; thus indicating the preference for case-by-case evaluation.

No rNRAs and most NRAs indicate that the cancelation of the registration does not occur automatically. Regarding this issue, the practices of the RTCA members vary.

For this question, there were significant divergences of opinions in two out of the fourteen cases in which the NRAs and the IND responded (BO, TT). Both NRAs responded that the registration/ marketing authorization is canceled, while both IND responded the opposite.

Thus, it can be concluded that there is no specific trend in the region about the impact of the suspension of the registration in the CPP-issuing country concerning the registration in the CPP-receiving country, but that, in most cases, the registration is not automatically canceled.

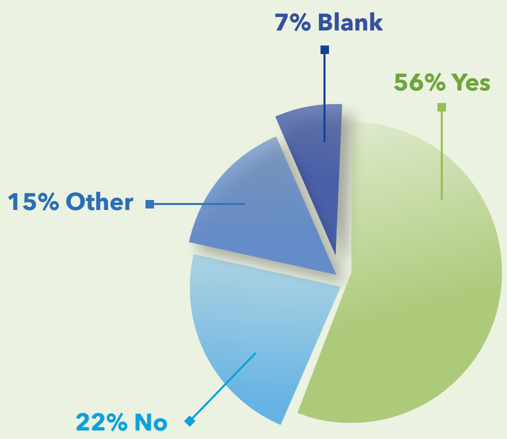
Finally, it is worth noting that the analysis of responses shows that the data in Section 7 may be influenced by the fact that there was no specific definition for “cancelation” or “suspension” of registrations in the survey. This lack of definition became a potential limitation of the results. It led to interpretation possibilities of the questions, especially for countries lacking regulated suspension of registrations.

Section 8

CPP and marketing status of the product

QUESTION 8.1

In the case of submissions of applications for new drugs/new pharmaceutical products, is the product required to have an active marketing status stated in the CPP provided for the registration process?

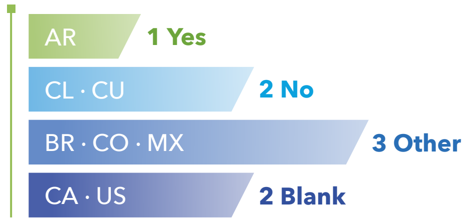


GRAPHIC 8.1a
Requirement for the product to have an active marketing status stated in the CPP provided for the registration process in case of submission of applications for new drugs/new pharmaceutical products.

Yes: *(15) AR, BB, BO, CR, GT, HN, JM, NI, PA, PE, DO, SR, TT, UY, VE.*
No: *(6) BZ, CL, CU, SV, HT, PY.*
Other: *(4) BR, CO, EC, MX.*
Blank: *(2) CA, US.*

For the countries requiring a CPP, most require the active marketing status of the product be stated in the CPP provided for the registration process, including most of the NRAs of the RTCA members. This requirement shows the characteristic trend in the region as a result of this study. However, this question might have raised significant divergences of opinion in eight out of the fourteen cases (8/14) in which the NRAs and the IND from the same country responded (AR, BR, CO, EC, JM, MX, SV, TT).

One of the NRAs (SV) remarks show that the product is required to have an active marketing status stated in the CPP provided for the registration process for an exceptional case. This explanation helped us understand that the responses of the IND and the NRAs are not divergent. Two out of the four NRAs responding *Other* (EC, MX) usually require that the product have an active marketing status stated in the CPP, but exceptions are accepted. One NRA (BR) states not requiring this information, except for the specific case of CPPs not issued by the country of origin of the product. The response of the fourth NRA (CO) allows to understand that, although an authorization in the country of origin is necessary, it is not necessary to state the active marketing status. These explanations clarify the responses of the IND in these countries, so they cannot be interpreted as divergent.

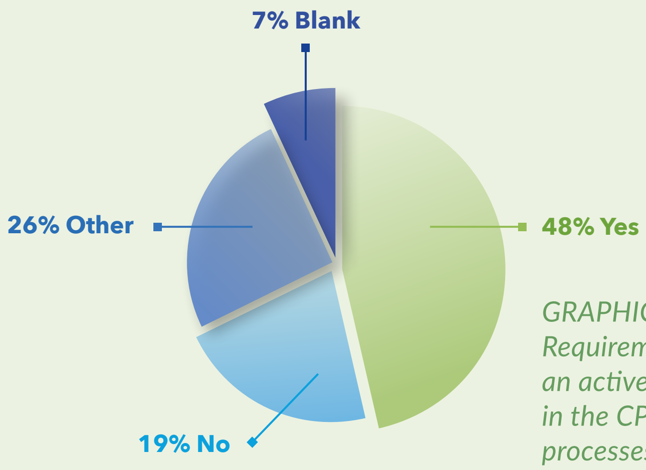


GRAPHIC 8.1b
Responses from the rNRAs.

The rNRAs responses indicate that the statement of active marketing status of the product in the CPP is usually required in two countries (AR, MX) and may be required in one specific case in another country (BR). Thus, there is a trend for rNRAs not to require information regarding the marketing status of a product in the CPP-issuing country.

QUESTION 8.2

In the case of renewals, is the product required to have an active marketing status stated in the CPP provided for the registration process?



GRAPHIC 8.2
Requirement for the product to have an active marketing status stated in the CPP provided for the registration processes in cases of renewals.

Yes: *(13) BO, CR, GT, HT, HN, JM, MX, NI, PA, PE, DO, UY, VE.*
No: *(5) BZ, BR, CL, CU, PY.*
Other: *(7) AR, BB, CO, EC, SV, SR, TT.*
Blank: *(2) CA, US.*

This question is directly associated with 2.1, in which eighteen countries (18) report they require a CPP for renewals, and one country requests it for some specific renewals. Considering the universe of nineteen NRAs that may require a CPP for renewals, the trend (13) is to require the active marketing status of the product stated in the CPP provided for the registration renewal process, including most of the RTCA members. This trend is even stronger when analyzing the comments of the countries requiring a CPP for renewals that respond *Other*: two NRAs (EC, SV) explain requiring information regarding the marketing status, with some exceptions.

Thus, for the countries requiring a CPP for renewals, there is a great coincidence between responses to questions 8.1 and 8.2, i.e., NRAs requiring an active marketing status of the product for registration also require it for renewal.

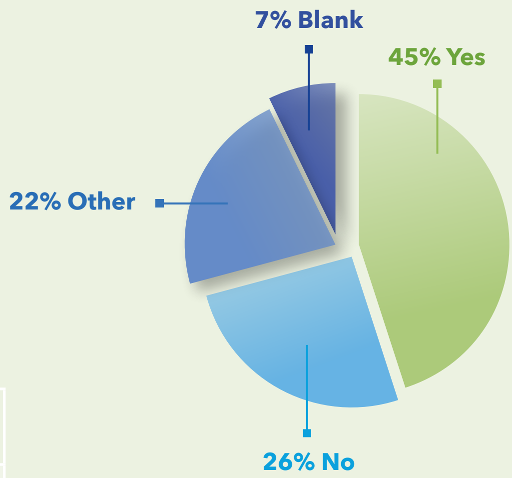
Given the questions' interdependence, this question should not apply to countries not requiring a CPP for renewals. However, there is an apparent contradiction in one country (MX). It reports not requiring an active marketing status of the product in the CPP provided for the registration renewal process. Maybe this NRA has made a wrong interpretation of the question because, when reviewing the IND response, it claims that the product doesn't need to state an active marketing status in the CPP provided for the registration process; only the GMPs certificate is required.

For rNRAs, the reported national practices for renewals lead to the conclusion that most of them do not require an active marketing status of the product in the CPP provided for the registration renewal process because many of the rNRAs do not require a CPP for renewals.

QUESTION 8.3

In the case of post-approval changes/variations, is the product required to have an active marketing status stated in the CPP provided for the registration process?

GRAPHIC 8.3
Requirement for the product to have an active marketing status stated in the CPP provided for the registration process in the event of post-approval changes.



Yes: *(12) AR, CR, GT, HT, HN, MX, NI, PA, SR, TT, UY, VE.*	
No: *(7) BZ, BO, BR, CL, CU, JM, PY.*	
Other: *(6) BB, CO, EC, SV, PE, DO.*	
Blank: *(2) CA, US.*	

This question is related to question 3.1. (Is a CPP required for post-approval change/variation applications of pharmaceutical products?). Considering those countries requiring a CPP for all or some post-approval variations (20), most (12) claim requiring the CPP to report an active marketing status of the product, including most of the NRAs signatories to the RTCA. Three other NRAs responding *Other* (EC, SV, PE) state that there is a requirement for specific renewals.

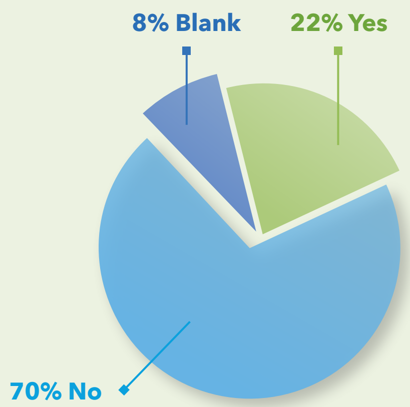
Thus, the trend is that NRAs require information on the active marketing status in the CPP submitted for renewals, which is consistent with the responses for questions 8.1 and 8.2.

Divergent opinions were found in only three of the fourteen responses of the NRAs and the IND from the same country: while the NRAs state what is the information needed in the CPP regarding the marketing status of the product for post-approval changes, the responses of two IND (CR, GT) state that the situation is applicable only for specific cases, and another IND (HN) states that the information is not necessary.

Most rNRAs do not require the submission of a CPP for all post-approval changes, nor do they request information on the marketing status of the product when evaluating variations.

QUESTION 8.4

Are there specific requirements related to the marketing status (e.g., marketing time frame)?



GRAPHIC 8.4
Specific requirements related to the marketing status.

Yes: *(6) AR, BB, BZ, JM, PY, TT.*
No: *(19) BO, BR, CL, CO, CR, CU, EC, SV, GT, HT, HN, MX, NI, PA, PE, DO, SR, UY, VE.*
Blank: *(2) CA, US.*

Responses help identify that most countries do not have specific requirements related to the marketing status, including all countries signatories to the RTCA.

Most rNRAs practices are consistent regarding that there are no specific requirements related to the marketing status of the product.

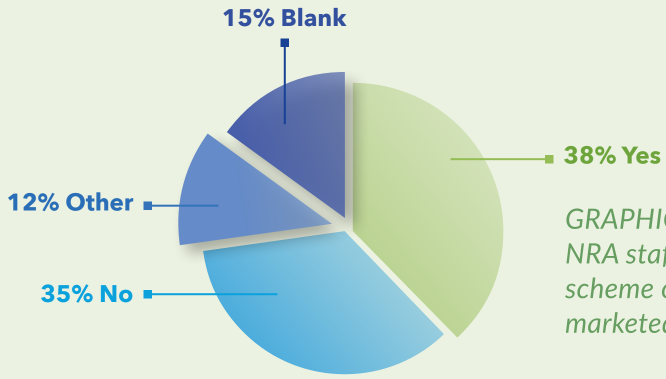
Section 9

Other relevant information

Due to the survey design, the countries in the region not requiring a CPP (CA, US) could not interpret the response options for some questions in this section according to their practice. Therefore, each question describes the specific situations and the remarks from such authorities to help contextualize the country's information.

QUESTION 9.1

Is the NRA staff trained in the WHO certification scheme on the quality of internationally marketed pharmaceutical products?



GRAPHIC 9.1
NRA staff trained in the WHO certification scheme on the quality of internationally marketed pharmaceutical products.

Yes: *(11) AR, BB, CA, CO, CR, SV, GT, PE, US, UY, VE.*
No: *(9) BZ, BO, BR, EC, HT, HN, JM, SR, TT.*
Other: *(3) CL, CU, MX.*
Blank: *(4) NI, DO, PA, PY.*

A significant number of countries, including one rNRA, have not provided in-house training on the WHO certification scheme on the quality of internationally marketed pharmaceutical products.

The authorities of the countries that respond having provided training state that these sessions were in-house training or in collaboration with the rNRAs. They also state that the evaluations are scheduled, or that a predefined training program is followed.

