
Production and control of tetanus vaccine

A training curriculum

INTRODUCTION



World Health Organization
Geneva

in collaboration with

National Public Health Institute
Helsinki

**PRODUCTION AND CONTROL OF TETANUS VACCINE
A TRAINING CURRICULUM**

INTRODUCTION

- MODULE I: PRINCIPLES AND PRACTICE OF QUALITY CONTROL**
- MODULE II: TETANUS - MICROBIOLOGY AND CLINICAL ASPECTS**
- MODULE III: PRINCIPLES OF TETANUS VACCINE PRODUCTION**
- MODULE IV: MICROBIOLOGICAL AND IMMUNOCHEMICAL TESTS**
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- MODULE VI: LABORATORY ANIMAL TESTS**
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- MODULE VIII: DOCUMENTATION AND RELEASE PROCEDURES**
- MODULE IX: QUALITY AUDITS**
- MODULE X: REFERENCE MATERIALS FOR QUALITY CONTROL**

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PRODUCTION AND CONTROL OF TETANUS VACCINE

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1. Introduction

Tetanus is one of the few diseases of humans completely preventable by immunization. Tetanus vaccine (tetanus toxoid) has been commercially available since 1938 and its use has resulted in dramatic decline of tetanus incidence in, at least, industrialized countries. During the last decade worldwide vaccination coverage has improved rapidly, in many countries supported by the activities of the Expanded Programme on Immunization (EPI) of the WHO. Nevertheless, tetanus, especially neonatal tetanus, still remains a major health problem in developing countries.

Today more than fifty countries produce their own tetanus vaccine. In some countries the manufacture is continued even though it may not be financially profitable. It is likely that the number of producing countries will increase as many countries wish to establish local tetanus vaccine production.

Production of tetanus toxoid can be managed with reasonably simple and inexpensive technology. Indeed, tetanus toxoid is well suited as the first product of a new vaccine production unit. However, what has not always been realized is the fact that quality control of vaccines is a demanding and expensive activity. Regrettably, there are only too many examples to demonstrate that inadequate quality control generally results in potency or safety problems.

This material has been prepared for use in training of quality control personnel, especially in countries or units starting vaccine production or setting up a National Control Laboratory (NCL). It has been compiled, by assignment of the WHO Biologicals Unit, at the Vaccine Quality Control Unit of the National Public Health Institute (KTL), Helsinki, Finland.

The complete curriculum consists of ten modules:

- Module I - PRINCIPLES AND PRACTICE OF QUALITY CONTROL
- Module II - TETANUS - MICROBIOLOGY AND CLINICAL ASPECTS
- Module III - PRINCIPLES OF TETANUS VACCINE PRODUCTION
- Module IV - MICROBIOLOGICAL AND IMMUNOCHEMICAL TESTS
- Module V - CHEMICAL AND PHYSICAL TESTS
- Module VI - LABORATORY ANIMAL TESTS
- Module VII - INFECTIOUS DISEASE SURVEILLANCE SYSTEMS

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Module VIII - DOCUMENTATION AND RELEASE PROCEDURES

Module IX - QUALITY AUDITS

Module X - REFERENCE MATERIALS FOR QUALITY CONTROL

The modules may be used as a complete programme, or any single module may be applied to meet the individual needs of the trainees. It is recommended that at least Modules I and VIII should be included in every training course. Comprehensive training will probably take four to six months, depending on the individual training aims.

The most important source materials utilized during the compilation of this document have been WHO documents and the RIVM course book on Quality Control of Bacterial Vaccines as well as F.M. Garfield's book Quality Assurance Principles for Analytical Laboratories (Module IX), reprinted from the Quality Assurance Principles Manual, Volume 1, 1992. Copyright 1992 by AOAC International.

2. Training programme plan

Prior to starting a module one should always evaluate the individual training needs of the students. After giving an introduction to the subject and scope of the complete curriculum the targets for the trainees' learning process should be clearly defined. Prognostic tests (evaluation or self-evaluation) may be used to facilitate a structured evaluation of the trainees' starting level.

Module I PRINCIPLES AND PRACTICE OF QUALITY CONTROL

- Duration of training: 2-3 days
- Individual/independent studies of course material
 - Module text
 - Examples of Quality Manuals
- Lectures
- Group discussion
 - Organization planning
 - Alternatives for quality system set-up
 - Problems of subordination
 - Scope of responsibilities

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Module II TETANUS - MICROBIOLOGY AND CLINICAL ASPECTS

- Duration of training: 2-3 days
- Individual/independent studies of course material
 - Module text
 - Textbook of clinical microbiology/infectious diseases
- Lectures
- Laboratory demonstrations:
 - Anaerobic sampling and culture techniques
 - Studying the colony morphology and stained specimens

