

Clinical aspects during Prequalification of vaccines

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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/nonclinical_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/pg_vaccine_evaluation/en/

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● 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 for 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

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

Points to consider

- b) a completed clinical trial model summary protocol (according to TRS No. 924, p. 95) for pivotal (often phase III) trials;

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
 - For preclinical studies performed after initial licensure, indicate the reasons for these studies
- TABULATED FORMAT

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 adverse 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