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Opportunities for improving access to vaccines in emerging countries through efficient and aligned registration procedures: An industry perspective ☆

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ABSTRACT

Vaccines play an essential role in preventing infectious diseases. Their registration in importing countries is often cumbersome and unpredictably lengthy, leading to delays in vaccine access for populations that need them most. This report builds on a previous publication identifying challenges for registration of vaccines in emerging countries. As a matter of social responsibility, it was judged necessary to address the challenges and offer a set of solutions for open dialogue. Based on regular exchange of information and experiences, a group of regulatory experts from the vaccine industry developed three sets of proposals for consideration by vaccine stakeholders, with a view to improving the situation, by fostering regulatory convergence, with viable options for streamlining registration procedures through reliance on other experienced regulators or international agencies. Further, it offers options for alignment of structure and contents of Common Technical Document modules and presents a harmonized template application form that could potentially be used by all countries.

1. Introduction

The vaccine registration landscape at the global level is complex. Requirements and procedures applied in different countries are diverse and sometimes duplicative. Vaccine stakeholders, including regulators, regulatory networks and economic blocks such as the Eastern African Community, the Economic Community of West African States, the Arab Maghreb Union, Mercosur in Latin America, the European Union and the North American Free Trade Agreement have made numerous attempts to align requirements and streamline procedures. Despite these efforts, there is still a high level of divergence in regulatory procedures globally. The divergence relates mostly to the way in which the information is organized in product dossiers such as differences in numbering, headings and subheadings. In addition some administrative documentation required, e.g. translation and legalisation requirements, and different procedures in different countries contribute to divergences that have been previously quantitatively evaluated [1].

These diverse information processing structures impact access to vaccines for people in different parts of the world, due to increased preparatory administration of dossiers related to identical products distributed in different countries, thereby lengthening registration timelines [2]. Notably, the lack of alignment between regulatory dossiers reduces opportunities for exchange of information among regulatory agencies. A recently published article by Ahonkhai et al. [2] reveals a four to seven-year timeline for vaccine registration from the first regulatory submission in country of origin to final approval in Sub-Saharan Africa, for different reasons. They suggested, among other solutions, to harmonize regulatory standards and requirements.

Further, these regulatory challenges impact the direct procurement of vaccines by governments as well as vaccines that are prequalified by the World Health Organization (WHO) and supplied through United Nations (UN) procurement agencies (e.g. United Nations International Children's Fund (UNICEF) [3].

The Developing Countries Vaccine Manufacturers Network (DCVMN) [4] and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) [5] jointly convened a

☆ IMPORTANT NOTE: This report summarizes the joint proposals drafted by the DCVMN-IFPMA Regulatory Expert Working Group and reflects the views of an international group of experts as presented on 10-11 May 2018, and discussed in a given time and context, and does not necessarily represent the decisions or the stated policy of any institution or corporation.

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working group of regulatory experts from industry to identify and, wherever possible, quantify the challenges impacting vaccine registration in importing countries with the goal of making vaccines accessible to populations within reasonable timelines. The results of this analysis are described in a previous publication [1]. This report outlines three sets of proposals to address some of the challenges with the aim of increasing regulatory convergence with manufacturers input, as suggested by Ahonkhai [2]. Proposal A presents options to align registration procedures and requirements at three different levels within registration procedures: i) greater utilization of the WHO collaborative registration procedure (CRP); ii) increased reliance on other regulatory authorities for sample testing and site inspections; iii) foster scientific advice meetings between regulators and manufacturers prior to submission. Proposal B suggests approaches to improve the alignment of dossier structure and contents, reinforcing international standards, such as ICH, as suggested by Ahonkhai [2]. Proposal C offers suggestions for a common template for application forms. These three proposals can be implemented separately or together.

Enhancing regulatory convergence would ultimately facilitate the submission of registration dossiers, the evaluation of vaccines by regulators responsible for applications and, most importantly, provide populations with more timely access to vaccines, while saving resources for the National Regulatory Authorities (NRAs) and other stakeholders.

2. Methodology

DCVMN and IFPMA established a working group of vaccine industry regulatory experts aimed at sharing with stakeholders such as WHO, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) [6], and regulatory networks worldwide, concerns about the complexity and lack of predictability of registration procedures in countries, and to propose options for improvement based on their practical registration experience.