Module III PRINCIPLES OF TETANUS TOXOID PRODUCTION

- Duration of training: 1-2 weeks
- Individual/independent studies of course material
 - Module text
 - WHO Manuals
- Lectures
- Following the production process in a production department

Module IV MICROBIOLOGICAL AND IMMUNOCHEMICAL TESTS

- Duration of training: 2-3 weeks
- Individual/independent studies of course material
 - Module text
 - Relevant textbooks
- Lectures
- Laboratory practice
 - Aseptic and clean area working techniques
 - Individual tests
 - Validation and quality control of the tests

Module V CHEMICAL AND PHYSICAL TESTS

- Duration of training: 2 weeks

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- Individual/independent studies of course material
 - Module text
 - Relevant textbooks
- Lectures
- Laboratory practice
 - Basic working methods
 - Individual tests
 - Validation and quality control of the tests

Module VI LABORATORY ANIMAL TESTS

- Duration of training: 4 weeks
- Individual/independent studies of course material
 - Module text
 - Relevant textbooks
- Lectures
- Practice at the animal house
 - Animal housing
 - Animal handling and care
 - Injection and sample taking techniques
 - Anesthesia and euthanasia
 - Reading the results of the tests

Module VII INFECTIOUS DISEASE SURVEILLANCE SYSTEMS

- Duration of training: 1-2 weeks
- Individual/independent studies of course material
 - Module text
 - Relevant textbooks
- Lectures
- Introduction to the use of EPI INFO programme on PC
- Evaluating adverse event reports
- Laboratory practice
 - Basic working methods
 - Individual tests

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- Validation and quality control of the tests

Module VIII DOCUMENTATION AND RELEASE PROCEDURES

- Duration of training: 1 week
- Individual/independent studies of course material
 - Module text
 - WHO Manuals
- Lectures
- Evaluation of incomplete or erroneous protocols
- Evaluation of satisfactory protocols
- Compilation of a protocol from individual test results

Module IX QUALITY AUDITS

- Duration of training: 1 week
- Individual/independent studies of course material
 - Module text
 - Relevant textbooks
- Lectures
- Participation in an audit visit to a production unit

Module X REFERENCE MATERIALS FOR QUALITY CONTROL

- Duration of training: 1 week
- Individual/independent studies of course material
 - Module text
 - Relevant textbooks
- Lectures
- Laboratory practice
 - Calculating the results
 - Validation and quality control

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3. Glossary

AUDIT

Inspection of facilities, functions, or records.

BIOLOGICAL PRODUCT

Any microbe, therapeutic serum, toxin, toxoid, antitoxin, blood, blood component derivative, including products derived by DNA technology, or allergenic product applicable to the prevention, diagnosis, treatment, or cure of disease or injuries in humans.

BULK PURIFIED TOXOID

The processed purified material, prepared from either a single harvest or a pool of a number of single harvests. It is the parent material from which the final bulk (vaccine) is prepared.

CALIBRATION

Estimation of potency relative to a reference material (relative potency).

CEPHALIC TETANUS

A rare disease developing after injuries to the scalp, face or neck, associated with palsies of cranial nerves III, IV, VI, VII, IX, X, XII, and invariably associated with some degree of trismus.

CEPHALOTETANUS

= Cerebral tetanus.

CEREBRAL TETANUS

Tetanus following a wound of the head, combining the generalized rigidity of the disease arising elsewhere and cranial nerve palsy, especially of cranial nerve VII (the facial nerve).

CHALLENGE

To administer infective or toxic material to an organism in order to ascertain whether experimental immunization has been effective.

CHRONIC TETANUS

A form of tetanus seen in humans in which the onset following infection is later, the progress of the disease is slower, and the prognosis more favorable than in acute form.

CRYPTOGENIC TETANUS

Tetanus which occurs without any wound or other ascertainable cause.

ECBS WHO Expert Committee on Biological Standardization

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ED₅₀ Effective Dose₅₀, the dose of a vaccine which protects 50% of the immunized animals against a challenge dose of the toxin

EXTENSOR TETANUS

That which affects especially the extensor muscles.

FINAL BULK (VACCINE)

The final homogeneous vaccine present in a single container from which the final containers are filled either directly or through one or more intermediate containers.

FINAL LOT

A collection of sealed final containers that are homogeneous with respect to the risk of contamination during filling. A final lot must therefore have been filled from a single container in one continuous working session.

FLEXOR TETANUS

That which affects especially the flexor muscles.

GOOD CLINICAL PRACTICE (GCP)

The organizational process and conditions under which clinical trials are planned, performed, monitored, recorded and reported, e.g. Nordic Guidelines on Good Clinical Trial Practise.

GOOD LABORATORY PRACTICE (GLP)

The establishment of procedures and conditions for the proper organization of laboratories in which studies to assess the potential health risks or safety of substances are planned, conducted, supervised, recorded and reported. It includes the organization of archives. A laboratory where GLP is followed possesses the capability to produce accurate test data, and can be relied upon in its day-to-day operations because of maintenance of high standards of performance.

