

Challenges and Opportunities to Global vaccines registration

Quality Management Systems

Training for professionals of the vaccine industry in cooperation with

IMBCAMS and Walvax

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Disclaimer

The information provided and the opinions expressed in this presentation are the sole responsibility of the speaker.

The information provided is based on my almost 20 years of work at the WHO, out of which many were dedicated to coordinating work for strengthening regulatory capacity. This experience and my present experience working with vaccine manufacturers led to the comments and conclusions expressed.



Objectives of the regulatory oversight of medicines including vaccines

- Facilitate access to needed medicines while ensuring their quality, safety and efficacy
- Exercise control over the medicines that are marketed in the country through registration, to prevent to the extent possible, the circulation of substandard or even counterfeit products
- Ensure that medicines circulating in their territories are of standard quality, are safe and effective
- Be able to monitor occurrence of adverse reactions, investigate them and introduce necessary corrective measures (if applicable)
- Be able to monitor the quality of products once they are introduced in the market and throughout their lifecycle



The Regulatory System

- Defines the responsible Institutions as well as their respective functions, roles and organizational structure
- Defines the scope of products covered
- The legislation, at different levels, (law, regulations, decrees) provide the legal framework on which the regulatory system is built.
- The highest level is represented by the law, which provides the overall and very general guidance. Regulations, decrees, procedures, etc provide increased level of detail as to the way in which the system works.



The Regulatory System (2)

Every effort should be done to develop a «ROBUST» regulatory system that will take into account different situations and conditions of use of the vaccines

Different provisions embedded in the regulatory framework are required to provide the necessary flexibility to achieve this

Transparency, well defined and published processes and procedures applied in a consistent manner, established fees, etc are key elements of a robust system



The Regulatory functions

Six **functions** have been identified as important for the regulation of vaccines

However,

- ✓ not every country needs to develop them all
- ✓ Strategies used by countries to ensure adequate performance of each function may vary (different routes lead to Rome).

The aim is to exercise an effective and efficient regulatory oversight of the products while making the best use of existing resources and available knowledge about the product's quality, safety and efficacy.



WHO recommended functions according to vaccine source

(prioritization strategy)

Vaccine Source	MAA & licensing	PMS	Lot release	Lab access	Regulatory Inspections	Authorization & monitoring CT
UN agency supply	Regulatory System		Exporting country NRA+ WHO-PQ			All countries where CTs are performed
Direct purchase			Exporting Country NRA			
Producing country						

Summary of recommended functions

Producing countries: All six critical functions need to be established

Non- producing countries procuring vaccines through United Nations procurement agencies need to establish Marketing Authorization and Post-Marketing Surveillance

Countries procuring vaccines directly need to establish Marketing Authorization, Post-Marketing Surveillance, lot release and laboratory access

All countries that are target to performance of clinical trials need in addition to establish Authorization and Monitoring of Clinical Trials

Increased complexity of vaccine products implies increased complexity in regulatory approaches

Review of new vaccine products requires among others

- Specific expertise in the product and in the technology used for production
- Specific expertise for review of non-clinical and clinical data for the specific vaccine in question
- Testing capacity difficult to establish and very costly
- Risk benefit assessment as part of product evaluation
- Review of risk management plans
- Specific pharmacovigilance commitments or phase IV studies
- Ability to assess the potential Public Health Impact particularly for vaccines for which efficacy may be lower than generally observed
- Understanding of Quality by Design concept for well characterized products
- Understanding of adaptive clinical trials concept



Regulators worldwide are challenged

There is consensus among regulators globally, particularly from well developed regulatory agencies, that ***not a single agency has the required resources to address all the relevant regulatory aspects for all product categories; and therefore collaboration, information sharing and worksharing become essential.***

Avoidance of unnecessary testing is considered critical

Avoidance of redundant inspections of manufacturing facilities is considered critical

Trend is to focus on risk benefit equation, potential public health impact of the intervention and measures to monitor quality, safety and efficacy and to minimize risks