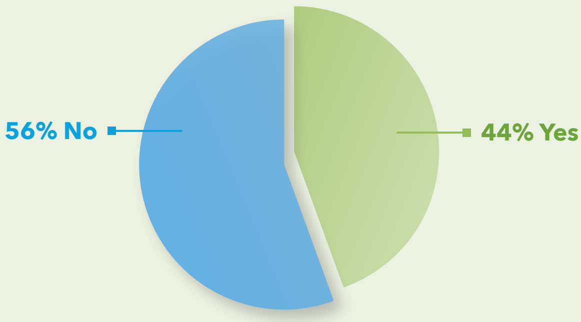
Among the NRAs of the RTCA member states responding to the survey, only one claims not to have conducted training for the staff.

It should be clarified that question 9.1 is considered specific to NRAs and, therefore, responses from countries with information only from the IND (NI, DO, PA, PY) were excluded.

For the rNRAs responding *Other*, one rNRA states that training is provided during the performance of their functions, without following formal programs (CL); and another rNRA reports that they train evaluators during the elaboration of regulations and evaluation procedures and forums on the CPPs (CU). Two rNRAs responded that they do provide on-the-job training during the beginning of CPP-issuing process (CA, CO). In general, the advisability of formalizing training on the subject is evident.

QUESTION 9.2

Does the NRA accept CPPs in electronic format?



GRAPHIC 9.2
Acceptance by the NRA of CPPs in electronic format.

Yes: *(12) AR, BB, BR, CL, CR, JM, NI, PA, PE, DO, US, UY.*
No: *(15) BZ, BO, CA, CO, CU, EC, SV, GT, HT, HN, MX, PY, SR, TT, VE.*

Most NRAs in the region do not accept electronic CPPs and are not prepared to work with them, although the number of NRAs that already accept it is not negligible.

In countries where the NRA does not accept the CPP in electronic format, some countries comment that the current regulations date back from years when such format was inexistent, or that the requirement of the document in printed format (BO, CO) is maintained, while some countries that accept it require special conditions.

In this question, there were divergences of opinion in six countries out of fourteen in which the NRAs and the IND responded to the question. In three cases, the NRA responds that it accepts CPPs in electronic format (AR, JM, UY), while the IND responds that they do not. In another three cases (SV, GT, HN), the NRA responds that they do not accept electronic format against the IND's opposite responses.

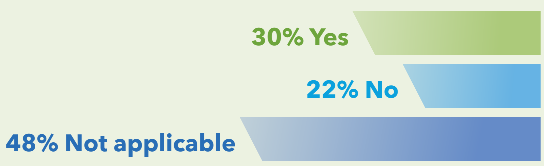
The practices of the NRAs of the RTCA vary in relation to the acceptance of electronic CPPs.

Regarding the responses from the rNRAs requiring a CPP, three of them report accepting the electronic format. In contrast, another three do not accept it and explain that the current standard requires to deliver the document in printed format or that there are no regulations to accept the electronic format. Thus, paper documents are still used.

For this question, there was no option choice for NRAs not requiring a CPP (CA, US). However, the question may have been interpreted from the perspective of the voluntary receipt of electronic CPPs, or electronic documents in general, or the issuing of electronic CPPs by the NRA for the use of other authorities, since both NRAs issue CPPs in electronic format.

QUESTION 9.3

If the CPP is accepted in electronic format, are there additional requirements for this format?



GRAPHIC 9.3
Additional requirements for the CPP in electronic format

Yes: *(8) BR, CA, CL, CR, NI, PA, DO, UY.*
No: *(6) AR, BB, GT, JM, PE, US.*
Not applicable: *(13) BZ, BO, CO, CU, EC, SV, HT, HN, MX, PY, SR, TT, VE.*

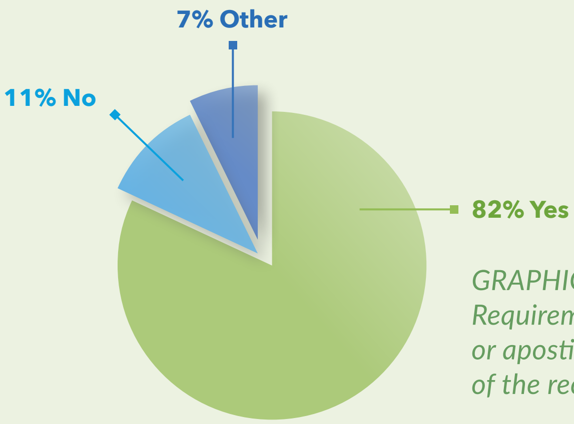
Of all the countries accepting electronic CPPs, there is a trend for additional requirements, such as apostilled documents, notary certification, mandatory printing, or that the issuing authority legalizes the electronic format.

The two NRAs of the RTCA member states accepting the CPP in electronic format have additional requirements in line with the regional trend.

The three rNRAs requiring the CPP claim to accept it in electronic format. Two of them clarify that, as part of their additional requirements, all documents must be legalized and accompanied by a printed copy for verification, and that a translation must be provided in the dossier (BR, CL).

QUESTION 9.4

Is it necessary for the CPP to be legalized or apostilled at the embassy or consulate of the receiving country?



GRAPHIC 9.4
Requirement that the CPP be legalized or apostilled at the embassy or consulate of the receiving country.

Yes: *(22) AR, BB, BZ, BO, BR, CL, CO, CR, CU, EC, SV, GT, HT, HN, JM, MX, NI, PA, PY, DO, TT, UY.*
No: *(3) SR, US, VE.*
Other: *(2) CA, PE.*

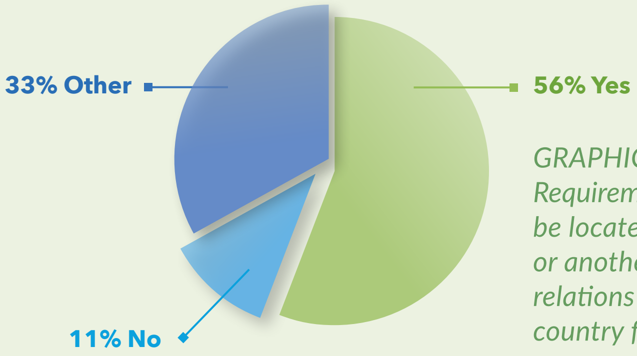
It is a common practice for the NRAs in the region, including all NRAs of the RTCA signatory countries, to require the legalization of the CPP. Of the NRAs responding *Other*, one NRA (CA) explains that it is not a requirement in their country, but it is in the countries receiving the CPP issued by their authority. It is equivalent to a *No* response. Another NRA (PE) explains that the requirement may not apply depending on the authority issuing the CPP, i.e., the CPP is required to be legalized or apostilled for specific cases.

All rNRAs requiring a CPP report requiring the legalization of the document. Some rNRAs state that the CPP must be legalized or apostilled at the embassy or consulate of the receiving country, depending on the country of origin and the apostille's status. So, for countries that are not part of The Hague Convention, the legalization must be done at the consular authority in charge of the jurisdiction where the document was issued.

In this question, there were divergences of opinion only in one country (BR) out of the fourteen cases in which the NRAs and the IND from the same country responded to this question. The NRA stated that the CPP must be legalized or apostilled at the embassy or consulate of the receiving country. In contrast, the IND states that CPP's authentication is not necessary.

QUESTION 9.5

If CPP legalization is required, is the embassy/consulate required to be located in the issuing country or another country with diplomatic relations with the receiving or issuing country?



GRAPHIC 9.5
Requirement that the embassy/consulate be located in the issuing country or another country with diplomatic relations with the receiving or issuing country for CPP legalizations.

Yes: *(15) AR, BO, CL, CO, CR, CU, GT, HT, HN, JM, MX, PA, PY, DO, TT.*
No: *(3) BZ, NI, VE.*
Other: *(9) BB, BR, CA, EC, SV, PE, SR, US, UY.*

Given the interdependence with the previous question, no response was expected from four countries: Two of them because they do not require the legalization of the CPP (SR, VE) and the other two because they do not require a CPP (CA, US). However, as the *N/A* option was not available for this question, they have chosen the options *Other* or *No* for a response.

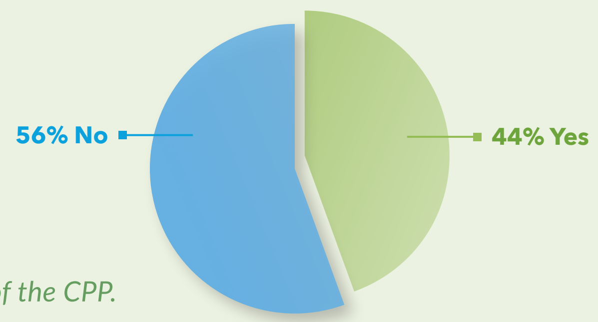
For the twenty-three countries to which this question is applicable, there is a clear trend to require that the CPP be legalized in the issuing country or another country with diplomatic relations with the receiving or the issuing country. In addition to the fifteen countries responding *Yes*, the explanations from at least five countries responding *Other* allow their response to be interpreted as *Yes*. Most explanations are associated with the interpretation that the legalization requirement is applicable only to countries not members of The Hague Convention, and, for non-member states, the location of the embassy/consulate matters.

Seven countries showed divergences of opinion between the NRAs and the IND (AR, CO, CR, SV, HN, JM, TT) out of the fourteen cases in which the NRAs and the IND from the same country responded to this question. The NRAs responded that the embassy/consulate is required to be located in the issuing country or another country with diplomatic relations with the receiving or issuing country. Meanwhile, the IND responds *No* to this question.

The practices of the NRAs of the RTCA vary in relation to this requirement, but they follow the general trend. The rNRAs practice is to require that the legalizing embassy/consulate be located in the issuing country or another country with diplomatic relations with the CPP receiving or issuing country, which is consistent with the observed trend.

QUESTION 9.6

Is there a validity period for the acceptance of the CPP?



GRAPHIC 9.6
Term for the acceptance of the CPP.

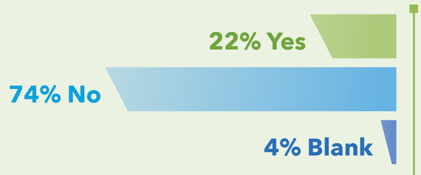
Yes: *(23) AR, BB, BO, CA, CL, CO, CR, CU, EC, SV, GT, HT, HN, JM, MX, NI, PA, PY, PE, DO, SR, UY, VE.*
No: *(4) BZ, BR, TT, US.*

The vast majority of NRAs usually have a validity period for accepting the CPP, which is also a trend for all the NRAs of the RTCA and most rNRAs.

No significant divergences of opinion were found in this question for the cases in which the NRAs and the IND from the same country responded.

QUESTION 9.7

May the CPP be requested by a company that is neither the holder of the marketing authorization of the product nor its legal representative?



GRAPHIC 9.7
Possibility that the CPP be requested by a company that is neither the holder of the marketing authorization of the product nor its legal representative.

Yes: *(6) AR, CA, CL, HN, JM, SR.*
No: *(20) BB, BZ, BO, BR, CO, CU, CR, EC, SV, GT, HT, MX, NI, PM, PY, PE, DO, TT, UY, VE.*
Blank: *(1) US.*

Most NRAs claim that they do not accept a company that is neither the marketing authorization holder nor the legal representative of the product request a CPP, a trend found for the RTCA member states and, to a lesser extent, for rNRAs.

One NRA responding *Yes* (SR) states not having understood the context of the question but explains that a single product can have more than one registration holder and, therefore, responded *Yes*. Hence, only for five countries a company that is neither the marketing authorization holder of the product nor its legal representative is allowed to request a CPP.

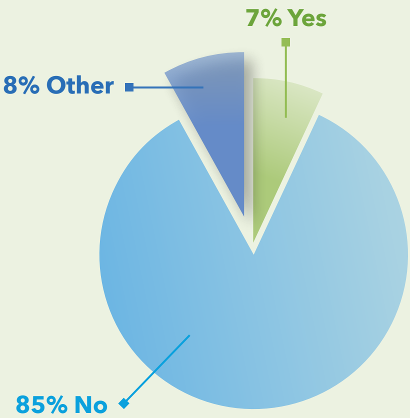
QUESTION 9.8

If Yes, does the NRA request authorization to issue a CPP requested by a third party?