GOOD MANUFACTURING PRACTICE (GMP)

Activities performed under conditions that ensure the consistency of manufacture of good quality products, conforming to established specifications. These include production processes, documentation of these processes and control testing, state and maintenance of facilities, staff expertise, retention and training, and regular inspection to assure the quality of these activities.

HEAD TETANUS

= Cerebral tetanus.

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HYDROPHOBIC TETANUS
= Cerebral tetanus.

IDIOPATHIC TETANUS
Tetanus without an obvious lesion (= cryptogenic tetanus).

INCUBATION PERIOD
The period *from* entrance of infecting organism into the body (infection) *to* the appearance of clinical symptoms. In tetanus, short incubation period is associated with fulminant disease and poor prognosis.

INNOCUITY (TEST)
= General safety test.

I.U. International Unit is the specific activity contained in a stated amount of the International Standard preparation as defined by the WHO ECBS

JANIN'S TETANUS
= Cerebral tetanus.

KOPF-TETANUS
= Cerebral tetanus.

KLEMM'S TETANUS
= Cerebral tetanus.

LD₅₀ Lethal dose₅₀, the amount of toxin that kills 50% of a group of animals within four days (the LD differs for different animal species)

Lf Limes flocculation is the amount of toxin or toxoid as defined by the International Reference Reagent of Tetanus Toxoid for Flocculation Test.

LOCALIZED TETANUS
Tetanic spasm of a single part.

MLD Minimum Lethal Dose, the amount of tetanus toxin that will result in death within four days, as determined in laboratory animal tests.

MPD Minimum Paralyzing Dose, the amount of tetanus toxin that will result in paralysis of a given severity, as determined in laboratory animal tests.

MODIFIED TETANUS
= Localized tetanus.

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MONITOR

To control something actively

NATIONAL CONTROL AUTHORITY (NCA)

An independent entity within a country responsible for establishing procedures to assure that biological products intended for use in that country are safe, potent, and efficacious. These procedures include legislative authority, licensing criteria, production requirements, testing to demonstrate consistency of production and compliance with these requirements, post-marketing surveillance activities, inspections to assure compliance with Good Manufacturing Practice. The National Control Authority may include within its organization a National Control Laboratory, or the National Control Laboratory may be a separate entity.

NATIONAL CONTROL LABORATORY (NCL)

A laboratory advisory to the National Control Authority which performs at least the following functions:

- provision of advice to the NCA on technical matters
- evaluation of manufacturers' procedures and protocols
- pre-licensing control testing of lot samples, particularly for consistency of production, and testing for lot release
- evaluation of shelf-life specifications and stability
- development, evaluation, establishment, and implementation of testing procedures and release criteria, including establishment and distribution of national reference materials
- review of reports of quality defects and provision of advice on withdrawal
- undertaking of research in relation to the above activities.

ONSET PERIOD

In tetanus, the period from the first symptom to the first generalized spasm. As a rule, the shorter the onset period, the worse the prognosis.

PARALYTIC TETANUS

= Cerebral tetanus.

POSTSERUM TETANUS

Tetanus which develops after the administration of anti-tetanus serum.

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POTENCY

The specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data, obtained through administration of the product in the manner intended, to effect a given result. It is thus equivalent to the concept that the product must be able to do what is claimed for it, and if possible, this must correspond with some measurable effect in the recipient or be correlated with some quantitative laboratory finding.

PUERPERAL TETANUS

That which occurs in women after childbirth.

PURITY

The degree of freedom from extraneous matter whether or not harmful to the recipient or deleterious to the product. In most instances, however, the concepts of purity and safety coincide, and purity relates to freedom from such materials as pyrogens, contaminants and residual chemicals from the manufacturing process.

QUALITY ASSURANCE (QA)

The combination of organized activities performed to demonstrate, prove and ensure that the output (product or data) meets quality criteria and specifications for its intended application.

QUALITY CONTROL (QC)

A system concerned with sampling and testing, along with organization, documentation and release procedures. It assures that the necessary tests have been carried out and that the quality has been demonstrated to be satisfactory before a specific material is used in production or a product is released for sale. Put simply, QA assures that the data are reliable; QC, that the product meets the necessary standards.

RELATIVE POTENCY

Potency relative to a reference material. A relative potency is estimated as the ratio between equivalent (equipotent) doses of a test preparation and a standard preparation. If the standard preparation defines an International Unit (or is calibrated in IU) the relative potency of the test preparation can then be expressed in international units per unit volume.

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REQUIREMENTS

Specifications, procedures and standards applicable to an establishment or to the manufacture or release of products, which are prescribed in regulations and which are designed to ensure the continued safety, purity and potency of biologic products. Requirements for the production of biologicals are issued by the WHO and local NCA.