		VACCINE CATEGORY	PRODUCING COUNTRY	PROCURING COUNTRY	PROCURING THROUGH UN
<div>WHO recommended approaches to vaccine licensure</div> <div> QUALITY COMPLIANCE REGULATION BIOLOGICS </div>		<u>INDIGENOUS</u>	<u>Full CTD dossier review:</u> required <u>Ability to test:</u> required <u>Inspection of facilities:</u> required <u>Performant system to monitor safety and efficacy after licensure:</u> required <u>Recommendation:</u> Ability to evaluate the product in full, including establishing testing capacity and performing regular inspections of facilities A performing post-marketing surveillance system is critical.	<u>Not applicable</u>	<u>Not applicable</u>
		IMPORTED NON-PREQUALIFIED	<u>Full CTD dossier review:</u> may be needed or not depending on maturity of the NRA in producing country (if licensed there) and/or that of the NRAs in other countries where the vaccine may have already been licensed. Need to review clinical data to ensure relevance to indigenous population and programmatic needs. <u>Ability to test:</u> Not necessarily required. Based on release certificate by licensing authority, testing not needed. Access to a laboratory able to test a specific vaccine in case of problems <u>Inspection of facilities:</u> Not necessarily required. Access to GMP certification by licensing NRA, use of CPP or access to inspection reports from licensing or other NRAs should suffice. <u>Performant system to monitor safety and efficacy after licensure:</u> required <u>Recommendation:</u> Need for full CTD review depends on maturity of NRAs that have already licensed the product including that of the producing country if relevant. Testing and inspection should be avoided unless under special circumstances. A performing post-marketing surveillance system is critical.		<u>Not applicable</u>
		IMPORTED PREQUALIFIED	<u>Full CTD dossier review:</u> Not required. Full review performed by NRA in country of origin plus WHO PQ, <u>Ability to test:</u> Not needed. Continued compliance with specs monitored by WHO PQ and NRA in country of origin. Data available on request <u>Inspection of facilities:</u> Not needed. GMP compliance monitored by NRA in country of origin and WHO PQ <u>Performant system to monitor safety and efficacy after licensure:</u> required <u>Recommendation:</u> Implement a facilitated and expedited procedure for registration of this category of vaccines. Focus resources in establishing and sustaining a performing post-marketing surveillance system-		

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WHO NRA strengthening activities

For non-producing countries the focus is on Marketing Authorization and Post-marketing surveillance

- Reliance on WHO PQ is requested. Use of Expedited procedure for review of imported prequalified vaccines has been promoted in past years (WHO/IVB/07.08).
- Now replaced by Collaborative procedure between the World Health Organization Prequalification of Medicines Programme and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines.

http://www.who.int/immunization_standards/vaccine_quality/collab_registration_rev2july2014.pdf

- Full development of post-marketing surveillance system including reporting, case investigation, communication and corrective actions.

Experience with use joint review approach to facilitate registration

Men A example

- Emergency vaccine eligible for fast track registration in India, fast track prequalification and registration in countries using the expedited review procedure
- Training for implementation of the procedure provided to 26 countries through two joint review workshops (in French and English)
- Participants requested WHO to share the PQ reports and some requested to receive CTD for filing/practice
- Upon return to home countries, expected to register the vaccine within 30 days
- Actual timeframes varied between 3 months and 34 months. A few have not yet completed the registration process
- Nevertheless vaccine was introduced in all countries as planned. Registration waiver???



Experience with use of joint review approach to facilitate registration (2)

IPV example

- Information on endgame strategy for polio eradication provided to countries (MOH) by WHO, UNICEF and GAVI through their DGs in 2013
- Information provided to NRAs on proposed IPV licensure strategy provided by RSS coordinator early 2014, with request of expression of interest in receiving support for registration using either collaborative procedure or independent review procedure
- Third communication sent to NRAs that agreed to participate with TORs and commitments to be met, mid-2014
- Workshops for the actual joint of the vaccine data conducted in October and November 2014



Experience with use of joint review approach to facilitate registration

IPV example

- Information from heads of NRAs did not cascade down to reviewers participating in workshops
- Files were not always sent to countries in timely manner
- Participants appreciated the technical-scientific support provided by WHO and the producing country NRAs
- Participants appreciated the opportunity to discuss directly with manufacturers the questions raised during the review
- Participants could not fully commit to prompt registration based on the reports produced during review meeting because of a variety of reasons