Eighteen professionals from vaccine industry and industry associations met in Geneva in January 2018, to share experiences and design the proposals to improve the registration challenges previously identified [1]. The group was divided into four subgroups of 3–5 professionals each, to elaborate on the specific proposals for alignment of (a) Module 1, (b) alignment of Modules 2–5 [7], (c) application form template and (d) procedures, after having conducted a comparative analysis across countries. The DCVMN secretariat compiled the proposals with the support of an expert consultant, who prepared the first draft of this report. The draft was circulated to the working group members for further comments and clarifications and discussed in two teleconferences. The results of this effort (proposals A-C) are described herein.

3. Proposal A – align registration procedures and requirements across countries and regions

3.1. Apply procedures to improve vaccine registration associated with procurement mechanisms

Countries can directly procure vaccines required by their national immunization programs (NIPs), and those for the private market, through national or international tender without the intervention of external agencies. They can also opt to procure vaccines through centralized procurement mechanisms such as those offered by UN procuring agencies, or through a combination of these two mechanisms. Regardless of which supply mechanism is used, vaccines must first be registered in the manufacturing country and eventually in the importing country, and vaccines supplied through UN procuring agencies must be prequalified by WHO.

WHO evaluation ensures the vaccines meet the needs of the NIPs in target countries including programmatic suitability, suitability for co-administration with other vaccines and relevance of available clinical data to the target population [8]. Under such circumstances, it is expected that countries importing WHO prequalified vaccines could leverage the two prior evaluations and facilitate their registration to expedite access to the vaccines.

WHO advocates the use of CRP between WHO and the importing country's NRA for prequalified vaccines [9]. This procedure is based on a report-sharing mechanism coordinated by WHO in which the evaluation reports, test results from WHO contracted laboratories and reports of site inspections conducted by WHO are shared with interested NRAs. Collaboration is established through a signed agreement between the importing country's NRA and the WHO prequalification team, leading to a facilitated and faster local registration procedure for the vaccine. A guidance document on best practices for implementation of the CRP is available for comment on the WHO website [10]. Although the collaborative procedure has so far been quite successful for drugs, implementation of the procedure for vaccine registration remains low.

The working group suggests greater utilization of the CRP and increased reliance on WHO prequalification to streamline the registration procedures in countries that primarily access vaccines through UN agencies [1].

3.2. Improve registration procedures by implementing the principles of reliance

New technologies used in vaccine development increase the complexity of manufacturing and control thereby increasing the level of expertise required to adequately evaluate and regulate these sophisticated products. Testing methods for such products are also a challenge; therefore, in the context of a license application, many highly developed NRAs are relying on testing data generated by other regulators and on outcomes of site inspections conducted by other agencies. Reliance is one of the principles of good regulatory practices [11]; however it is perhaps underused in many importing countries evaluating vaccines for introduction in their markets. Reliance has significant advantages for vaccine recipients and regulators: reduced costs, avoiding duplication of efforts, freeing resources for other important activities and faster access to healthcare. Examples of reliance include the Mutual Recognition Agreement between the European Medicines Agency (EMA) and the United States (U.S.) [12], implemented since June 2018, and the reinforcement of collaboration between the EU and Japan since July 2018 [13].

A successful collaboration mechanism was established by the EMA through implementation of Article 58 of Regulation (EC) No 726/2004. It establishes a mechanism, in cooperation with WHO, whereby the EMA may give a scientific opinion, similar to the evaluation of certain medicinal products for human use, intended exclusively for markets outside the EU [14], providing support for licensure of vaccines made in the EU, when the vaccine is not used there.

