Clinical data dossier requirements

Briefing on Vaccine Prequalification for manufacturers

24 October 2016

World Health Organization

Chapter 8: Clinical experience

- Note 1 : Reference documents
  - TRS 978, Annex 6 (2012, PQ procedure) http://www.who.int/entity/immunization_standards/vaccine_quality/TRS_978_61st_report_Annex_6_PQ_vaccine_procedure.pdf
  - TRS 850 (1995, GCP); http://apps.who.int/prequal/info_general/documents/TRS850/WHO_TRS_850-Annex3.pdf
  - TRS 924 (2004; clinical evaluation of vaccines); http://who.int/entity/biologicals/vaccines/clinical_evaluation/en/index.htm
  - TRS 927 (2005; non-clinical evaluation of vaccines) http://who.int/biologicals/vaccines/nonclinial_evaluation_of_vaccines/en/
  - Points to consider for manufacturers of human vaccines: clinical considerations for evaluation of vaccines for prequalification http://www.who.int/immunization_standards/vaccine_quality/pq_vaccine_evaluation/en/
  - Any specific TRS
  - Related WHO position paper

Chapter 8: Clinical experience

- Note 2
  - For vaccines originally licensed many years before application for prequalification, emphasis should be given to document history of safe and effective use.
- Note 3
  - Provision on request of raw data

8.1 Clinical development program

- Format: tabulated summary (1 or more tables)
- Objective: identification of critical parameters that may have changed during the clinical development of the product

ANNEX 1 CLINICAL DEVELOPMENT PROGRAMME: CHARACTERISTICS OF CLINICAL VACCINE LOTS USED IN CLINICAL STUDIES.

Table 1: Changes to the manufacturing process or to the formulation of lots used in clinical studies

Parameters	Final Commercial Formulation	Clinical Study					
		No. 123 Phase 1	No. 234 Phase 2	No. 345 Phase 2	No. 456 Phase 3	No. 567 Phase 3	No. 678 Phase 3
Batch size	1500 L	20 L	20 L	20 L	20 L	20 L	1500 L
Manufacturer of intermediates (facility location)	Best Vaccine LTD, Geneva	GoodVac LTD, NY	GoodVac LTD, NY	GoodVac LTD, NY	GoodVac LTD, NY	Best Vaccine LTD, Geneva	Best Vaccine LTD, Geneva
Formulation facility	Best Vaccine LTD Rio de Janeiro	GoodVac LTD, NY	GoodVac LTD, NY	GoodVac LTD, NY	GoodVac LTD, NY	Best Vaccine LTD, Geneva	Best Vaccine LTD Rio de Janeiro
Excipient(s)	Albumin	No Albumin	No Albumin	Albumin	Albumin	Albumin	Albumin
Preservative	Thiomersal	No thiomersal	No thiomersal	No thiomersal	No thiomersal	thiomersal	thiomersal
Vaccine presentation	Multidose (10 ml)	One dose	One dose	One dose	One dose Syringe	One dose Syringe / multidose	multidose
Concentration / composition of antigen or adjuvant	PS type Z (10 µg) Carrier prot-6 (5 µg) w/o emulsion + Immstim® (2 µg)	PS type Z 5 µg Carrier prot-6 Alum	PS type Z 20, 10, 5 µg Carrier prot-6 Alum	PS type Z 10 µg Carrier prot-6 Alum + Immstim® (2 µg)	PS type Z 10 µg Carrier prot-6 Alum or w/o emul + Immstim® (2 µg)	PS type Z 10 µg Carrier prot-6 w/o emulsion + Immstim® (2 µg)	PS type Z 10 µg Carrier prot-6 w/o emulsion + Immstim® (2 µg)
Others……							

8.2 Clinical trial information (1)

- 8.2.1 Applicant's sponsored clinical trial overview
  - List of all clinical trials conducted (in all countries relevant to the application for WHO PQ)
    - For each study sponsored by the applicant (before and after initial licensure)
      - Approved protocol (by NRA and Ethics Committee)
      - Evidence of registration in a CT registry (WHO ICTRP)
      - Compliance with GCP

8.2 Clinical trial information (2)

- 8.2.1 Applicant's sponsored clinical trial overview (cont'd)
  - For each study, to be provided (in a table or brief summary)
    - Type of study
    - Rationale
    - Study sites
    - Dates
    - Statement of final conclusions
    - Copies of publications and abstracts to be provided
  - List of ongoing trials
    - Details of the study plan
    - Expected date of results

8.2 Clinical trial information (3)

- 8.2.2 Other studies with the applicant's product
  - Not sponsored by the applicant
  - Vaccine as intervention of main interest or used as comparator
  - Also observational studies (e.g. case-control studies)
  - Identified by literature search

8.2 Clinical trial information (4)

- 8.2.3 Clinical summary – (similar to CTD 2.5)
  - Detailed summary and interpretation of the safety and efficacy data of all studies (pre- and post-licensure)
  - Relevance to support worldwide use
    - WHO recommended schedules
    - Co-administration with other vaccines
  - Expected to complement (not replace) the summary written by an independent clinical expert (8.2.5)