RETAINED SAMPLES

Samples retained from each lot produced. Samples must be retained at least one year after the expiration date of the product lot. Both National Control Authorities and manufacturers should retain a predetermined number of samples.

ROSE'S TETANUS

= Cerebral tetanus.

SAFETY

The relative freedom from harmful effect to the recipient, when a product is correctly and appropriately administered, taking into consideration the character of the product and the condition of the recipient at the time. Safety cannot be assured in absolute sense. For example, special care must be taken in administering otherwise safe products derived from chick embryos, e.g., influenza vaccines, to the rare individual who is hypersensitive to chickens, chicken feathers or eggs.

SEED LOT

A quantity of bacterial suspension that is derived from one strain, has been processed as a single lot and has a uniform composition. It is used for preparing the inoculum (working seed) for the production.

SINGLE HARVEST

The toxic filtrate or toxoid obtained from one batch of cultures inoculated, harvested and processed together.

SPECIFICATION

The specified properties that a given product must have, e.g. potency, innocuity, concentration of preservative or adjuvant.

SPLANCHNIC TETANUS

A form in which the muscles of deglutition (swallowing) and of respiration are severely involved and in which there is severe dysphagia.

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STANDARD PREPARATION

A reference preparation, such as bacterial or viral antigen, or a serum with a defined specific activity, which can be used in evaluating relative potency. There are international, national and in-house standard preparations. Often *standard preparations* are referred to only as *standards*. Usually, it will then be obvious from the context that the meaning is a material standard preparation, but care is needed to avoid misunderstandings.

STANDARD TEST METHOD

Test that has been carefully validated and standardized and approved by an internationally recognized laboratory.

TETANOLYSIN

The hemolytic component of the exotoxin (tetanus toxin) produced by *Clostridium tetani*, which may or may not contribute to the pathogenesis of tetanus. See also tetanospasmin. (tet'ah-nol'i-sin) [*tetanos* + lysin].

TETANOSPASMIN

The neurotoxic component of the exotoxin (tetanus toxin) produced by *Clostridium tetani*, which causes the typical muscle spasms of tetanus. See also tetanolysin. (tet'ah-no-spaz'min) [Greek *tetanos* + Latin *spasmos* = spasm + in chemical suffix].

TETANUS

Infectious disease in which tonic muscle spasm and hyperreflexia result in trismus (lockjaw), generalized muscle spasms, arching of the back (opisthotonos), glottal spasm, seizures, and respiratory spasms and paralysis; it is caused by the neurotoxin of anaerobically vegetating *Clostridium tetani*, with onset one to two weeks after inoculation of spore forms into a traumatized area. (tet'ah-nus) [Greek *tetanos*, from *tenein* = to stretch].

TETANUS ANTICUS

Tetanus in which the body is bowed forward.

TETANUS INFANTUM

= Tetanus neonatorum.

TETANUS LATERALIS

Tetanus in which the body is bent sideways.

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TETANUS NEONATORUM

Tetanus of newborn infants, usually due to the infection of the umbilicus.

TETANUS PARADOXUS

Cephalic tetanus in which trismus is combined with paralysis of the facial or other cranial nerve.

TETANUS POSTICUS

Tetanus in which the body is bowed backward.

TRAUMATIC TETANUS

That which follows wound infection with *Clostridium tetani*.

UTERINE TETANUS

= Puerperal tetanus.

VALIDATION

Collection and evaluation of data in order to ascertain that the process under investigation will produce the required results. Validation is conducted like scientific investigation: it must be based on a study protocol, performed in defined conditions and the validation process and results must be appropriately documented in a validation report.

V/V Volume to volume

WHA World Health Assembly, the decision making organ of WHO.

WHO World Health Organization, the international health organization of the United Nations.

W/V Weight to volume

4. Contributors

The curriculum has been compiled and edited by Kari S. Lankinen, M.D., D.T.M.&H., Acting Head of the Vaccine Quality Control Unit.

Major contributions were received from:

Rose-Marie Ölander, M.Sc. (Animal Physiol.), Senior Researcher, Vaccine Quality Control Unit: Modules VI, VII (Chapters 6.2 to 7) and X.

Hanna Nohynek, M.D., Assistant Physician, Department of Infectious Disease Epidemiology: Module VII (Chapters 1 to 6.1).

Kaija Vuontela, B.Sc., Assistant Researcher, Vaccine Quality Control Unit: Modules IV and V.

The effort was coordinated by Tuuli Koski, M.Sc. (Pharm., Microbiol.), Head of the Vaccine Quality Control Unit.

(Contact address: National Public Health Institute, Mannerheimintie 166, FIN-00300 HELSINKI, Finland, Tel. +358-0-47441, Fax +358-0-4744408)

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