Other means of facilitating the registration procedure can be considered for vaccines that are not WHO prequalified, such as consulting with NRAs that have previously registered the same vaccine from the same manufacturer, relying on approval by stringent regulatory authorities, bilateral or regional arrangements for information sharing, including sharing test results and inspection reports. The EMA Scientific Opinion mechanism can also be applied for vaccines that are not intended to be WHO prequalified [14]. A good review or desk audit of documentation can eliminate the

need for testing through review of the testing methods, their validation and accuracy of the results obtained by the manufacturer. In addition, results of tests performed independently of the manufacturer, such as those conducted by the national control laboratory (NCL) in the manufacturing country, can be obtained from the applicant upon request. Furthermore, WHO recently established the National Control Laboratory Network for Biologicals whose main objective is to share quality information to facilitate access to vaccines through the recognition of the responsible NRA's lot release by recipient countries [15]. NCLs from countries producing prequalified vaccines and NCLs contracted by WHO to perform testing for the vaccine prequalification program are eligible to become full members of WHO-National Control Laboratory Network for Biologicals (WHO-NNB), and countries importing vaccines are eligible to become associate members. Both full and associate members have access to the network's information sharing platform and can also directly contact the focal points of other member country NCLs to obtain detailed information on specific products, if needed.

Samples are unduly requested if the registration procedures in a country do not require vaccine local testing. International transfer of biological samples requires substantial documentation preparation, administrative procedures and approvals by customs officers, in addition to the safety and cold chain provisions for transportation. Vaccine samples can also be visually inspected and/or tested after registration, when vaccine shipments are received.

Similarly, repetitive inspections of the manufacturing facility by the importing country NRA may be waived. Information about the good manufacturing practice (GMP) status of the site can be obtained remotely through the mechanisms described below without the need for additional inspections.

- The manufacturer can provide the GMP certificate issued by the manufacturing country's NRA, with recent reports from inspections carried out by the country's NRA, or other reliable NRA.
- The manufacturer can provide the certificate of pharmaceutical product (CPP) issued by the manufacturing country's NRA [16]. This document contains a GMP compliance statement and can be used in lieu of the GMP certificate.
- In the case of WHO prequalified vaccines, the public inspection reports (WHO PIR) are available on the WHO website [17], and if the CRP is being adopted, additional information would become available.
- Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) member countries recognize each other's inspections. An inspection can be avoided if the evaluating NRA is informed that the company has been inspected by a PIC/S country NRA [18].

PIC/S has published a document on GMP inspection reliance on how to remotely conduct GMP assessments of overseas facilities in instances where GMP compliance can be confirmed by another regulatory authority. The document provides criteria identifying such instances and gives high-level guidance on the requirements [19]. Provision of the site master file is a key element of the reliance assessment procedure.

Some countries are adopting similar initiatives by recognizing GMP inspections conducted by other NRAs. The cooperation between ANVISA (Brazilian Regulatory Authority) and INVIMA (Colombian Regulatory Authority) is a recent example. Both agencies are certified by PAHO as reference NRAs in the region of the Americas [20]. This high level of recognition based on assessments conducted by PAHO is expected to lead to mutual recognition agreements. ANVISA recently certified two Colombian medicines manufacturers without requiring a site inspection [21].

In summary, increased use of reliance approaches may streamline registration procedures and save time and resources for the NRAs involved.

Reliance approaches for WHO prequalified vaccines include:

- granting a marketing authorization based on reliance on WHO prequalification without any further review of the product;
- allowing supply of the vaccine in the country based on the WHO prequalification until the official registration procedure is completed, within a predefined reasonable timeframe, to avoid delays in supply;
- implementing the CRP advocated by WHO as the basis for decision-making about granting the marketing authorization (MA); and
- using the Committee for Medicinal Products for Human Use (CHMP) Scientific Opinion mechanism, applicable for products manufactured in the EU.

Reliance approaches for vaccines that are not WHO prequalified include:

- establishing bilateral or regional agreements to rely on the assessment performed by the NRA of the manufacturing country, or a reference NRA that has already registered the vaccine for use in their country; or
- conducting an independent review of the dossier and accepting test results, available from the manufacturer, that have been conducted independently (e.g. NCL of country of origin, WHO-NNB or other) and avoiding duplication of site inspections.

Regardless of which reliance mechanism NRAs choose, care should be taken to ensure that access to the vaccine is not unnecessarily delayed.