Of the five countries to which this question is applicable, in three of them (CA, CL, JM), the authorization of the holder of the registration is required; in another one (HN), of the legal representative. One of the authorities (NRA) responding *Other* does not provide explanations, but the response of the IND helps us understand that no authorization is necessary.

QUESTION 9.9

Are there any differences in the CPP content requirements depending on the type of product (e.g., chemical or biological products)?



GRAPHIC 9.9
Differences in the requirements for the CPP content depending on the type of product.

Yes: *(2) AR, DO.*	
No: *(23) BB, BZ, BO, BR, CA, CL, CO, CR, CU, EC, SV, GT, HT, HN, JM, NI, PA, PY, PE, SR, TT, UY, VE.*	
Other: *(2) MX, US.*	

The NRAs do not usually make differences between the CPP content requirements depending on the type of product, including all NRAs from RTCA member states and most rNRAs.

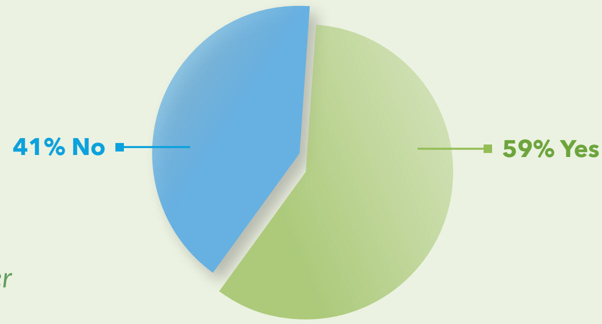
There were significant divergences of opinions in two out of the fourteen cases in which the NRAs and the IND responded (AR, HN). However, the evaluation of the remarks provided by the industry allows to understand that there is consistency with the NRA response.

Section 10

National Regulatory Authorities (NRAs) that issue CPP (only for NRAs issuing CPPs)

QUESTION 10.1

Are there specific deadlines for issuing the CPP after the marketing authorization holder submits an application?



GRAPHIC 10.1
Specific deadlines for issuing the CPP after the marketing authorization holder submits an application.

Yes: *(16) AR, BO, CA, CL, CO, CU, EC, SV, GT, JM, PA, PY, PE, TT, US, VE.*
No: *(11) BB, BZ, BR, CR, HT, HN, MX, NI, DO, SR, UY.*

Most countries responding *Yes* state that there are deadlines for processing the application, usually for a term from five to twenty business days, although the deadlines can be as long as two months.

Most rNRAs (6/8) set specific deadlines for the CPP issuance after the marketing authorization holder submits an application. Still, the information provided does not allow to identify the term regularly applied.

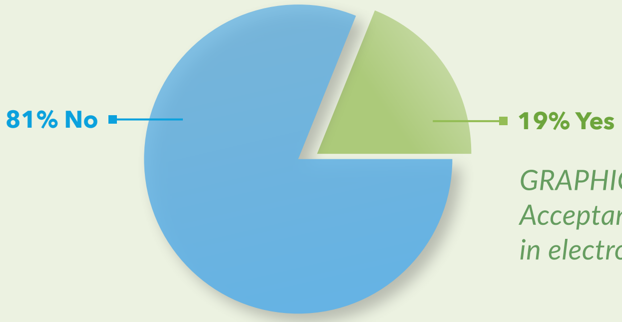
QUESTION 10.2

Load/provide a copy of the standard CPP form/document/template required by the local regulation, and attach the file, if any.

As stated above, these documents are assessed together with the documents provided for question 4.1 in section “Comparison of the WHO CPP form and the characteristics of the CPPs issued and received by the NRAs of the Americas” of this chapter.

QUESTION 10.3

Does the NRA accept CPPs in electronic format?



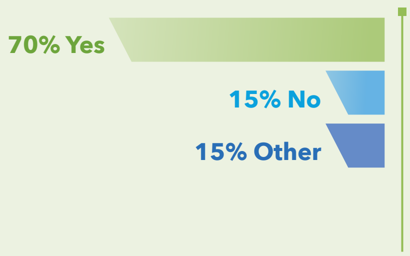
GRAPHIC 10.3
Acceptance by the NRA of CPPs in electronic format

Yes: *(5) AR, BR, CL, CO, DO.*	
No: *(22) BB, BZ, BO, CA, CR, CU, EC, SV, GT, HT, HN, JM, MX, NI, PA, PY, PE, SR, TT, US, UY, VE.*	

It is not yet the NRAs practice to issue electronic CPPs. Of the five claiming to do so, most responses correspond to the rNRAs. However, for one rNRA (CO) that claims to issue CPPs, the IND reports that the NRA does not issue electronic CPPs. In another case (CL), the authority itself reports that the document is produced electronically but printed for delivery.

QUESTION 10.4

Does the CPP issued have an expiration date?



GRAPHIC 10.4
Expiration date in the issued CPPs.

Yes: *(19) AR, BB, BO, BR, CA, CL, CO, CR, EC, SV, GT, HT, HN, PA, DO, TT, US, UY, VE.*
No: *(4) CU, NI, PY, PE.*
Other: *(4) BZ, JM, MX, SR.*

Most countries respond *Yes*, which is the practice of most NRAs from the RTCA and the rNRAs. However, many countries do not indicate the applicable expiration date. The countries that do indicate a term usually set a CPP validity period of 1 or 2 years.

One limitation observed in the evaluated responses is the possibility that some respondents may have misinterpreted the question, reporting not on the expiration date of the CPP issued by the country's NRA, but on the expiration date of the documents received by the authority.

Of the fourteen cases with responses of the NRAs and the IND from the same country, four showed divergent responses. In one case (AR), the NRA claims a validity period, but the IND claims that there is no regulatory provision. In another case (CR), the IND claims that there is no term. However, the NRA claims that there is one, although it explains that the term is not included in the regulation, and, therefore, it is a practice of the authority. There are no elements to interpret the divergences of the remaining two cases (GT, TT).

Regarding the declared time frames, there are also divergences between the NRAs and the IND of three countries (BO, CO, EC): in one case, the IND states a longer validity period than the NRA; in another case, the NRA declares a longer-term and, in a third case, the authority claims to set a term, but the IND reports that it does not exist. However, it cannot be concluded that all cases represent a true divergence between the NRAs and the IND, as their remarks verify that there was a misinterpretation of the question.

Comparison of the who CPP standard form and the characteristics of the CPPs issued and received by the NRAs of the Americas

The survey asked participants to load/provide copies of the CPPs: under question 4.1, a copy of the standard CPP form/document/template required by local regulation; under question 10.2, a copy of the standard CPP form/document/template issued by the country's NRA.

As a result of question 4.1, thirteen documents were provided according to the information in the following table:

Table X • CPP standard forms required by the local regulation received from the respondents

RECEIVING COUNTRY	DOCUMENT LOADED BY	DOCUMENT ISSUER	TYPE OF DOCUMENT
BOLIVIA	NRA	Bolivia	Blank template
	IND	Argentina	Copy of a true CPP
COLOMBIA	NRA	Uruguay	Copy of a true CPP
CUBA	NRA	Canada	Copy of a true CPP
		USA	Copy of a true CPP
		Cuba	Blank template
EL SALVADOR	NRA	El Salvador	Blank template
GUATEMALA	NRA	Europe	Copy of a true CPP
HONDURAS	NRA	Honduras	Blank template
JAMAICA	IND	Europe	Copy of a true CPP
MEXICO	IND	Mexico	Blank template
PERU	NRA	Bulgaria	Copy of a true CPP
TRINIDAD AND TOBAGO	IND	Europe	Copy of a true CPP

The initial analysis of the documents provided from respondents of question 4.1 indicated some major limitations that would not allow conclusions to be drawn on the regional trends regarding the type of CPP accepted by countries. Initially, the sample of countries is limited (10) since some of the NRAs (BO, SV, HN) have only loaded their own document form. This does not allow us to understand if the form received should be the same CPP form issued by the authority or an interpretation error. That seems to be the case, for example, in Mexico, whose NRA requires the submission of a CPP but does not issue it. For this country, the document provided corresponds to a Certificate of Free Sale (CFS) issued by the country's NRA. Thus, the data submitted by the respondents do not allow us to know if there is a regulation in the region on the CPP content received by each country.

Meanwhile, for question 10.2, eleven documents from ten countries were received according to the information in the following table:

Table XI • CPP standard forms issued by the NRA received from the respondents

RECEIVING COUNTRY	DOCUMENT LOADED BY	TYPE OF DOCUMENT
BOLIVIA	NRA	Blank template
BRAZIL	NRA	Blank template
COLOMBIA	NRA	Copy of a true CPP
CHILE	NRA	Blank template
CUBA	NRA	Blank template
ECUADOR	NRA	Blank template
EL SALVADOR	NRA / IND	Blank template
GUATEMALA	NRA	Copy of a true CPP
PERU	NRA	Copy of a true CPP
VENEZUELA	NRA	Blank template

Again, the data cover a limited number of countries (10). It is not enough to draw conclusions on the regional practices about the CPPs issued. However, we obtained a more significant number of forms issued by the NRAs by grouping the documents sent for questions 4.1 and 10.2, with a total of sixteen countries (BO, BR, CO, CL, CU, EC, SV, GT, PR, VN, MX, HN, US, CA, AR, UY), covering most of the CPP-issuing countries in the region.

Thus, in this section, we used all documents to compare the WHO CPP form and the characteristics of the CPPs issued and received from the NRAs of the Americas.

The comparison of the documents and the Certificate of Pharmaceutical Product form proposed by the WHO Scheme was focused on the following CPP content characteristics recommended by WHO:

1. Header containing the certificate number, identification of the exporting country (certifier) and the importing country (applicant).
2. The following four sections, with sixteen explanatory notes associated:
   - Name and dosage form of the product.
   - Authorization data of the product.
   - Periodic inspections of the manufacturing plant by the certification authority.
   - Information provided by the certificating authority.
3. Additional information.

The document issued by the NRA of Mexico was excluded from the analysis because it is not a CPP. It is a CFS not regulated by the WHO Scheme and therefore it does not allow for comparisons. Thus, the information presented in the following items considers the documents issued by fifteen countries in the region: BO, BR, CO, CL, CU, EC, SV, GT, PR, VN, HN, US, CA, AR, UY.

Header

All the evaluated documents include information for identifying the exporting country (certifier) and the importing country (applicant). For two countries (BR, EC), the document form received (blank template) does not contain the certificate number. However, it cannot be concluded that such information is not included in a true CPP issued by the NRA since the evaluation of the documents allows us to understand that some NRAs include the certificate number at the time of issuance.

Generally, there is a 96 % average match with the WHO form for the header's content.

Name and y dosage form of the product

In the first section of the WHO standardized CPP, all the evaluated documents require details of the name and dosage form of the product (item 1 of the WHO standard CPP), the active ingredient and the quantity per dosage unit (item 1.1), whether the product is authorized to be marketed in the exporting country (item 1.2), and whether the product is actually on the market of the exporting country (item 1.3). However, for one authority (CE), the last two items are presented differently from the WHO standard form.

For the description of the product's full composition, including excipients (annex to item 1.1), one country (US) does not include it. The information is incorporated differently from the WHO standard form in four other countries (AR, BO, CL, EC), it is described in the CPP and not as an annex.

Also, in this section, we find specific national practices that do not match the WHO form. One NRA (SV) details the name of the product and its classification for export purposes. Four NRAs (BO, SV, GT, VN) describe the product's mode of sale (prescription or over-the-counter). Three authorities (BO, SV, GT) describe the shelf-life of the product. Two authorities (SV, GT) detail the storage conditions. Two other authorities (BO, SV) inform the presentation of the product. Finally, four NRAs (BR, CO, SV, GT) indicate the validity period of the product registration in the country. All information is additional compared to the WHO standard requirements for a CPP, except for two countries (BR, CO) that include the registration validity period. It may be justified because the NRA adopts the CPP validity period (information required in the WHO form) as the registration validity period.