8.2 Clinical trial information (5)

- 8.2.4 Assessment reports
  - Whenever possible
    - Clinical section of the national regulatory authority (NRA) assessment report from the country of origin and/or country where initially licensed
    - Assessment reports for any subsequent variations to the license for changes relevant to clinical data
    - Assessment reports from other NRAs

8.2 Clinical trial information (6)

- 8.2.5 Clinical expert report
  - Independent clinical expert report
    - Evidence of expertise and independence to be provided
  - Particularly useful for products licensed long time before
    - Limitations put in the context of the requirements at the time of licensure
      - Ethical approval / GCP
      - Study design / sample size
    - Impact on disease control after introduction in vaccine programme
    - Post-marketing safety data

8.2 Clinical trial information (7)

- 8.2.6 Preclinical studies sponsored by the applicant
  - List of all preclinical studies sponsored by the applicant (TABULATED FORMAT)
  - For preclinical studies performed after initial licensure, indicate the reasons for these studies

8.3 Documentation of safety (1)

- 8.3.1 Pharmacovigilance plan
  - Introduced in the current PQ procedure (from 2012)
  - Important to determine whether evidence to support the use of the product in different populations (geographical areas, age groups, etc…) are planned
  - Some evidence will be expected as post-prequalification commitments

8.3 Documentation of safety (2)

- 8.3.2 Initial evaluation of vaccines that have been in the market for a long time (or reassessment of already prequalified vaccines)
  - Outline of the applicant's procedures for the collection, onward notification and assessment of adverse events
  - Listing of all reported AEFIs
  - Periodic Safety Update Reports (PSURs) may provide all the information needed
    - ICH format preferable

8.3 Documentation of safety (3)

- 8.3.3 Recently licensed vaccines
  - Ongoing phase IV studies
  - Ongoing active monitoring of the safety profile

8.3 Documentation of safety (4)

- 8.3.4 Documentation of serious advent events
  - Fullest possible description of each case, including any information there may be on investigations, actions, patient treatment and outcome
  - Periodic Safety Update Reports (PSURs) may provide all the information needed

Clinical Information in Package Insert

- PSF Chapter 4.4

  The information in the PI must be referenced to the clinical data.

  Indications

  - Dosage-regimen
  - Side-effects
  - Pregnancy
  - Special precautions

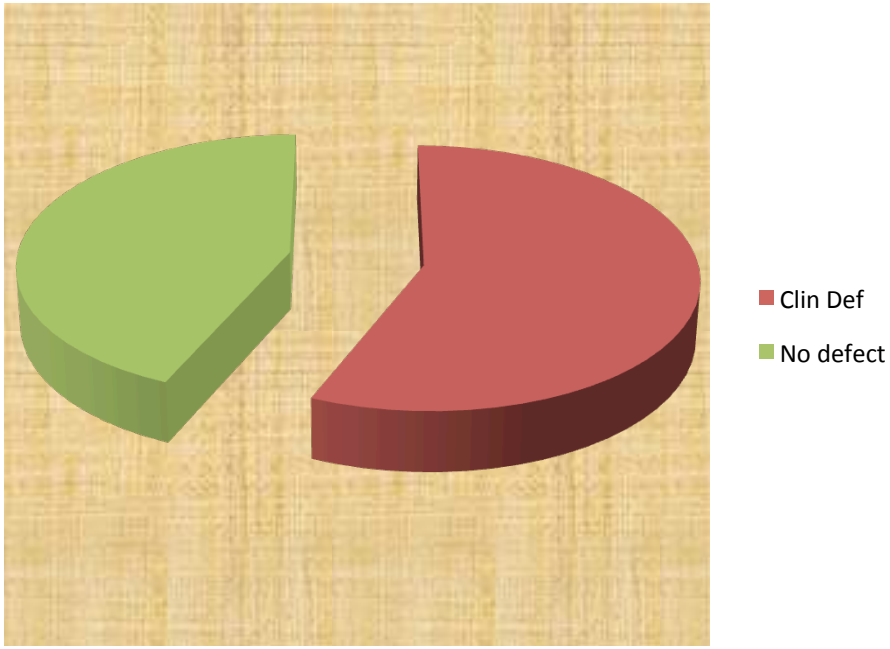
Specific deficiencies as par categories

Safety	Immunogenicity
Absence of list of AE Incomplete SAE details Insufficient safety follow up time Unclear definition of AE Inadequate safety information Inadequate safety data base No data on specific at risk population	Lack of evidence for surrogate of protection Discrepancies in numbers Unclear statistical analysis Unsatisfactory immunogenicity results No information on assays or validation Lack of information on Co-adm vaccines No data on specific at risk populations
Clinical development/Protocol	**Post Licensure**
Missing info on status and results of listed studies Lack of evidence CT registration Lack of info on sample size and stat analysis Missing information on ethical over sight Unacceptable comparators Lack of info on protocol versions, DSMB and studies procedures	Missing or incomplete PSUR Missing or incomplete PV plan

Deficiencies on submitted dossiers

85 Dossiers

48 with Clinical deficiencies



Deficiencies by categories

Safety – 18%

Immun – 35%

Clin D/Prot – 35%

Post PQ – 12%

News Flash!!!!

- Follow the recent guidelines rigorously
- Ask questions if anything is not clear to you

THANK YOU