3.3. Other considerations to improve registration procedures

3.3.1. Scientific advice meetings with regulatory authorities

Good communication between regulators and sponsors has been associated with increased rates of registration and market access [22]. Compliance with recommendations appears to be a predictor of a positive outcome [22]. Such advice would ensure clinical development is aligned upfront with regulatory needs, decreases unnecessary rework and generally builds on knowledge gained from previous studies, products and disease areas. Several regulators, including ANVISA (Brazilian regulatory authority), CDSCO (Indian regulatory authority), EMA (European Medicines Agency), TGA (Australian regulatory authority) and U.S. FDA (U.S. regulatory authority) currently have a procedure in place to have either scientific advice or ad-hoc meetings with manufacturers [23–27]. We would encourage other regulators to explore the possibility of implementing such a procedure taking into consideration the benefits and challenges listed in Table 1. It is recognized that this might not be feasible in all countries due to gaps in capacity and capabilities. In addition, care should be taken to ensure that the scientific advice/ pre-meeting procedural advice can be achieved in a timely fashion. Timelines should be clear to allow applicants to consider the advice. Still, advice should not be binding.

3.3.2. Careful consideration of the need for clinical trials

Clinical data are the basis for market authorization applications; however sponsors often receive requests for additional clinical data, with no clear rationale. These often represent a duplication of studies already conducted elsewhere, frequently in several countries and regions [28]. Acknowledging that there may be

Table 1
Top three benefits and challenges of implementing scientific advice meetings between regulators and manufacturers prior to submission of marketing authorization application, as prioritized by the working group.

Benefits	Challenges
• Reduced timelines and discussions during the application review. • Faster access for patients. • Clarity and visibility on mutual expectations for all stakeholders.	• Requires stakeholders to implement and adhere to a formal procedure. • Requires dedicated resources and capabilities. • Establishing reasonable timelines to avoid delays in the application procedure and delays in access for patients.

relevant reasons to request additional data (e.g. country-specific vaccination schedules, ethnic factors [29], underlying diseases and the general health of a given population), regulators should carefully consider the need for additional clinical studies for registration. Existing post-marketing surveillance systems are likely to compile such information. In addition, potential ethical issues may surface when repeating clinical studies with no clear scientific rationale, instead of making the live-saving vaccine readily available.

3.3.3. Pharmacovigilance

Pharmacovigilance or safety surveillance of adverse events following immunization (AEFIs) is critical to ensure safety data and minimize risks for subjects. Although access to vaccines has improved in many countries in the past two decades, there has not been proportional improvement in pharmacovigilance infrastructure and activities to monitor adverse events and address safety issues [30]. The group's recommendation is to focus on establishing a functional pharmacovigilance system, WHO's Triple-S project (smart safety surveillance) represents a useful approach to achieving this goal [30]. Key principles include:

- the development of a single system for both vaccines and other medicines where possible;
- leveraging existing systems and platforms, such as the Council of International Organizations of Medical Sciences (CIOMS) or ICH;
- using reliance where possible;
- building an infrastructure step by step to facilitate sustainability; and
- improving knowledge and understanding of international pharmacovigilance systems by industry and regulatory professionals.

4. Proposal B – improve alignment of the dossier structure and contents

The working group proposes that countries adopt the ICH CTD as a common template, which offers an opportunity for alignment thereby facilitating exchange of information between regulators, as well as dossier preparation.

4.1. Proposed structure for Module 1 of the registration dossier

When looking at alignment, or convergence, for registration dossiers (CTD), the regulatory expert working group began by analyzing Module 1. While there are many examples of country-specific Module 1 requirements, there is no global guidance that could be referenced, as each country or region uses a different structure [1]. In fact, according to ICH, Module 1 is expected to contain regional information [7]. Remaking Module 1 for each country creates a complex scenario where documentation could be missed, delaying the registration and consequently impacting access to vaccines. This can also create additional burden for NRAs with limited resources. A better aligned Module 1 structure would enable the creation of a standard set of documentation that could be used by NRAs globally.

To create a common structure for Module 1, the regulatory expert working group conducted a comparative analysis across ten different countries and regions worldwide to determine the extent of divergence and gain a general view of the contents requested. The analysis showed that while the structure of Module 1 was 70% divergent, the content was 62% similar [1]. The most frequently used structure and headings are proposed for alignment. Table 2 illustrates where country or regional information would fit into the potentially aligned Module 1, providing the background for the proposed new structure and content. Some points to consider include:

- If information is not required for a country, the section could be skipped (not deleted); it is suggested that the numbering for other sections be maintained.
- Documents related to the suggested content of the section listed in Table 2 could also be placed in that section.
- If some requirements are not covered by the suggested content, section 1.13 and any additional sections may be used for including those data.