Reasons provided by participants that limited the success of the JR exercise

IPV example

- Participants informed WHO Secretariat that files should be submitted by the manufacturer through the official channels in order to proceed with the registration procedure
- Official channels means submission through national agents
- Official channels means also compliance with additional “country specific requirements” (e.g. labelling, vaccine samples, etc)
- Some countries communicated that their country procedures included inspection and testing and they did not know if these would be waived
- Timelines remained unclear, in part because manufacturers had not in all cases submitted the files in advance to the meeting



Lessons learned

Main achievements observed

Joint review meetings seem to

- ✓ Provide a good platform for information sharing,
- ✓ Accelerate the process of strengthening the expertise of reviewers in receiving countries,
- ✓ Help establishing trust among regulators in a specific area or region,
- ✓ Facilitate collaboration and networking among regulators
- ✓ Presence of manufacturers and of producing country NRAs at the IPV joint reviews helped resolve questions that otherwise would have taken long for resolution

Joint reviews are necessary but not sufficient to facilitate and accelerate approval and registration of vaccines in receiving countries



Lessons learned

Main shortcomings observed

- Inefficient internal communication within NRAs (cascading from management to technical staff)
- Failure by manufacturers to submit dossiers in timely manner
- Additional country specific requirements
- Imposing submission and communication through national agents
- Commitment to using only the report from joint review meeting could not be assured by all countries
- Timelines for registration unclear (ill-defined, non transparent process)
- Unclear if legal framework allowed for reliance on WHO PQ to facilitate registration



Constraints observed in some countries as reported by manufacturers

- Application form prior to submission, variety of formats
- Testing imposed as part of registration process
- Prior approval in a «reference country» in order for submission to be accepted
- Stability data for three consecutive lots, extensive real time stability data required
- Requirements for country specific artwork that needs to be approved by the national regulatory authority
- Compliance with National Pharmacopoeias
- License of facilities prior to product registration
- Variability in dossier format, including country specific requirements
- Local clinical trials are mandatory in some countries for initial registration but also for variations' approval
- One site per license
- Repetitive GMP inspections
- Repetitive testing of product



Approval of variations

Scenario A. Manufacturers wish to apply for registration with the latest “version” of the product. Sometimes this “version” is not yet approved in country of origin and therefore in many cases cannot be submitted to third countries until approved by the producing country NRA. This delays implementation of changes.

Scenario B. There are countries where the manufacturer may submit a file containing the variation even if not yet approved in country of origin, in such cases “two versions” of the product have to be maintained for an uncertain period of time, which creates difficulties for management of stocks and production lines .

Summary of constraints

- Inadequate and/or rigid legislation that does not allow for flexibilities as required based on scientifically sound reasons. Lack of provisions for reliance on work performed by others including in cases where the products are needed on an emergency basis.
- Technical or scientific limitations, where the necessary resources and expertise for an adequate evaluation may not exist or be insufficient, and inadequate use of already available knowledge about the product
- Some cases where specific requirements are imposed as part of the registration process even if the capacity to perform such activities is not established or the activity is not required (e.g. testing, local clinical trials)
- Cumbersome, inadequate or not fully defined procedures leading to inconsistent and lengthy registration processes.
- Lack of transparency about procedures in place



POTENTIALLY USEFUL INTERVENTIONS

- ✓ Availability of guidance documents (model regulatory framework, model process for registration), WHO is best suited for this.
- ✓ Training provided to facilitate implementation of the guidance, WHO and other partners
- ✓ Further efforts towards alignment and harmonization of requirements, mostly through networks, economic blocks agreements, etc
- ✓ Collaboration between regulators (reliance and recognition including mutual recognition) through networking initiatives
- ✓ Technical/scientific expertise provided joint review activities, twining between NRAs and other means
- ✓ Role of manufacturers to suggest options for improvement

Questions to the audience

- What opportunities are there to ease the procedures and to improve timeliness for marketing authorization of vaccines?
- Are there any specific initiatives that manufacturers can take to help?
- How would you propose to foster alignment among regulators across the world?
- Are there any specific aspects in which the WHO could help?





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