As a trend for the first CPP section, there is an average of 99% requirements of the WHO form included in the countries' forms. Regarding the amount of information required by the NRA in the CPP form, there are three countries that stand out (BO, GT, and especially SV).

Product approval data

Sections 2A and 2B of the WHO CPP form are mutually exclusive. This section is associated with the response to question 1.2 (Is this product authorized to be marketed in the exporting country?). If the response to 1.2 is *Yes*, continue with section 2A and skip section 2B. If the response to 1.2 is *No*, skip section 2A and continue with section 2B. The information gathered is detailed below.

All evaluated certificate forms have section 2A. For this section, it is observed that all countries state the product authorization number and date of issue (item 2.A.1), name and address of the product authorization holder (item 2.A.2), the status of the product authorization holder (item 2.A.3), and name and address of the manufacturer producing the dosage form (item 2.A.3.1). However, it is worth mentioning that one NRA (PE) partially complies with item 2.A.1 since it does not report the registration date but its expiration date.

One single NRA (EC) does not provide the summary of the technical basis for the approval of the registration (item 2.A.4) if the attached information on the conditions of approval of the product is complete and in compliance with the authorization (item 2.A.5). Finally, two NRAs (BO, BR) do not report item 2.A.6 (name and address of certificate applicant if different from the authorization holder). However, for these authorities, removing this field from the CPP can be justified because, in these countries, the CPP cannot be requested by a company that is not the registration holder.

Likewise, if justifiable exceptions are excluded, there is a 96% general average match with the WHO form for the content of section 2A.

Section 2B includes information on the name and address of the applicant for the certificate (item 2.B.1), the status of the applicant (item 2.B.2), the name and address of the manufacturer producing the dosage form (item 2.B.2.1), information on the reasons why the marketing authorization is not available (item 2.B.3), and comments (item 2.B.4).

The characteristics of the documents provided limited the assessment of trends for section 2B. In some cases, the evaluated documents correspond to a true CPP issued for a product, which would justify the elimination of section 2B if the response to question 1.2 was *Yes*. That is the case for documents issued by two NRAs (AR, US). It is not possible to draw conclusions for these countries regarding the inclusion of section 2B in the CPP form. For a third authority (CL), the submitted template corresponds to an electronic CPP and does not contain section 2B. However, it is not possible to conclude that this section does not exist.

The CPP of two other NRAs (BO, BR) does not include section 2B. It is worth noting that the templates submitted by these countries include item 1.2 pre-filled with the response *Yes*. It allows the interpretation that the NRA issues CPPs exclusively for products authorized to be marketed in their local markets; thus, section 2B would never apply to these countries.

For all these reasons, data are limited and do not allow a generalization of regional trends concerning section 2B. If we consider all fifteen documents submitted, the average coincidence with the WHO form is 67%. However, excluding the five cases mentioned above (three documents that do not allow conclusions because sections 2A and 2B are mutually exclusive, and two countries issuing CPPs only for products registered in their territory), the remaining documents yield a level of coincidence of 98% with the WHO form. One single NRA (EC) does not comply with item 2.B.4.

Periodic inspections of the manufacturing plant by the certification authority

The third section of the WHO CPP form includes four items. Item 3 questions whether the authority performs periodic inspections of the manufacturing site where the dosage form is produced. This information is described in all documents evaluated. Except for one NRA (EC), all of them comply with reporting the frequency of routine inspections (item 3.1). Two countries (BO, EC) do not detail whether they have inspected the manufacture of this type of dosage form. Additionally, two authorities (EC, VE) do not report if the facilities and processes comply with the Good Manufacturing Practices, as recommended by WHO. One of these NRAs (VE) adapted its national CPP form, and the information required includes the national GMPs (not the WHO's) as reference for the question.

Generally, comparing items 3, 3.1, 3.2, and 3.3 of the WHO form, the documents issued by the NRAs yield a 92% average of coincidence.

Information provided by the certificating authority

Finally, the fourth and final section of the WHO standard CPP asks whether the information provided by applicants satisfies the certifying authority regarding all aspects of the product's manufacture. This part is filled in when the registration holder is not the manufacturer of the product. All evaluated documents contain this information.

The WHO CPP form requests explanations for *No* responses from the certifying authority. For three authorities (CL, EC, US), the evaluated CPP form does not include this information. One case (AR) provided a copy of a true CPP issued by the authority; thus, it is impossible to determine if the CPP form does not include this item or if the item is not included in the document because the response to item 4 was *Yes* (and therefore no explanation would be needed). For two other NRAs (BO, BR), the templates provided by these countries include item 4 pre-filled with the response *Yes*, which would indicate that the NRA issues CPPs exclusively when the applicant's information satisfies the certifying authority in all aspects of the product's manufacture. Thus, this item would never be applicable to these countries. This condition seems to be in line with the position of the NRAs of only issuing CPPs for products authorized to be marketed in their national markets (question 1.2 pre-filled with response *Yes*). For this item, excluding the two cases in which the explanations do not apply to the country's practice and the case that does not allow conclusions to be drawn from the universe of analysis, the level of coincidence with the WHO form would be 75%.

Additional information

According to the WHO form, certificating authorities must submit or fill in additional data in the issued CPP. Such information is as follows:

- **Address of the authority:** included in all evaluated documents.
- **Telephone:** included in thirteen of the fifteen documents evaluated (except BR, CA).
- **Fax number:** included in only five evaluated documents (CO, CU, HN, PE, VN), which is understandable due to the global fax disuse trend.
- **Name of the authorized person and signature:** included in twelve of the fifteen documents evaluated, except AR, BO, SV, but it is impossible to conclude that this information will not be included later in the CPP: in two cases, the NRA provided a blank template, and the name of the authorized person and signature might be included at the time the document is issued; in another case, the document provided is a copy of an actual CPP, but apparently this information is omitted, and there is an indication that the document contains the name of the authorized person and signature showed by the text of an affidavit at the end of the document. In two cases (CL, CO), the document's signature matches the electronic signature.
- **Stamp:** eight of the fifteen evaluated documents have a stamp or report that the CPP must be stamped. However, this does not mean that the other NRAs do not include the stamp in their CPPs. For four cases (BO, EC, EL, VE), the evaluated document is a blank template. The stamp might be included at the time of issuance of the CPP. For another case (AR), the document provided is a copy of an actual CPP, but apparently this information is omitted. In two cases (CL, CO), the stamp may not be applicable since the form provided for evaluation is an electronic CPP.
- **Date:** included in fourteen of the fifteen documents evaluated (except EC).
- **Certificate expiration date:** included in eight of the fifteen documents. However, it is noted that, for two of these NRAs (CU, PE), this information is not applicable since it is known that their CPP has no validity period. For two other NRAs (BR, CO), the CPP validity period is equivalent to the registration validity period, and this is reported in the CPP. Thus, for three countries only (UY, HN, GT), the certificate’s validity period can be considered not to be included.

As a general trend of the evaluated documents, the national forms show a high degree of coincidence with the information stated in sections 1 to 4 of the WHO CPP form.

Practices of the countries

Considering the limitations described in the analysis of the content of the documents provided (for example, items not applicable to the practice of the country, items adapted to the WHO form, items for which, due to the characteristics of the documents, it is impossible to draw conclusions), it is difficult to define the degree of coincidence of each country with the WHO form.

Considering only the WHO form items, which are certainly not included in the national documents, most NRAs usually do not implement only 1 or 2 items (out of 34 existing ones), which represents no more than 6% of mismatch with the international standard form. There is only one NRA (EC) against this trend. Its CPP does not observe the form and/or content of the WHO in at least 32% of the items.

IV. LEGAL BASIS

As part of the survey to evaluate the requirements and use of CPPs for drug registration processes by the NRAs in the region of Americas, the survey required information on each country's legal and technical basis for their responses.

Since it was optional to provide such references for each specific requirement, the data compiled below is not exhaustive. In many cases, both NRAs and the industry indicated that the implementation was performed through a national legislation, a NRAs standard, or other standards, as three alternatives, expressed in a generic way, were the possibilities to select in the survey.

The term "national legislation" referred to a country's legislation, such as laws, regulations, decree-laws, resolutions, and any other used for the registration and use of the CPP. As the rules and practices of the NRA, it was necessary to interpret the internal or public procedures developed to implement the national and regional legislation, as the case may be. These procedures could be written or could constitute the usual procedure in standard situations. All information related to the legal and technical basis reported by survey participants was consolidated and validated in a table attached for reference in Annex No. 2.

Central American Technical Regulations

There is only one legally binding document in the region proposing harmonizing the requirements related to the CPPs: the Central American Technical Regulation (RTCA). This international agreement applies to the registration of medicines for human use, and is included in an annex to Resolution No. 333/2013 issued by the Council of Ministers of Economic Integration (COMIECO). The RTCA was intended to standardize the minimum requirements to register a product in Central America. It directly shapes the regulatory frameworks and practices of its Member States regarding the use of CPPs. The Member States that subscribe to this regulation are Costa Rica, El Salvador, Guatemala, Honduras, and Nicaragua.

The RTCA applies to medicines for human use manufactured or imported by natural or legal persons for marketing them in the Central American territory. This regulation does not apply to magistral preparations and combinations of drugs or active ingredients registered in El Salvador before the date of its entry into force. Biological and biotechnological medicines are registered following the national legislation of each Member State. When any of these products is not covered by a national legislation, this regulation applies to them.

The mandatory submission of the CPP is a requirement provided by the RTCA for registrations, renewals, and variations in the registration of imported medicines for human use. The original or authenticated photocopy of the legalized document must be submitted (or, alternatively, the Certificate of Free Sale [CFS]). By definition, as provided in the regulations, the Certificate of Pharmaceutical Product must be submitted in the format proposed by the WHO.

A · Legal basis for the use of the CPP received

The following is a summary of the information gathered and the general guidelines on the legal basis of the CPPs requirement for the different regulatory processes in the region of Americas. This information includes all the countries within the survey's scope, except Canada and the United States, since their NRAs do not require a CPP for any of the following processes associated with the registration of pharmaceutical products (n = 25).

Registration of a new pharmaceutical product

The evaluation of the information provided by respondents in section 1 of the questionnaire indicates that most countries (17/25) require a CPP for the registration of a new pharmaceutical product based on the provisions of the national legislation (AR, BB, BZ, BO, BR, CL, CO, CU, EC, JM, MX, PA, PY, PE, DO, UY, VE). To a lesser extent, three respondents claim to require a CPP according to the NRA rules (HT, SR, TT). The five members of the RTCA (CR, GT, HN, NI, SV) adopt the CPP requirement for the registration of new pharmaceutical products included in that Regulation. However, two of them refer to another legal basis: the NRA rules (GT), and the national legislation in addition to the NRA rules (SV).

Renewal of pharmaceutical products registrations

According to the survey data, three NRAs do not require CPPs for renewal procedures (AR, BR, and MX), and only one NRA (BR) reports that the NRA rules support the exemption.

Of the twenty-two countries requiring CPPs for renewals, half of the respondents (11) report that the renewal of pharmaceutical product registrations is regulated by the national legislation (BZ, BO, CL, CO, CU, EC, PA, PY, PE, SR, VE). A smaller portion of respondents (6) report that they follow the NRA rules (BB, HT, JM, DO, TT, UY). In turn, the five countries signatory of the RTCA establish it as a legal basis for the renewal of registrations, although one of them (GT) reports doing so also according to its national legislation and the NRA rules.

Variation of pharmaceutical products registrations

In section 3 of the survey, twenty countries request a CPP for post-approval change submissions. However, they mention numerous variations that are not related to a new CPP, so it is required only in particular cases. Of these, eight (BZ, CO, MX, PA, PY, PE, DO, VE) report that the requirement follows the national legislation, and five (CU, HT, SU, TT, UY) follow their NRA rules. The five countries signatories of the RTCA establish it as their legal basis for the renewal of registrations, although one of them (GT) reports doing so also according to its national legislation and the NRA rules. As a particularity for this section, two other countries (AR, EC) report that they approach such variations as stated in their national legislation and NRA rules simultaneously. Of the countries reporting that they do not require a CPP for post-approval variations, two (BO, CL) state that this situation is included in their national legislation and the other two (BR, JM), in the NRA rules. In one case (BB), the country reports that it does not receive submissions of post-approval changes, so the question is not applicable to its practice.