4.2. Proposed numbering structure for Modules 2–5

To create a structure for Modules 2–5, the expert working group conducted a comparative analysis across five countries and regions worldwide to determine the extent of divergence and the type of content requested. All CTDs were compared against the ICH CTD. The level of divergence between countries/regions was found to be significant in content and structure (numbering) except for ICH and the Association of Southeast Asian Nations (ASEAN) which had similar contents but were completely different in structure [1]. Since the ICH CTD is the model from which all other CTDs have been derived, it would seem reasonable to encourage use of this CTD structure and content. Applying the ICH CTD numbering system across CTDs worldwide would enable all stakeholders to refer to the same information categories. Regarding content, the differences in requirements could potentially be addressed by the following measures:

- Harmonizing the numbering system against the EU/ ICH CTD. This structure is also recognized by WHO for their prequalification procedure. While many countries utilize the ICH CTD structure, the EMA dossier is used or recognized by many countries worldwide. Additionally, unlike the U.S. version, it does not require quality information that is primarily reviewed during inspections.
- Harmonizing the headings and contents under each item according to the EU Notice to Applicants [31]. If certain information is not required by a specific country/region, the section could be eliminated for that country, or to keep consistency between all countries, it could be submitted with the knowledge that the agency does not require it. If skipped, it is suggested that the numbering for other sections be maintained.
- Information not included in the EU/ICH CTD could be integrated in the respective sections of the CTD. Table 3 provides examples of information items required by specific countries and illustrates where this information could be provided in the EU/ ICH CTD without altering the numbering of other sections.

Table 2
Suggested template for harmonization of Module 1 of the registration dossier. The table lists the main headings of sections composing the Module 1 of the dossier (left column), which includes local/regional relevant information, and lists the designation of the main documents to be included/described under each section (right column).

Section		Suggested documentation
1.0	Cover letter	Cover letter
1.1	Comprehensive table of contents	Table of contents
1.2	Application form (administrative data)	Application form Administrative information Patent information Legal and statutory documents
1.3	Product information	Labelling Mock-ups Packaging inserts Summary of product characteristics Description and composition Patient information leaflet
1.4	Information about experts	Information about quality and clinical experts
1.5	Specific requirements for procedures - applications	Specific requirements for different types of applications Information on the application/submission type Literature-based documents Information for generic, 'hybrid' or biosimilar applications Co-marketed or combination medicines information Conditional marketing Orphan drug status/information/exclusivity Brief profile of the manufacturer's research activityExclusivity (market or data) Pricing (list, certificates) Foreign regulatory information Invoices Other related documents
1.6	Correspondence	Response to questions Meeting request, minutes, correspondence Scientific advice Additional data agreed upon to be provided Life cycle management trackingInformation amendments (not part of Modules 2–5)
1.7	Environmental risk assessment	Environmental risk assessmentGenetically modified organism (GMO) status
1.8	Information relating to pharmacovigilance	Pharmacovigilance (PV) Risk management plan (RMP) Protocols for PV plans
1.9	Clinical/ bioequivalence *Data that is not already included in the NRA submission in Modules 2–5.*	Information relating to clinical trials (synopsis, ongoing trials, study reports, Post-marketing studies, etc.) Bioequivalence Biopharmaceutical studies Clinical information
1.10	Regulatory certification	GMP, CPP, manufacturing licenseTechnical contract (open part) in case of contract manufacturing (if applicable) Health authority approval of the latest plasma master file
1.11	Manufacturer declarations and certificates	Certificates of suitabilityLetters of access (master files, etc.) Declaration letter from the manufacturer for name and address of the manufacturer, marketing authorization holder, invoice, export and release
1.12	Lot / batch information	Certificates of analysis, lot release certificate, summary lot protocols
1.13	Additional country data	Data requirements that do not fit in the above categories

Table 3
Mapping of potential locations in the EU/ICH CTD where additional information that is not required in the ICH CTD can be added. The first column provides typical additional information requested, while the second column provides the suggested section to place this information.

