Registration of vaccines: Current challenges and opportunities

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DCVMN webinar 11 & 12 November 2015

Presentation outline

- Rationale for concept paper
- WHO efforts to strengthen regulatory capacity
- Lessons learned from Men A and IPV examples
- Challenges/constraints faced for vaccine registration
- Summary of constriants
- Addressing the constraints
- Proposed unique list of documents
- Comments and inputs

Rationale for concept paper

- WHO and other stakeholders have worked for years in helping countries establish/ strengthen National Regulatory Authorities (NRAs) for the regulation of vaccines.
- This has created awareness and willingness in NRAs to establish robust regulatory systems which however, is in many cases far from being met. Some NRAs require for certain functions (e.g. registration) much more than needed and have developed procedures that are non-efficient and that delay access to life saving vaccines
- DCVMN has requested the development of a concept paper describing the problem, looking at the origin of the problem, identifying the current issues and proposing potential solutions.

WHO efforts to strengthen regulatory capacity

WHO recommended approches to vaccine licensure

VACCINE CATEGORY	PRODUCING COUNTRY	PROCURING COUNTRY	PROCURING THROUGH UN
INDIGENOUS	**Full CTD dossier review: required** **Ability to test: required** **Inspection of facilities: required** **Performant system to monitor safety and efficacy after licensure: required** **Recommendation: 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.**	**Not applicable**	**Not applicable**
IMPORTED NON-PREQUALIFIED	**Full CTD dossier review: 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.** **Ability to test: 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** **Inspection of facilities: 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.** **Performant system to monitor safety and efficacy after licensure: required** **Recommendation: 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.**		**Not applicable**
IMPORTED PREQUALIFIED	**Full CTD dossier review: Not required. Full review performed by NRA in country of origin plus WHO PQ,** **Ability to test: Not needed. Continued compliance with specs monitored by WHO PQ and NRA in country of origin. Data available on request** **Inspection of facilities: Not needed. GMP compliance monitored by NRA in country of origin and WHO PQ** **Performant system to monitor safety and efficacy after licensure: required** **Recommendation: 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 recommended approches to vaccine licensure

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Robust system and functions need to be developed
Collaboration and Networking with other NRAs is encouraged

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WHO recommended approches to vaccine licensure

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Signature of a collaborative agreement between WHO and the NRAs to commit to grant MA based on WHO PQ reports

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Establish an efficient system that can benefit from reliance on the producing country NRA through information sharing, networking and collaboration with agreement from the manufacturer

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Men A and IPV registration examples

- WHO provided technical support through workshops to facilitate, and accelerate the registration of MenAfriVac and later that of IPV in priority countries
- Workshops were provided both for countries that agreed to use the expedited procedure proposed by WHO for prequalified vaccines and for countries that did not follow such procedure and based their decions on a full evaluation process
- The workshops were well organized and preceded by a series of communications between the WHO, the relevant NRAs and the manufacturers
- Commitments from the different parties were required and agreed upon in order to participate in the workshops.

Lessons learned from Men A and IPV registration examples

- 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 official submission and communication through national (local) agents
- Commitment to using only report from joint review meeting not 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

- 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
- High variability in requirements for stability data
- Compliance with National Pharmacopoeias
- License of facilities prior to product registration
- Requirement of local clinical trials prior to registration or for variations approval
- One site per license
- Repetitive GMP inspections
- Repetitive testing of product

Challenges for vaccine registration (annex)

Aspects of regulatory process	Constraints observed in some countries	Role of manufacturers	Role of NRAs	Role of WHO and other partners
Procedural	• Company/facility registration prior to product registration	• Compliance	• Based on certification by producing country NRA	• Reasonable requirement, based on certification by producing country NRA
	• Application form requirement prior to submission.	• Compliance,	• Clear rationale for requirement, planning?	• Reasonable if used for planning work
	• Requirement for prior registration in countries with NRAs considered as reference	• Compliance	• Clear rationale, for reliance, to facilitate registration process? Should it not be optional and subject to different review pathways rather than mandatory?	• Reasonable if linked to reliance on reference NRA and used to facilitate registration process, but it not registered in a reference country product should be accepted for review anyway, perhaps following a longer review pathway
	• Absence/unclear process steps leading to registration (often based on working practice)	• NA	• Improve/upgrade systems and procedures in place	• Offer guidance on best practices for registration and review
	• **Designation of local agents required.**	• **Advocate for regional agents?**	• **Consider replacing for regional agents**	
	• No / limited harmonisation,	• NA	• Work towards alignment of requirements	
	• Lack of sustainable expertise/systems within NRAs	• NA	• Training of staff, incentives to retain trained staff, improve systems	
	• Unpredictable timelines and outcomes / poor transparency	• NA	• Improve transparency, governance	• Provide support to strengthening governance in regulatory agencies

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Challenges for vaccine registration (annex)