B · Legal basis for the NRA practices associated with the CPP

For the different questions of the questionnaire regarding the NRA practices connected with the CPPs received and issued, respondents were asked for information regarding the legal basis on which the NRA acts. For some questions in this section, where applicable, the responses of Canada and the United States were considered. This information is detailed below.

CPP form

Regarding the CPP form required by the countries, seven of the countries (AR, BO, CO, EC, PA, PE, VE) follow the legal basis mentioned in the national legislation, and two countries (CU, SR) follow the NRA rules. The CPPs form in the five countries signatories of the RTCA is governed by this Regulation, although two countries (SV, GT) report they also follow the national legislation and the NRA rules. Seven countries (BB, BR, CL, HT, JM, DO, TT) state that their legislation or regulations do not include specific CPP form requirements. In turn, three countries (BZ, MX, UY) do not report on the legal basis regarding the form. No responses were provided by one respondent (PY).

For the two countries not requiring a CPP but issuing CPPs (CA, US), the form is established in the NRA rules, In both cases, the form established by the WHO is mentioned.

Evaluation of the CPP during the different regulatory processes

This question is not applicable to Canada and the United States. Most of the countries consulted (15/25) refer that the CPP evaluation by the NRA is included in their national legislation (AR, BB, BO, BR, CL, CO, EC, JM, MX, PA, PY, PE, DO, UY and VE). Other countries (4/25) state that the requirement is included in the NRA rules (BZ, CU, HT, TT), and only one country (SR) mentions that the requirement is included in both the national legislation and the NRA rules. The five RTCA member states carry out the assessment in accordance with the Regulation. Still, one of them states that the mandatory requirement of assessing the CPP is also stipulated in its national legislation and the rules of the NRA (GT), and another one (SV) also states that it is established in its national legislation.

Evaluation of the prior registration status in the country of origin

This analysis includes only the eleven responses from the countries claiming to assess the statement of prior registration status in the country of origin, according to question 6.1 of the survey. In most cases (8/11), such evaluation is conducted by the NRAs following the national legislation (AR, BR, CO, EC, JM, PA, DO, UY). In two cases (HT, TT), it is assessed according to the NRA rules, and in one case (CR), the RTCA is mentioned as the legal basis for this requirement.

Obligations and impact when there is a cancelation of the registration in the CPP-issuing country

According to the responses in section 7 of the questionnaire, in twenty-one countries, the registration holder is responsible for notifying the NRA in the event of a cancelation of the registration in the CPP-issuing country. However, in two of them, this is notified only in specific situations. Concerning the obligation to notify the NRA about the cancelation of the registration in the CPP-issuing country, twelve countries (BZ, BO, CL, CO, EC, JM, PA, PY, DO, UY, VE) state this is included in the national legislation; six countries (AR, BB, CU, SV, HT, TT), in the NRA rules; two countries (GT, SR), in both regulations, and one country (HN), in the RTCA.

From the twenty countries reporting that the cancelation of the registration in the issuing country has an impact on the receiving country, seven countries indicate that the consequences of the cancelation are included in the national legislation (BO, CL, CO, JM, PA, UY, VE); five countries, in the NRA rules (BZ, SV, HT, PE, TT) and two countries (GT, SR), in both regulations. The remaining countries do not report the legal basis.

Requirement to report an active marketing status in the CPP for registrations

In this question of the questionnaire, there are fifteen countries for which the product is required to have an active marketing status in the CPP provided for the registration process. Six countries (AR, BB, BO, PA, DO, VE) report that the requirement is described in the national legislation; two countries (TT, UY), in the NRA rules; four countries (GT, JM, PE, SR), in both regulations, and three countries (CR, HN, NI), in the RTCA.

Legal basis for the acceptance of CPPs in electronic format

Eleven countries require the CPP for registration processes and claim to accept it in electronic format. Six of them accept it following the national legislation (AR, BB, CL, CR, PA, PE); four accept it following the NRA rules (BR, JM, NI, UY). Another country (DO) reports accepting it only if the issuing NRA uses that format.

Of the fourteen countries requiring a CPP and whose response is that they do not accept it in electronic format, six countries state that the impediment is stated in their national legislation (BZ, BO, CO, EC, PY, VE); three countries, in the NRA rules (SV, HT, TT); one country, in both legislations (GT), and one country, in the RTCA (HN). Three other countries do not report a legal basis (CU, MX, SR). Still, in the comments, they mention that the possibility of electronic CPPs is not stated in their legal or regulatory documents, a situation that constitutes a legal vacuum.

Legal basis for the deadlines for the CPP issuance

Sixteen countries report having specific deadlines for issuing the CPP after the marketing authorization holder submits an application to the NRA. Six of these countries set such deadlines according to their national legislation (BO, CO, EC, PE, TT, VE) and eight countries according to the NRA rules (CA, CL, CU, SV, US, GT, JM, PY). One country (AR) states that deadlines are established in both, its national legislation and the NRA rules, and another country (PA), in the internal NRA processes.

In this chapter, we presented elements for a better understanding of the legal basis supporting the different NRAs requirements and practices in relation with the issuance or the use of CPPs. The purpose is not to compare authorities since it is considered that the legal grounds for the activities associated with the issuance or receipt of a CPP are specific and depend on the particularities within the legal framework of each country. And, even though there are limitations on the data gathered by the survey, the information recorded in this chapter provides insight into the legal situation in the countries of the region, providing elements for discussion on how to achieve greater efficiency in the regulatory processes concerning the CPPs.

V. CONCLUSIONS

This chapter aims to present, as a conclusion of the mapping, the main trends obtained from the analysis of the results included in chapters III and IV. The trends of the Central American countries signatories to the RTCA and the rNRAs are described whenever they are divergent from the general one. The trends were derived from the responses provided by the countries. They are limited because of inconsistencies and omissions on the part of the participants when filling in the survey. In some cases, there are also divergences between the responses of the industry and the NRAs.

The study allowed us to understand that the CPP is mostly used as a document required by the NRAs to register new medicines/new pharmaceutical products in the region of Americas since only Canada and the United States, although they issue the CPP, do not request it. Most countries in the region require a CPP for all registration submissions based on national legislation requirements rather than the NRA's own rules. For Central American countries, this obligation is also specified in the Central American Technical Regulations (RTCA).

More than half of the countries responding to the survey indicate that the CPP does not need to be issued by a NRA recognized as a reference, strict or supervisory authority. However, the CPP must be issued by the regulatory authority of the product's country of origin or country of consignment.

Most countries consider that the prior registration of the product in the country of origin is mandatory. However, the region has not an entirely harmonized approach, which could be related, among other reasons, to a difference in the concept "country of origin". There is no pattern defined for the Central American countries on this particular issue.

The practice within the region is to consider the manufacturing site of the finished product as the country of origin. Another trend is not to associate the concept of country of origin with the quality control testing site (release) of the finished product. Most NRAs requiring mandatory prior registration of a product in the country of origin also request a statement of this registration status.

The vast majority of countries requiring CPPs accept them if they are issued by NRAs that have registered/approved the product, even if they are not from the manufacturing country. They also accept them when a positive assessment results from the inspections of compliance with Good Manufacturing Practices, carried out by another NRA, i.e., a third party.

The requirement for a CPP with the initial submission is almost unanimous. Most countries accept the substitution of the CPP with other documents, and most NRAs which do so state that there are conditions for this substitution. Also, almost all countries conduct detailed evaluations of drug registration applications and require complete dossiers, even if they require and receive the CPP.

As a general policy of the region, no fast track procedures are used after the submission of the CPP. The practices of Central American countries vary, so a common policy cannot be defined. However, there is a limitation in this data. It is important to keep in mind that, since there are no fast track register procedures in the country, the respondent only had the option *No* as a possible response.

More than half of the countries responded that whenever a CPP is provided, as a requirement or voluntarily, no abbreviated files are accepted (with less documentation, information, or data). In other words, the general policy in the region is the absence of information simplification procedures for submitting a CPP.

In the case of the twelve countries claiming that they accept the use of fast track/accelerated/simplified procedures or abbreviated files, that decision is based on the recognition of certain authorities and not of the CPP. The most recognized NRAs are the following: EMA (8), FDA (8), Health Canada (5), Swissmedic (3), MHRA (3), TGA (3), PMDA (2). The remaining NRAs of regional reference (ANMAT, ANVISA, COFEPRIS, INVIMA, CECMED and ISP) are acknowledged by four countries. Central American countries show no trends because they do not report information in this question.

Most countries in the region require that the CPP meets specific conditions for applications to be assessed under accelerated procedures or for an abbreviated file to be accepted.

When evaluating data on the CPP requirement for registration renewal of pharmaceutical products, the trend can only be measured considering solely the countries with renewal procedures since this is not a common practice. The vast majority of countries in the region that conduct renewal procedures require a CPP for this purpose. This trend is not observed for the rNRAs since three of the six rNRAs using the WHO Scheme and performing registration renewals require a CPP.

Most countries requiring a CPP for renewals do so based on national legislation requirements rather than the NRAs' own rules. For Central American countries, this obligation is also specified in the RTCA.

Most countries requiring CPPs for renewals maintain the same requirements as those applied for registrations. However, there is no clear trend in the region that the CPP must be issued by the same NRA that did it so for the initial registration. Criteria are divided, with a slight predominance of countries that do not require it to be issued by the same NRA as for the initial registration.

Regarding the need to submit a CPP for applications for post-approval variations and/or changes in the registration of pharmaceutical products, most NRAs in the region require it. Of all the NRAs asking for a CPP for variations, fewer countries require it for all applications (3), other countries assess the issue on a case-by-case basis (4), and most countries do it so only for specific cases (14).

The trend for countries requiring CPPs for post-approval registration variations and/or changes is to do so based on the national legislation, although the number of countries that determine it based on NRA rules is not negligible. For Central American countries, this obligation is specified in the RTCA.

The regional practices aim to keep the same CPP requirements for both post-approval changes/variations and submission of the registration application. In contrast, most Central American countries state they apply different requirements.

Likewise, the practice related to changes is not to require that the submitted CPP be issued by the same NRA that issued the original CPP. Central American countries do not follow a standardized policy for this requirement.

As regards the content of the CPP, there is no marked trend on the respective legal basis since, for some countries, the requirements are stated in the national legislation; for others, there is no specific legal provision on the content of the CPP; for Central American countries, the legal basis is provided for in the RTCA and, for a few countries, in the NRA rules. For the two countries in the region not requiring a CPP, but that issue CPPs, the form is determined by the rules of the regulatory authority.

Most countries require that the CPP includes information on the marketing status of the product. There is a slight trend for countries to require a list of all manufacturing sites involved in bulk production, packing or primary packaging, and final release of the product, as well as information on the diluent. Most countries do not require the patient information leaflet, or instruction leaflet (IL), or the summary of product characteristics (SPC) attached to the CPP.

All NRAs surveyed report that they carry out the CPP evaluation and most of them explain that this requirement is stated in their national legislation. In the case of Central American countries, this is provided for in the RTCA.

Countries in the region report having experience with total or partial rejections, summary rejections or requests for additional information due to incomplete CPPs, rejections due to lack of product name or information regarding the marketing status, illegible information, or lack of product's qualitative-quantitative formula.

Most countries in the region require the product to have an active marketing status in the CPP provided for registrations, renewals, and changes/variations submissions. There is a slight trend for the legal basis of the requirement to be stated in the national legislation. Contrary to the regional provision, there is a trend for most rNRAs not to require this information. Most countries do not require specific information and/or requirements related to the marketing status (e.g., marketing time frame).

The vast majority of the NRAs requiring a CPP do not have particular considerations in the evaluation according to the marketing time frame stated in the document.

For the countries requiring a statement of the prior registration status in the country of origin, such status is assessed in the CPP. In turn, for the NRAs requiring prior registration of the drug in the country of origin and also requiring the marketing status be included in the CPP, the trend is to ask for additional information for submissions if the product is not marketed in the country of origin.