Additional information required by countries	Location in EU/ICH CTD
Thermostability	3.2.P.8.3
Excursion stability – shipping	3.2.P.8.3/3.2.S.7.3
In use/reconstitution stability	3.2.P.8.3
Cold chain validation	3.2.P.3.5
Shipping qualification	3.2.P.3.5
Bulk leachability	3.2.S.6
Full validation protocol	3.2.P.3.5
Stability at end of shelf life for multidose vaccines	3.2. P.8.3
In-country clinical trial	5.3.5
Clinical literature	5.4

5. Proposal C – common application form

The application form is an essential administrative component of all marketing authorization applications. It encompasses all the information essential for product registration, life cycle initiation and management. In addition, it contains technical and legal information that is duplicated in the dossier sections. This duplication highlights the need for optimization of its contents. A harmonized application form template would help achieve efficiency in product registration and compliance.

An application form has three main sections that contain information about the applicant and the legal representative in the country, the product and its regulatory status. Based on the comparison of application forms of various countries [1] the regulatory expert working group developed a standard template for a harmonized application form which covers all the administrative

Table 4
Template for a harmonized application form for vaccine registration. The content of the proposed harmonized application form consists of 3 main sections: section 1 to cover information about the manufacturer, the applicant and the legal representative in the country; section 2 to cover information about the product; and section 3 to cover information on regulatory status. The outline for each section is tabulated in two columns. The left column indicates the heading for each sub section and the right column indicates the description of the required information.

	Heading	Description of required information
1.0	Information about the applicant and the legal representative in the country	
1.1	Name of pharmaceutical company	The name of the pharmaceutical entity concerned with finished product registration.
1.2	Name and address of manufacturer of drug substance(s)	The name and address of the manufacturer(s) of the drug substance(s) used in manufacturing the finished product.
1.3	Name and address of manufacturer of the finished product	The name and address of the manufacturer(s) of the finished product.
1.4	Name and address of applicant/legal representative/ marketing authorization holder	The name and address of the marketing authorization holder (MAH) of the finished product. This may be a pharmaceutical company, a legal representative of any local consulting firm, any authorized and designated person thereof or any person authorized to place the product on the market.
1.5	Name and address of other manufacturer(s) involved in the manufacturing process	The name and address of all manufacturers involved in any part of the manufacturing process of the finished product.
1.6	Contact person for quality and pharmacovigilance	The name and address of the authorized representative(s) on behalf of the applicant/MAH. The contact person for quality is responsible for the overall quality of the finished product intended for marketing and the contact person for pharmacovigilance is responsible for the overall health and safety of the intended patient population and also responsible for any returns and recalls of finished products due to safety concerns.
1.7	Person/company authorized for communication between the MAH and NRA and official(s) responsible for batch testing and batch release of finished product	The name and address of the authorized representative(s) on behalf of the applicant/MAH. NRAs should forward any communication regarding the intended products/applications only to the person/company authorized for communication between the MAH and NRA. All product batches destined to be marketed in countries that require batch release should have a designated person/company responsible for releasing the batches of finished product.
2.0	Information about the product	
2.1	Name of the medicinal product including non-proprietary name or common name of vaccine	Non-proprietary/generic/invented name of the finished product or common name of the vaccine for which the registration application is applied.
2.2	Pharmaceutical form	The dosage form in which the finished product is intended to be marketed for use.
2.3	Physical description of pharmaceutical form	Complete physical appearance throughout shelf life of the finished product.
2.4	Commercial presentation(s)	The amount/quantity of unit dose per pack of finished product intended to be marketed.
2.5	Indication(s)	The therapeutic indication(s) for which the finished product is intended to be approved.
2.6	List of excipients, product shelf life, storage conditions, packaging configuration(s)	The list of excipients used in the manufacturing of finished product, proposed product shelf life and/or in-use shelf life of product; storage conditions during shelf life and primary packaging of the finished product intended for marketing.
2.7	Dosage and administration	Posology of the finished product and method of administration.
2.8	Qualitative and quantitative composition	Full details of drug substance(s) and excipients. Quantity of drug substance(s) and excipients should be expressed per dosage unit/per unit volume/per unit of weight, as per internationally recognized standard terms.
2.9	Name of drug substance(s)	Name of drug substance(s) present in finished product.
3.0	Regulatory status	
3.1	Date and registration number in country of origin	The date of first authorization in country of origin and registration number assigned to that approval as per the prevalent regulations of NRA(s).
3.2	List of countries where the finished product is registered	The list of countries where the intended finished product is registered.
3.3	List of countries where the product is marketed	The list of countries where the intended finished product is marketed.
3.4	Scientific advice before submission	Any scientific advice sought before submission from the respective NRA(s) should be outlined here.
3.5	Type of application	The type of application to be registered as per the regulatory guideline(s) of the respective NRA(s).
3.6	Annexed documents	Any additional information provided as separate documents.

