Regulatory challenges for registration of novel vaccines

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Public Health Objective

Access for all Member States to vaccines needed to fight infectious diseases of public health relevance at affordable prices. This requires enough availability and sustainable supply of vaccines of assured quality, safety and efficacy meeting the programmatic needs of countries, particularly those which are less resourced.

Access to priority vaccines

- Vaccine registration/ marketing authorization is a prerequisite to introduction in any country
- The evaluation of vaccines for marketing authorization, particularly that of novel vaccines may be challenging
- Authorities in producing countries and in high income countries usually have the required infrastructure and resources for a proper review
- Authorities in most of the user countries, particularly in less resourced countries may not have the required conditions to conduct a meaningful evaluation of such complex products

Regulatory process during vaccine development

IND-like process: Early communication between sponsor and regulators to discuss expectations and sharing of product development plan including the clinical development plan.

Scientific advice applied in Europe: As an example, EMA addresses specific questions from product developers and guides them in the development plan

Establishment of testing capacity by the NRA in collaboration with the sponsor. Transfer of testing methods for future lot release

Pre-submission meetings to discuss submission requirements, legal considerations of the application, etc

Pediatric Investigation Plan (PIP) in case of vaccines targeting this age group is a requirement in Europe

Regulatory process for marketing authorization

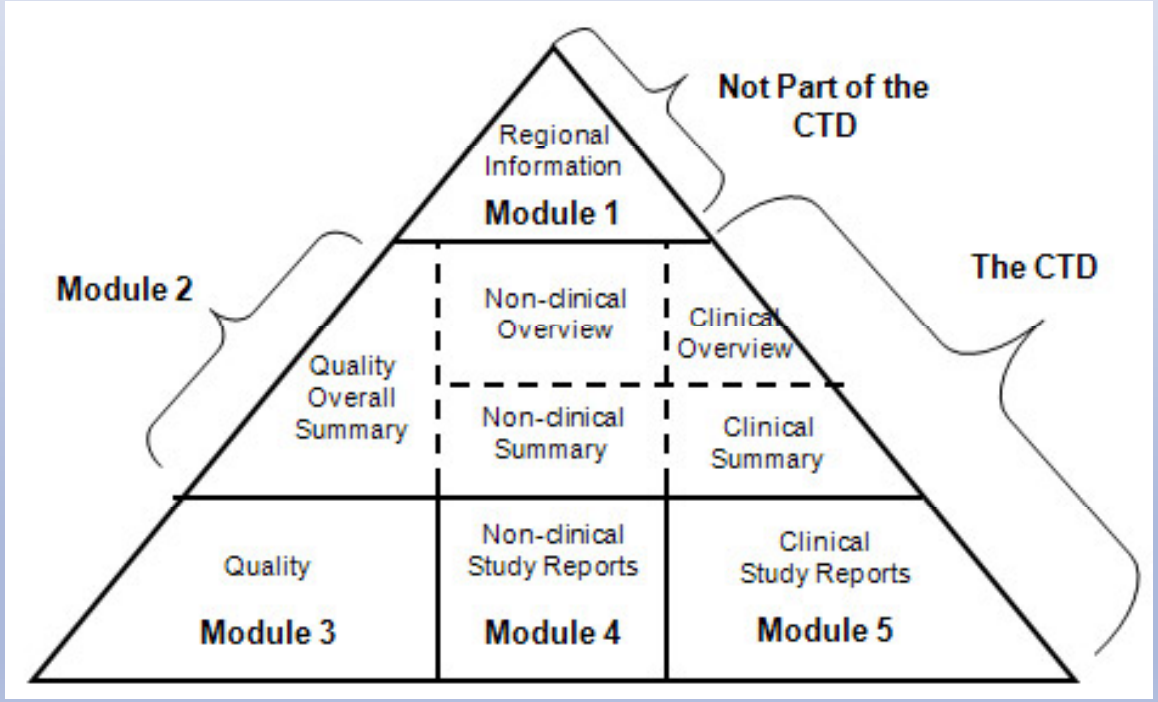
Pre-submission meetings

Intention to submit or application form

Marketing authorization application. Requirements may include:

- Submission of Product dossier; usually CTD format
- Testing of samples (some authorities)
- Inspection of production facilities (if required)
- Review of samples, labelling and inserts/ Summary of Product Characteristics
- Info on Pharmacovigilance system
- Risk Management Plan