This assessment is mostly carried out by the NRAs following the national legislation. Concerning this issue, no clear trend is identified for the countries of Central America.

The countries in the region consider as relevant all the information contained in the sections of the CPP so as to determine the future characteristics of the drug's registration. When the CPP includes information on the GMP of the product's manufacturing site, the trend in the region is to acknowledge the GMP certification.

When considering the consequences on the CPP of the cancelation or suspension of the registration in the issuing country, the practices in the region indicate that the vast majority require the holder to notify such cancelation or suspension to the recipient NRA. For most countries, this requirement is included in the national legislation.

As a consequence of such information, the trend observed is that the registration is not automatically canceled when there is a cancelation of the registration in the CPP-issuing country, but this measure has an impact as it can affect renewals and generate adjustments to the registration. There is no clear regional trend on the impact when there is a suspension of the registration, although it is possible to assert that the registration is not automatically canceled.

Although all countries in the region are CPPs- issuing or receiving countries, regarding the training of the staff, there is lack of consensus since when training was provided, it was an in-house procedure, which does not favor a convergent regulatory approach in the region. However, most countries provide some kind of training and clarify that it is in-house because they have not been provided external training.

Most NRAs in the region do not accept the CPP in electronic format (eCPP) and are not prepared to work with such documents. However, the number already accepting it is not negligible. In Central America, practices vary; the same was found for the rNRAs. Acceptance of the eCPP is included in the national legislation for most of the NRAs that use it. Those who do not accept this format report that the impediment is their national legislation or a legal vacuum. At the same time, most countries accepting the electronic format document require additional requirements, such as apostilled document, notary certification, mandatory printing, or that the issuing authority legalizes the electronic format.

It is clear that this new CPP format is gaining ground, although current regulations do not recognize it yet. However, the study is limited and does not allow complete conclusions to be drawn regarding this practice, as it does not investigate the adoption of automated systems by NRAs, or the possibility of accepting electronic signatures, etc.

It is a common practice for the NRAs in the region, including all Central American countries and all NRAs, to require the legalization of the CPP. The general policy is to require that the embassy or consulate be located in the issuing country or in another country with diplomatic relations with the receiving or issuing country.

The vast majority of the NRAs usually set a term for the acceptance of the CPP beginning on the date of issue.

In general, NRAs only accept CPP requests from the holder of the marketing authorization or its legal representative.

In general, NRAs do not make differences between the requirements for the content of the CPP depending on the type of product (e.g., synthetic drugs, biological drugs).

Finally, the data on the characteristics identified in the CPPs of the issuing NRAs are presented. Most countries report setting deadlines for processing the application, usually from five to twenty business days, but the deadlines can be as long as two months. In nearly all cases, deadlines are set according to the NRA rules. It is not a regional practice for NRAs to issue electronic documents. Neither NRAs tend to issue them. Most CPP-issuing NRAs in the region set a validity period between one and two years for their CPPs.

The CPPs issued by ten countries of the region were evaluated in detail. For this purpose, they were compared with the standard form suggested by the WHO. The vast majority of the documents showed coincidence with the WHO standard form in terms of content of the header, product name and dosage form information, product authorization data, information regarding periodic inspections at the manufacturing site by the certifying authority, and information provided by this authority.

It is observed that, especially for the section product name and dosage form, there is a trend to follow country-specific practices, including information that is not consistent with the WHO standard form. A few countries usually provide details when the information submitted by the applicant does not satisfy the certifying authority in all aspects of the product's manufacture.

For data of administrative nature, the vast majority comply with providing the address, telephone number, name of the authorized person, and date of CPP issue. Few of them include fax numbers, and some others do not provide a specific expiration date.

Future steps

This study is a broad characterization of the practices and requirements in the region of the National Regulatory Authorities of the countries of the Americas regarding the use of the CPP. The information gathered is valuable to evaluate and improve the regulatory systems according to the current demands and allows us to analyze the relevance of the current practices. Although this is not the first study conducted in the region, it has been the most extensive, the result of joint work between the industry and the NRAs, which provides additional value in the approach and in identifying the aspects to be improved.

The data included in the report may be used as a reference to evaluate the requirements applied by the NRAs in the region from a health perspective and, if appropriate, to identify opportunities for updating regulatory systems towards a more timely access to medicines and more unified approaches on such requirements. Therefore, formalizing training on the subject is an evident benefit.

This evaluation and the search for alternatives to eliminate or mitigate the time gap between global and Latin American submissions can positively impact the management activities of the industry and the NRA when reducing their administrative burden. The adequate outline of the CPP requirements following the national regulatory frameworks and the identification of the health value attributed to it by the NRA is expected to provide ideas on how to comply with drug standards in terms of safety, efficacy, and quality without delaying, in some cases, the availability of treatments.

There is an opportunity in the region to discuss the health value of the CPP in the NRAs processes. The data in this mapping can help identify points for improvement and, in that regard, pave the way for the adoption of more unified and efficient regulatory approaches. The time of publication of this report is in line with the discussions at the WHO on the revision of its Scheme, indicating a particularly important and timely circumstance for this consideration.

ANNEX No.1

Survey form

CECMED FIFARMA RED PARF PANDRH

Welcome

English

Dear PANDRH Members:

The execution of PANDRH's project "Assessing the Certificate of Pharmaceutical Product (CPP) requirements for the drug registration processes in the Region of the Americas, towards a more timely access to medicines and more convergent regulatory approaches" began in February 2018. More recently, the project's execution has reached a stage where participation of PANDRH Members is needed. In this phase of the project, an exhaustive mapping of the requirements and practices related to the CPP in our region will be developed. The resulting diagnosis aims at creating the base for a second phase, which has the objective of developing a structured discussion to identify opportunities for improvements in this context.

The information for the mapping is being collected through a survey as a capturing tool, which applies to all PANDRH Members. The effective participation of PANDRH Members and the provision of accurate information is critical so that we can have a true picture of the requirements and practices related to the CPP in the region. We would greatly appreciate your answers to the questionnaire by August 24th, 2018.

You will find below a brief guidance on the questionnaire and use of the survey tool. If you need clarification, please contact Celeste Sánchez (evareg@cecmed.cu), in case of National Regulatory Authorities (NRA), or Jaime Oliveira (jaime.oliveira@bayer.com) in case of industry.

User guidance to complete the survey:

- To start the survey please click in below button "Next".
- Please complete your personal information.
- Start answering the survey.

- Base on your answers is it possible that some questions are excluded, so it is normal if you find that some number questions are not showed.
- To go ahead to the next set of questions you should click on “next page” at the end of each page.
- In case you need to review, copy paste and/or edit any previous answer you should click the button “Previous page” until to arrive to the page you want to edit or review.
- Please **DO NOT USE** the navigation buttons “back or Next” of the navigator (IE/Chrome/Firefox) in case you need to return to a previous page.
- Each time you press the “Next” button of each page the information is saved.
- Any answer could be modified before the survey is finished (that happens when you click on “Done” in last page after final comments).
- After clicking on “Done” the saved information will be sent and the survey will be finished so no more modifications are possible.
- The survey is divided into 10 sections and composed of 55 questions. An additional question is attached to each of them, asking if the specific CPP requirement is established at the NRA’s level or by national legislation. The reference is OPTIONAL.
- Respondents can answer sections one at a time, save the answers by clicking "Next" and return to the survey to answer remaining sections later.

We look forward to your answers to the survey.

With cordial greetings,
CECMED-FIFARMA

Assessing the Certificate of Pharmaceutical Products (CPP) requirements for the drug registration processes in the Region of the Americas, towards a more timely access to medicines and more convergent regulatory approaches

Data from respondent:

Please complete:

Name of the Institution (National Regulatory Authority (NRA) / Associations / Industry) (with acronyms, if applicable)

Name of the respondent

Position of the respondent

Date (DD.MM.AAAA)

Country

E-mail

Phone

If necessary, use the following table to list all the members of the work team that responded to the survey.

Please include Institution / Name / Position / Country for them:

Assessing the Certificate of Pharmaceutical Products (CPP) requirements for the drug registration processes in the Region of the Americas, towards a more timely access to medicines and more convergent regulatory approaches

1 . Submission of applications for new drugs/new pharmaceutical products

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

1.1 Is a CPP required for the submission/registration of a new pharmaceutical product/new registration in the country?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1 . Submission of applications for new drugs/new pharmaceutical products (continuation)

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

1.2 What are the cases requiring CPP for the submissions of applications for new drugs or new pharmaceutical products?

- ◯ All submissions/ applications
- ◯ Specific submissions/applications (please, indicate the specific cases where the CPP is required) Additional observations:

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1.3 Is the CPP required to be issued by a NRA recognized by local legislation as a reference/strict/supervisory authority?

- ◯ Yes
- ◯ No
- ◯ Other (explain)

- If "Yes", please, indicate the NRAs recognized
- If "Other", please explain

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1.4 Is prior registration of a product in the country of origin mandatory?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1.5 Which country is considered the country of origin?

- [ ] Manufacturing site of the active ingredient
- [ ] Manufacturing site of the finished product:
- [ ] Packing or primary packaging site of the finished product
- [ ] Packing or secondary packaging site of the finished product
- [ ] Packing or primary and secondary packaging site of the finished product
- [ ] Quality control testing site of the finished product
- [ ] Exporting country of the finished product:
- [ ] Final release of the finished product:
- [ ] Headquarters of the Marketing authorization holder/registration holder:
- [ ] Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1.6 Is a statement of prior registration status in the country of origin required to submit a new drug/new pharmaceutical product/new registration in the country?

- Yes
- No

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1 . Submission of applications for new drugs/new pharmaceutical products (continuation)

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

1.7 Does the recipient NRA accept CPPs issued by a country where the product is registered/approved but not manufactured?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1.8 Does the recipient NRA accept CPPs issued by a country that granted product registration/approval based on the assessment and the inspection of the Good Manufacturing Practices (GMP) conducted by another NRA (a third party)?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1.9 At what stage/time of the application process is the CPP required?

- ☐ At initial submission of the CPP
- ☐ Any time at the evaluation process
- ☐ Other (please explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1.10 Can the CPP be substituted by another document(s) in the application process?

- ( ) Yes
- ( ) No
- ( ) Other (please, explain)

- If "Yes", please indicate the document that can replace the CPP
- If "Other", please explain

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1 . Submission of applications for new drugs/new pharmaceutical products (continuation)

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

1.11 Are there any conditions for replacing a CPP with a different document?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

- If "Yes", please indicate the conditions
- If "Other", please explain

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1.12 Whenever a CPP is provided, either as a requirement or voluntarily, does the application for drug registration go through a full NRA evaluation?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1.13 Whenever the CPP is provided, as a requirement or voluntarily, is the use of fast track/accelerated/simplified procedures allowed?

OBS.: Consider fast track/accelerated/simplified pathways any procedures with shorter deadlines and/or reduced review steps.

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

- If "Yes" please briefly explain what the fast track/accelerated/simplified consists of.
- If "Other", please explain.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information.

1.14 Whenever a CPP is provided, as a requirement or voluntarily, are abbreviated files accepted?

Comment: Consider as abbreviated files any file with less documentation, information, or data needed.

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

- If "Yes", please explain which documents are waived in the dossier.
- If "Other", please explain.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

1.15 In the case of fast track/accelerated/simplified procedures or abbreviated files, from which NRAs are CPPs accepted?

- ◯ Not applicable
- ◯ Indicate the NRAs from which you accept a CPP to be used in the fast track/ accelerated/simplified pathways or abbreviated dossiers:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

1.16 Does the CPP have to meet specific conditions to assess the drug submission according to the fast track/accelerated/simplified procedures or for an abbreviated file to be accepted?

- ○ Yes
- ○ No
- ○ Not applicable

- If YES, please indicate the conditions.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

2 . Submission of renewal applications

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

2.1 Is a CPP required for the renewal of pharmaceutical product registrations?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

2.2 Are the requirements/conditions applicable to the CPP for registration renewals different from those required for the submission of application for new drugs/new pharmaceutical products?