and regulatory aspects of finished product. The three main sections were retained in the proposed template which is presented in Table 4 together with a brief description of each sub-heading.

6. Discussion and conclusions

The DCVMN-IFPMA regulatory expert working group considered several areas where registration procedures could be improved and developed three proposals that have a science and risk-based approach and share a common strategic element: reliance. The group proposes to pursue and expand the use of a common dossier and, for practical reasons, the adoption of the EU/ ICH CTD at a global level, due to the fact that this dossier version is already shared by many countries. They also suggest aligning the structure and content of the different dossier Modules, including Module 1, without affecting or modifying country requirements, and propose that countries use a standard application form template for (first) submission of the dossier. Although the working group did not specifically consider life cycle management, many of the approaches discussed in this article would be equally applicable for filing renewals or variations to existing registered products.

The working group focused on the need to make use of existing reliance mechanisms such as the WHO CRP, the CHMP Scientific Opinion, or others, including establishing bilateral or regional agreements for work-sharing and leveraging work performed by other regulatory agencies.

International fora such as the International Conference of Drug Regulatory Authorities (ICDRA), the Cooperation Council for the Arab States of the Gulf (GCC), the Association of Southeast Asian Nations (ASEAN), the Southern African Development Community (SADC) [32], the Pan American Network for Drug Regulatory

Harmonization (PANDRH), Asia- Pacific Economic Cooperation (APEC, that includes countries from PANDRH, ASEAN, ICH) or the International Coalition of Medicines Regulatory Authorities (ICMRA) provide an ideal environment for regulators to discuss and reach common understanding of approaches to improving efficiencies in regulatory activities. These all are places where the proposals could be discussed.

Additionally, the regulatory expert working group found that a considerable educational effort is needed, as many regulators currently focus on small molecules, lacking expertise in vaccines, and may not be fully aware of the latest developments in regulatory science. Collaboration among stakeholders to establish a dialogue to improve existing efforts will generate efficiencies and accelerate registrations.

This paper proposes small feasible improvements to current registration procedures. While not requiring any modifications to regulations, these improvements would lead to significant alignment which would in turn promote information sharing among NRAs, streamline registration procedures and save resources based on reliance and information sharing. Registration procedures would be facilitated not only for manufacturers, but also for regulators worldwide leading to a shorter review and, more importantly, accelerating access to these lifesaving products. Manufacturers hope with these proposals, to contribute to the solution for improved alignment of regulatory procedures and dossiers across countries and regions, thereby accelerating access to much-needed vaccines, particularly in emerging countries.

7. Collaborating Co-authors

Working Group members who significantly contributed to the drafting of this paper include (in alphabetical order of surname): Prashant Akut (Serum Institute of India Pvt. Ltd., Pune, India), Norbert De Clercq (GSK Vaccines, Wavre, Belgium), Samir Desai (Zydus Healthcare, Ahmedabad, India), Jacqueline Dias (Pfizer, Brussels, Belgium), Mic McGoldrick (Merck & Co. Inc. (Subsidiary of Merck Sharp & Dohme Corp.), West Point, PA, USA), Ida Nurnaeni (PT Biofarma, Bandung, Indonesia), Lorenz Scheppler (Janssen Vaccines, Bern, Switzerland), Monique Stavale (Bio-Manguinhos/Fiocruz, Rio de Janeiro, Brazil).

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Declarations of interest

All authors: none reported.

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