Aspects of regulatory process	Constraints observed in some countries	Role of manufacturers	Role of NRAs	Role of WHO and other partners
Procedural	• Variability of file format: CTD, Asean CTD, AMRO CTD, PSF for WHO • Market specific requirements: labelling, product characteristics, specifications, country specific artwork, etc	• Compliance • Propose a standard and comprehensive package to meet the different requirements	• Differences are probably not so big between CTD versions • Consider aligning requirements between countries	• Consider feasibility of using exclusively CTD for PQ purposes • Offer guidance on best practices for registration procedures including list of critical documents and implementation of reliance principles. Advocate for alignment and wherever possible harmonization

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Challenges for vaccine registration (annex)

Aspects of regulatory process	Constraints observed in some countries	Role of manufacturers	Role of NRAs	Role of WHO and other partners
Science (data requirements)	• Testing of samples required	• Understand purpose of requirement, for visual inspection or testing? Assess testing capabilities before providing reagents	• Training and guidance to understand how quality of product and GMP compliance can be ensured through reliance on other NRAs' activities. No need to do everything	• Improve communication of WHO position about product evaluation and how resources can be effectively used by relying on work done by other regulators. Assist with what data is needed and how it has to be used.
	• Inspection of production facilities required	• Advocate for waiver based on inspection reports from others	• Alignment based on guidance docs	• Provide necessary guidance docs.
	• Stability data: variable requirements among countries	• Compliance		
	• **Requirements for local clinical data despite availability of data relevant to the population**	• **Advocate for waivers based on existing, relevant data**	• **Requirements for local clinical data should be assessed on a case by case basis. Expertise required to make informed decisions. Revise regulations to allow for flexibility**	• **Provide guidance on the rationale for requiring local data, for which products, under which circumstances, etc**
	• Pre-clinical and clinical data required for vaccines licensed many years ago in accordance to earlier requirements not acceptable today			
	• Specific pharmacovigilance and risk management plan	• Prepare to provide clear pharmacovigilance and risk management plans as this is future trend	• Training to assess RMP and strengthen pharmacovigilance	• Assist NRAs to strengthen the understanding of performance evaluation based on proper pharmacovigilance data and adequately designed RMP

Challenges for vaccine registration (annex)

Aspects of regulatory process	Constraints observed in some countries	Role of manufacturers	Role of NRAs	Role of WHO and other partners
Regulatory framework	• Differing regulations between countries • Lack of provisions for reliance on other NRAs • Lack of provisions for reliance on WHO PQ • Lack of provisions for registration of medicines for emergency use, orphan vaccines, and other priority products • Rigid requirements, ie. Impossibility for approval of more than one site, local clinical trials as mandatory requirement	• NA	• Work towards convergence • Need to improve regulatory frameworks to include the necessary provisions	• Provide guidance and examples of best practices to develop adequate regulatory frameworks. Advocate for alignment and harmonization wherever possible

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,
- Cumbersome, inadequate or not fully defined procedures leading to inconsistent and lengthy registration processes

Addressing the constraints

A combination of interventions seems to be required to overcome the described constraints. Four elements seem key to make progress:

- availability of guidance documents (model regulatory framework, model registration procedures, WHO recommendations on stability data, etc) ,
- training to facilitate implementation of the guidance,
- alignment and harmonization of requirements and,
- collaboration between regulators (reliance, work sharing and recognition including mutual recognition) through networking initiatives

Contribution from manufacturers

Share with NRAs processes, procedures and requirements in place in other countries and applied by other NRAs that may be more efficient and scientifically sound.

Gather a comprehensive list of the countries' specific requirements and propose to NRAs a unique and consolidated list of documents attempting to address the diversity of requirements.

Attempting to get agreement from country authorities to establish a certain number of regional agents to replace the need for local agents in each country.

The quality of submissions by manufacturers is also heterogeneous and not always of the highest standard. A recently published document by APAC "Good Submission Practice" may be useful to address this constraint

Work with partners (WHO, UNICEF, GAVI and others) to jointly assist the simplification of registration procedures based on reliance principles and harmonization of requirements (e.g formal request to WHO to advocate for regional agents or the unique list of docs, etc)

Consolidated list of documents

Scenarios for use of the list

Prequalified		Non- Prequalified	
Collaborative procedure	Independent evaluation	Full evaluation process	Abbreviated evaluation process
Submission of dossier complying with Natl requirements with technical part identical to WHO-PQP file	Submission of dossier complying with Natl requirements	Submission of dossier complying with Natl requirements	Country specific file format and data requirements
Expression of interest	NA	NA	
Payment of fees	Payment of fees	Payment of fees	Payment of fees
Country specific data	Country specific data	Country specific data	NA

Questions/inputs regarding the concept paper

- You are kindly requested to provide comments to the concept paper and the proposed list of documents.
- Are the proposed interventions feasible, potentially useful to improve the current situation?
- Do the issues identified in the «annex» document reflect correctly your real life experience? Anything to remove or add?
- Do you have additional ideas, proposals of what can /should be done?

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Questions/inputs regarding the proposed unique list of documents

- Are those presented the different possible scenarios regarding approaches to registration of vaccines?
- Could it be feasible to harmonize the country specific requirements through the implementation of a «comprehensive» list of documents?
- Would it be worth pursuing support from WHO and other partners (UNICEF, GAVI) to promote the use of such a list?
- Do you have additional ideas, proposals of what can /should be done?

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