Common Technical Document (CTD)



Increased complexity in product development

- ✓ Novel vaccines require product specific expertise and understanding of disease burden, morbidity and mortality rates, in areas where the disease is prevalent,
- ✓ Many are targeted to countries in regions without enough development of regulatory agencies
- ✓ Clinical trials to be conducted in countries where the disease is prevalent, require capacity for the regulation of clinical trials
- ✓ Use of new production technologies requires specific expertise for meaningful review

Support for the regulation of clinical trials

TWO IMPORTANT TOOLS AVAILABLE

Networking

- To jointly develop common procedures and forms for the approval and monitoring of clinical trials and for the evaluation of clinical data
- To support each other for the review and approval of CT applications
- To benefit from the support by regulators from robust NRAs and from WHO

The African Vaccine Regulatory Forum (AVAREF) is a good example

The Developing Country Vaccine regulators Network (DCVRN) is another good example

Joint review meetings

- Support offered by WHO to assist regulators mostly in Africa to review CT applications
- For high priority vaccines, such as malaria and ebola candidates

SUCCESSFUL APPROACH

QUALITY COMPLIANCE REGULATION BIOLOGICS

Dr. Nora Dellepiane- Consultant on Quality and Regulation of Biological Products

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-clincal and clinical data for the specific vaccine in question
- 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 safety and minimize risk

Support for the evaluation of MA applications

Vaccines supplied through centralized procurement (e.g. UN)

Marketing Authorization (MA) granted in country of origin

Prequalification by WHO: ensures that vaccine meets the needs of the programme in target countries

A facilitated MA process expected in receiving countries: Expedited procedure for the review of imported prequalified vaccines. Now revised to *Collaborative procedure between WHO and NRAs for the assessment and*

NOT VERY SUCCESSFUL

Vaccines supplied through direct procurement (not necessarily prequalified by WHO)

Marketing Authorization (MA) may or may not have been granted in country of origin

Marketing Authorization (MA) may have been granted in third countries

Full responsibility for evaluation lies with NRA in procuring country, unless **provisions for reliance** on other regulators are in place

AVAILABLE IN SOME COUNTRIES

and Regulation of Biological Products

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AVAILABLE IN SOME COUNTRIES

- ✓ Support national review of MA evaluation with MA in country of origin (CPP) and/or in third countries considered as reference authorities
- ✓ Use of own expertise and resources for review of MA applications
- ✓ Use of bilateral agreements with other NRAs to assist evaluation process
- ✓ Use of Networking initiatives to assist evaluation process

CONSTRAINTS

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A facilitated MA process expected in receiving countries: Expedited review procedure for *Collaborative procedure between WHO and NRAs for the assessment and accelerated registration of prequalified medicines*

NOT VERY SUCCESSFUL

What needs to be in place

- ✓ Adequate regulatory framework with provisions for reliance on other NRAs or WHO PQ
- ✓ Defined and transparent process for marketing authorization, with clear requirements, steps and timelines for approval
- ✓ Alignment of requirements between countries and regions
- ✓ Technical/scientific expertise for proper assessment of the application

CONSTRAINTS

- ✓ Inadequate regulatory framework with provisions for reliance on other NRAs or WHO PQ
- ✓ Not well defined and non-transparent process for marketing authorization, without clear requirements, steps and timelines for approval
- ✓ Lack of alignment of requirements between countries and regions
- ✓ Limited technical/scientific expertise for proper assessment of the application

Frequently seen constraints that impair or delay implementation of the expedited or collaborative procedure; and lead to unpredictable timelines for registration

REMAIN TO BE ADDRESSED

Support provided by WHO and collaborating regulatory agencies
Support provided based on bilateral agreements between countries, etc

ALREADY BEING ADDRESSED MORE NEEDED

POTENTIALLY USEFUFUL INTERVENTIONS

- ✓ Availability of guidance documents (model regulatory framework, model process for registration),
- ✓ Training provided to facilitate implementation of the guidance,
- ✓ Further efforts towards alignment and harmonization of requirements,
- ✓ 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
- ✓ Scientific guidance provided through expert committees (e.g. SAGE) on risk benefit analysis, potential public health impact of intervention, etc; available to NRAs to assist in registration process
- ✓ Strengthening of National Immunization Technical Advisory Groups (NITAGs) to assist decision making at country level

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