Please, consider the questions of section 1. (1.3-1.16)

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)
- ◯ N/A (Not applicable))

- If "Yes", please indicate the differences in the CPP requirements.
- If "Other", please explain

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

2.3 If the CPP is required for renewals, is it mandatory that the CPP be issued by the same regulatory authority that issued the CPP for the initial registration?

- ○ Yes
- ○ No
- ○ Other (please, explain)
- ○ N/A (Not applicable))

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

3 . Submission of post-approval changes/variations

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

3.1 Is a CPP required for post-approval change/variation applications of pharmaceutical products?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

3.2 Which post-approval changes/variations require the CPP?

- ◯ All changes/variations
- ◯ Requirement depending on the case
- ◯ Specific changes/variations
- ◯ N/A (Not applicable)

- If specific changes/variations, please indicate which changes/variations require the CPP

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

3.3 Are the requirements/conditions applicable to the CPP for post-approval changes/variations different from those required for the submission of applications for new drug/new pharmaceutical product?

Please, consider questions of section 1. (1.3-1.16)

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)
- ◯ N/A (Not applicable))

- If "Yes", please indicate the differences in the CPP requirements.
- If "Other", please explain

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

3.4 In the case of post-approval changes/variations requiring a CPP, is it mandatory that the CPP be issued by the same regulatory authority that issued the CPP for the initial registration?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)
- ◯ N/A (Not applicable))

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

4 . CPP form/document content

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

4.1 Load/provide a copy of the standard CPP form/document/template required by the local regulation, and attach the file if any.

Only PDF, DOC, DOCX, PNG, JPG, JPEG, GIF files are compatible.

Choose File No file chosen

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

4.2 Is the CPP required to include information on the marketing status of the product?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

4.3 Is the CPP required to include a list of all manufacturing sites involved in bulk production, packing or primary packaging, and final release?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

☐ National legislation

☐ NRA's rules

☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

4.4 Is the patient information leaflet/instruction leaflet (IL) or the summaries of product characteristics (SPC) required to be attached to the CPP?

○ Yes

○ No

○ Other (please, explain)

- If "Yes", indicate in which cases.
- If "Other", please explain.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

☐ National legislation

☐ NRA's rules

☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

4.5 Does the information on the diluent included in the submission, if applicable, have to be stated in the CPP?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

- If "Yes", indicate in which cases.
- If "Other", please explain.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

5 . Evaluation of the CPP by the NRA

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

5.1 If the CPP is submitted during the regulatory processes (registration, renewal and/or post-approval changes), is it assessed by the NRA?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

- If "Yes", please indicate which aspects of the CPP are evaluated.
- If "Other", please explain.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

5.2 If the CPP is not assessed, the reason for requiring the CPP is that it constitutes supporting information for the process and supports the drug approval decision?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

5.3 Does the NRA have experience with rejected applications because the CPP does not contain all the necessary information?

- ◯ Yes
- ◯ No

If "Yes", please explain which aspects were considered.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

5.4 Are there particular considerations in the evaluation according to the marketing time frame stated in the CPP?

- Yes
- No

If "Yes", please explain which aspects were considered.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

5.5 What information in the CPP sections is relevant to determine the future characteristics of the drug's registration by the NRA of the receiving country?

- ◯ None
- ◯ All
- ◯ Other (please, explain)

Additional observations

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

5.6 When the CPP includes information on the Good Manufacturing Practice (GMP) of the product's manufacturing site, does the NRA acknowledge this status?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

6 . Assessment of the prior registration in the country of origin

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

(Applicable only in the cases when a registration is required in the country of origin) according to your answer in 1.6

6.1 Is the statement of prior registration status assessed in the country of origin?

- Yes
- No

If "Yes", please explain which aspects were considered.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- National legislation
- NRA's rules
- Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

6.2 If the product is registered/approved in the country of origin, but not marketed in that country, is additional information required for submissions of applications of new drugs/new pharmaceutical products?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

- If "Yes", please indicate the additional information required.
- If "Other", please explain.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

6.3 If the product is not registered/approved in the country of origin and not marketed in that country, is additional information required for the submission of applications for new drugs/new pharmaceutical products?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

- If "Yes", please indicate the additional information required.
- If "Other", please explain.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

7 . Effects of the registration/marketing authorization cancelation or suspension in the CPP-issuing country

Effects of marketing authorization/registration cancellation or suspension in CPP's issuer-country

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

7.1 Indicate the obligations of the product's registration holder before the NRA when its registration/marketing authorization is canceled in the CPP-issuing country.

- ◯ None
- ◯ Notification to the NRA is required
- ◯ Notification is required in specific situations(please, explain)
- ◯ Other (please, explain)

- If required communication in specific situations, please explain.
- If Other, please explain

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

7.2 Indicate the impact of the registration/marketing authorization cancelation in the CPP-issuing country on the registration/marketing authorization in the CPP-receiving country.

- ○ It is not canceled
- ○ It is canceled
- ○ It is not canceled, but a new CPP must be submitted
- ○ It is not canceled, but the renewal of the registration may be affected
- ○ Other (please, explain)

Observaciones adicionales:

Is this specific requirement implemented following national legislation or NRA requirements ?

☐ National legislation

☐ NRA's rules

☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

7.3 Indicate the obligations of the product's registration holder before the NRA of the CPP-receiving country when the product's registration/marketing authorization is suspended in the CPP-issuing country.

◯ None

◯ Notification to the NRA is required

◯ Notification is required in specific situations (please, explain)

◯ Other (please, explain)

- If required communication in specific situations (please, explain)
- If "Other", please explain.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

7.4 Please indicate the impact of the suspension of the registration/marketing authorization in the CPP-issuing country on the registration/marketing authorization in the CPP-receiving country.

- ○ It is not canceled
- ○ It is canceled
- ○ It is not cancelled, but the renewal of the registration may be affected
- ○ It is not canceled, but a new CPP must be submitted
- ○ Other (explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

8 . CPP and marketing status of the product

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

8.1 In the case of submissions of applications for new drugs/new pharmaceutical products, is the product required to have an active marketing status stated in the CPP provided for the registration process?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

8.2 In the case of renewals, is the product required to have an active marketing status stated in the CPP provided for the registration process?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

8.3 In the case of post-approval changes/variations, is the product required to have an active marketing status stated in the CPP provided for the registration process?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

☐ National legislation

☐ NRA's rules

☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

8.4 Are there specific requirements related to the marketing status (e.g., marketing time frame)?

◯ Yes

◯ No

If "Yes", please explain the specific requirements.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

☐ National legislation

☐ NRA's rules

☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

9 . Other relevant information

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

9.1 Is the NRA staff trained in the WHO certification scheme on the quality of internationally marketed pharmaceutical products?

- ◯ Yes
- ◯ No
- ◯ Other (please, explain)

- If "Yes", please inform when the training was applied.
- If "Other", please explain.

Additional observations:

9.2 Does the NRA accept CPPs in electronic format?

- ◯ Yes
- ◯ No

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

9.3 If the CPP is accepted in electronic format, are there additional requirements for this format?

- ○ Yes
- ○ No
- ○ N/A (Not applicable)

If "Yes", please explain the specific requirements..

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

9.4 Is it necessary for the CPP to be legalized or apostilled at the embassy or consulate of the receiving country?

- ◯ Yes
- ◯ No
- ◯ Other (explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

9.5 If CPP legalization is required, is the embassy/consulate required to be located in the issuing country or another country with diplomatic relations with the receiving or issuing country?

- ◯ Yes
- ◯ No
- ◯ Other (explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

☐ National legislation

☐ NRA's rules

☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

9.6 Is there a validity period for the acceptance of the CPP?

○ Yes

○ No

If YES, please inform the term of validity for a CPP

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

☐ National legislation

☐ NRA's rules

☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

9.7 May the CPP be requested by a company that is neither the holder of the marketing authorization of the product nor its legal representative?

- ◯ Yes
- ◯ No

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

9.8 If Yes, does the NRA request authorization to issue a CPP requested by a third party?

- ◯ From the marketing authorization holder
- ◯ From its legal representative
- ◯ From both
- ◯ From none
- ◯ Other (explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

9.9 Are there any differences in the CPP content requirements depending on the type of product (e.g., chemical or biological products)?

- Yes
- No
- Other (explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

10 . National Regulatory Authorities (NRAs) that issue CPP (only for NRAs issuing CPPs)

National Regulatory Authorities (NRA) that issue CPP (applicable only to NRA that issue CPP)

Please include for each response, in the "Additional Observations" field, any additional information that you consider appropriate to complement / explain your response, when your answer is "Other" or when you want to include legal / technical references for this requirement (National Legislation, NRA rules or other), including how to obtain the information.

10.1 Are there specific deadlines for issuing the CPP after the marketing authorization holder submits an application?

- ◯ Yes
- ◯ No

If YES, please inform timeline.

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- ☐ National legislation
- ☐ NRA's rules
- ☐ Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

10.2 Load/provide a copy of the standard CPP form/document/template required by the local regulation, and attach the file, if any.

Only PDF, DOC, DOCX, PNG, JPG, JPEG, GIF files are compatible.

Choose File No file chosen

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

10.3 Does the NRA accept CPPs in electronic format?

- ( ) Yes
- ( ) No

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

10.4 Does the CPP issued have an expiration date?

- ( ) Yes
- ( ) No
- ( ) Other (explain)

Additional observations:

Is this specific requirement implemented following national legislation or NRA requirements ?

- [ ] National legislation
- [ ] NRA's rules
- [ ] Other (please, explain below)

OPTIONAL: Please, indicate the legal/technical references for this specific requirement, including the way to retrieve information:

Assessing the Certificate of Pharmaceutical Products (CPP) requirements for the drug registration processes in the Region of the Americas, towards a more timely access to medicines and more convergent regulatory approaches

Additional comments

Please express freely, if you will, any comment related to any aspect that was not covered by the survey/questionnaire

○ I have no additional comments. Thank you.

○ I have additional comments:

If you wish, you can submit any further comments in a separate document. Please attach it below:

Choose File   No file chosen

Any answer could be modified before the survey is finished:

- In case you need to review, copy paste and/or edit any previous answer you should click the button "Previous page" until to arrive to the page you want to edit or review.
- Please DO NOT USE the navigation buttons "back or Next" of the navigator (IE/Chrome/Firefox) in case you need to return to a previous page.

The survey ends when you click on "Done" in last page after final comments.

After clicking on "Done" the saved information will be sent and the survey will be finished so no more modifications are possible.

ANNEX No. 2

Legal and technical references for the CPP in the countries of the Americas***

COUNTRY	LEGAL/TECHNICAL REFERENCES
Argentina	• Decree of the National Executive Power No. 150/1992 (text in force 1993), and complementary regulations, intended as an Abbreviated Registration System; issued as a stimulus to competition and access. Decree name: “Normas para el registro, elaboración, fraccionamiento, prescripción, expendio, comercialización, exportación e importación de medicamentos. Ámbito de aplicación. Disposiciones generales” [Rules for the registration, elaboration, fractioning, prescription, sale, marketing, export and import of medicines. Scope of application. General provisions]. • Law on medicines No. 16,463. • Decrees of the National Executive Power No. 150/1992 and No. 1490/1992, and ANMAT Resolutions No. 1128/1995, and No. 5755/1996. • Legislation for biological products: ANMAT Resolutions No. 7075/2011, No. 7729/2011 and No. 3397/2012.
Barbados	• Rule 41 of Financial (Drug Service) Rules, 1980.
Belize	• Food and Drugs (Registration, Licensing, and Inspection) Regulations. Statutory Instrument No. 54 of 2017.
Bolivia	• Supreme Decree 25235, approved by RM 050 of October 2, 2000. • Manual for Health Registration, approved by RM 909 of December 7, 2005. • Law on Medicines 1737, approved by RM 050 of October 2, 2000.
Brazil	• Decree No. 8660/2016. • Federal Law 6360/1976. • Technical note No. 31/2015-SUMED/ANVISA. • RDC No. 2/2012. • RDC No. 20/2013. • RDC No. 200/2017. • RDC No. 204/2005. • RDC No. 39/2013. • RDC No. 55/2010 - Additional references: ANVISA´s check-list. • RDC No. 73/2016.

*** These legal references correspond to those reported by respondents during the survey period (2018).

COUNTRY	LEGAL/TECHNICAL REFERENCES
Canada	• Guidance document on the application for a Certificate of a Pharmaceutical Product and Good Manufacturing Practice Certificate (GUI-0024). • Food and Drugs Act (R.S.C., 1985, c. F-27). Current to August 11, 2020. Last amended on July 1, 2020.
Chile	• National Legislation.
Colombia	• Decree 677 of 1995 as amended by Decree 426 of 2009, article 31, paragraph 2, in accordance with 251 of the General Procedural Code (Law 1564 of 2012). • Decree 1782 of 2014. Requisitos y procedimiento para las Evaluaciones Farmacológica y Farmacéutica de los medicamentos biológicos en el trámite del registro sanitario [Requirements and procedure for Pharmacological and Pharmaceutical Evaluations of biological medicines in the health registration procedures]. • Decree 843 of 2016, simplifying the procedure for the renewal and variation of health registrations for chemically synthesized medicines and medicinal gases and providing the actions to be taken to ensure the availability and control of medicines in the country. • Decree 386 of 2018, stating the procedure for obtaining the registration of antivenoms, simplifying the procedure for its renewal or variation, and providing the actions to be taken to ensure the availability. • Decree 549 of 2001 as amended by article 1 of Decree 162 of 2004. Decree 549, stating the procedure for obtaining the Certificate of Good Manufacturing Practices by the laboratories manufacturing medicines that are imported or produced in the country. • Resolution 3269 of 2016 from the Ministry of Foreign Affairs. Resolution 3269, adopting the procedure for apostille and/or legalization of documents and superseding Resolution 7144 of October 24, 2014 NOTE OF VALIDITY: Resolution superseded by article 23 of Resolution 10547 of 2018. • Code of Administrative Procedure and the Contentious Administrative. Law 1437 of 2011.
Costa Rica	• Public Resolution No. 333-2013 (COMIECO-LXVI) of 12/12/2013 and annexes: RTCA Reg. 11.03.59:11 Pharmaceutical Products, Medicines for human use. Registration requirements, annex 1. Procedure for the mutual acknowledgment of registrations of medicines, annex 2. • Regulations for the operation and use of the “Regístrelo” website, No. 37988-S, article 10. • Executive Decree No. 39433-S. Acknowledgment of the Evaluation and Approval of Final Reports of Clinical and Non-Clinical Studies by the Regulatory Authorities of reference as evidence for the Registration of Medicines. • Law No. 46, Organic Law of the Consular Service. • General Law of Public Administration No. 6227. • Civil Code of Costa Rica. Title VIII: Mandate. Chapter I: General provisions. Articles 1251 and subsequent.

COUNTRY	LEGAL/TECHNICAL REFERENCES
Cuba	**Resolutions of the Ministry of Public Health with national legal character:** • Ministerial Resolution No. 321/2009 “Reglamento para el Registro Sanitario de Medicamentos de Uso Humano” [Regulations for the Registration of Medicines for Human Use]. • Ministerial Resolution No. 170/2000 “Política Farmacéutica Nacional” [National Pharmaceutical Policy], V. WHO certification scheme on the quality of pharmaceutical products moving in international commerce. **NRA:** • CECMED Resolution 64/2012 (Regulation No. 61-2012) “Requisitos para el Registro Sanitario de Medicamentos de Uso Humano” [Requirements for the Registration of Medicines for Human Use]. • CECMED Resolution 221/2015 (Regulation M 83-15) “Requisitos para el Registro Sanitario de Productos Biológicos de Uso Humano” [Requirements for the Registration of Biological Products for Human Use]. • CECMED Resolution 59/2007 (Regulation No. 46-2007) “Requisitos para el Registro Sanitario Temporal de Medicamentos de Uso Humano” [Requirements for the Temporary Registration of Medicines for Human Use]. • CECMED Resolution 78/2011 (Regulation No. 55-2011) “Requisitos para el Registro Sanitario Condicional de Medicamentos de Uso Humano” [Requirements for the Conditional Registration of Medicines for Human Use]. • CECMED Resolution 72/2015. Regulations for the Application of the Official Price List of the Scientific and Technical Services of the CECMED, Annex No. 3. Terms for the execution of some services (business days). **Standardized Procedures** 1. PNO 01.004 Methodology for the evaluation of the administrative and chemical-pharmaceutical information of applications for procedures on Medicines. 2. PNO 01.011 Methodology for elaborating the certificates and letter of approval of a variation of the Registration of Drugs and Biological Products. 3. PNO 01.037 Methodology for evaluating administrative, chemical-pharmaceutical, and biological information of applications for the registration of biological products. 4. PNO 01.040 Methodology for the clinical evaluation of applications for the registration of biological products. 5. PNO 01.042 Methodology for non-clinical evaluation of drug registration applications. 6. PNO 01.043 Methodology for the clinical evaluation of drug registration applications. 7. PNO 01.052 Methodology for non-clinical evaluation of applications for registration of biological products.
Dominican Republic	• Decree No. 246-06. Regulation on Medicines. • Resolution No. 000021, August 24, 2018.

COUNTRY	LEGAL/TECHNICAL REFERENCES
Ecuador	• Substitute regulation of the registration of medicines in general (Agreement No. 00000586). Supplement to the Official Registration No. 335, December 7, 2010. Regulation: In force. Last update: Official Registration 89, 27-XI-2019. • Ministerial Agreement 3344, Regulation for the registration, control, and surveillance of biological medicines for human use and consumption (Official Registration 21, June 24, 2013). • The Hague Convention. • Resolution 12, Technical Sanitary Regulations for products of human use and consumption exclusively for export (Official Registration 1010, May 23, 2017). • External Instructions: Procedure for obtaining the certificate of pharmaceutical product and health certificate for export.
El Salvador	• General Regulations of the Law on Medicines. • RTCA, Annex 1 (Regulatory) of 11.03.59:11. • Regulations for the Acknowledgement of Foreign Registrations. • Standardized Procedures, NRA rules: **1.** C02-RS-01-URV POE01 Procedure for new registration of innovative drugs, biologicals, biotechnological products, and vaccines. **2.** C02-RS-01-URV POE02 Procedure for new registration of generic drugs and nutritional supplements. **3.** 02-RS-01-URV POE03 Procedure for new registration of homeopathic medicines and natural products.
Guatemala	• Government Agreement 712-99: Regulations for the sanitary control of medicines and related products. • Central American Technical Regulations RTCA 11.03.59:11: pharmaceutical products, medicines for human use. • Government Agreement 104-2018: Amendments to the Governmental Agreement No. 712-99, Regulation for the sanitary control of medicines and related products. • Standard 077-2018: Acknowledgement of the registration of medicines approved by Regulatory Agencies Level IV according to the Pan American Health Organization (PAHO) as a basis for processing the official approval of registration in Guatemala.
Haiti	• DPM/MT Standards and Procedures, 2008 edition.
Honduras	• Regional legislation RTCA 11.03.59:11. • Regulations for the sanitary control of products, services, and health related facilities. • Decree PCM-032-2017, Creation of the Sanitary Regulation Agency, Competences.
Jamaica	• The Food & Drugs Act, 1964. • The Food & Drugs Regulations, 1975.

COUNTRY	LEGAL/TECHNICAL REFERENCES
México	• Reglamento de Insumos para la Salud [Regulation of Inputs for the Health] (RIS). • Technical evaluation procedures carried out by COFEPRIS, as per agreement published in the Official Gazette of the Federation on October 5, 2012 (DOF: October 5, 2012). AGREEMENT recognizing as equivalent the requirements established in articles 167 and 170 of the Regulation of Inputs for the Health and the technical evaluation procedures carried out by the Federal Commission for Protection against Sanitary Risks for the granting of the registrations of inputs for the health referred to in articles 2, section XV, paragraph b; and 166, section II, of the Regulation of Inputs for the Health, to the requirements requested, tests and evaluation procedures carried out by the Ministry of Health of Canada to approve the sale, distribution and use of such inputs for the health in its country. • General Law on Health. • Federal Law of Administrative Procedure - August 4, 1994. Last update published in the DOF May 18, 2018. • NOM-073-SSA1-2015, Stability of drugs and medicines, as well as herbal remedies. • Official circular CAS/1/OR/20/2016 dated July 18, 2016 “Lineamientos que establecen los requisitos que se deben cumplir para la acreditación de los certificados de Buenas Prácticas de Fabricación para la solicitud de Modificaciones, Prórrogas y Registros Sanitarios de Medicamentos” [Guidelines for the requirements to be met for the accreditation of GMP certificates for applications of variation, extension and registration of medicines].
Nicaragua	• Central American Technical Regulations (RTCA) 11.03.59:11: pharmaceutical products, medicines for human use.
Panama	• Law 1 of January 10, 2001. “Sobre Medicamentos y otros Productos para la Salud Humana” [About drugs and other products for human health]. (Official Gazette 24218 of January 12, 2001). • RTCA. • Executive Decree No. 303 of the Ministry of Health. December 11, 2003. Regulating the registration of Orphan Drugs. • Executive Decree No. 58 of the Ministry of Health. March 28, 2017. Stating the abbreviated procedure for the registration of medicines, their renewal, and variations. • Executive Decree No. 331 of the Ministry of Health. November 8, 2017. Modifying and adding articles to the Executive Decree No. 178 of July 12, 2001, regarding notifications and variations to the registration. • Executive Decree No. 320 of the Ministry of Health. July 7, 2018. Modifying Executive Decree No. 58 of March 28, 2017. Stating the abbreviated procedure for the registration of medicines, their renewal, and variations.
Paraguay	• National Legislation. • MERCOSUR requirements.

COUNTRY	LEGAL/TECHNICAL REFERENCES
Peru	• Law No. 29459 - Law on Pharmaceutical Products, Medical Devices and Health Products. • Legislative Decree No. 1272 amending Law No. 27444, Law on General Administrative Procedure, and superseding Law No. 29060, Law on Administrative Silence. • Supreme Decree No. 011- 2016/SA. Modifying article 103 of the regulation for the registration, control, and sanitary surveillance of pharmaceutical products, medical devices, and health products, and approving the regulation on the submission and the content of the documents required in the registration and renewal of registration of biological products: Biotechnological products. • Supreme Decree No. 016-2011/SA, Regulation for the registration, control, and sanitary surveillance of pharmaceutical products, medical devices, and health products. • Supreme Decree No. 001-2012/SA. Modifying articles of the Regulation for the registration, control, and sanitary surveillance of pharmaceutical products, medical devices, and health products. • Supreme Decree No. 013-2016/SA. Regulation governing the submission and the content of the documents required in the registration and renewal of registrations of biological products that choose the similarity procedure. (Technical Criteria for the Evaluation of Pharmaceutical Specialties Dossier). • Supreme Decree No. 016-2017/SA. Modifying the regulation for the registration, control, and sanitary surveillance of pharmaceutical products, medical devices, and health products. • Supreme Decree No. 016-2018/SA. Regulation governing the issuance of the lot release certificate of biological products: vaccines or human plasma derivatives. • Directorial Resolution No. 169-2014-DIGEMID-DG-MINSA. Approving the list of competent authorities for the issuance of the Certificate of Pharmaceutical Product or Certificate of Free Sale of Products or Devices. • Directorial Resolution No. 102-2017-DIGEMID-DG-MINSA. List of documents considered equivalent to the Certificate of Good Manufacturing Practices.
United States	Request for Certificate of Pharmaceutical Product to CDER (Center For Drug Evaluation and Research): • CDER eCATS: Electronic CPP Request. • FDA form 3613F: Form Approved: OMB N.° 0910 – 0498; Expiration Date: Current to August 30, 2021.
Suriname	• NRA rules. • National Legislation.
Trinidad & Tobago	• Food and Drugs Act, Chapter 30.01.
Uruguay	• Decree 324/999. Medicines and related products for human use. • Decree 38/015. Approval of the document for the registration of biotechnology drug. • Decree 521/984. Regulation of the Law 15,433 related to the regulation of medicines.
Venezuela	• Standards of the Pharmaceutical Product Review Board.

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PANDRH
Pan American Network for Drug Regulatory Harmonization

CECMED
Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos

FIFARMA