Pharmaceutical Quality Management

QUALITY CONTROL OF VACCINES

By:

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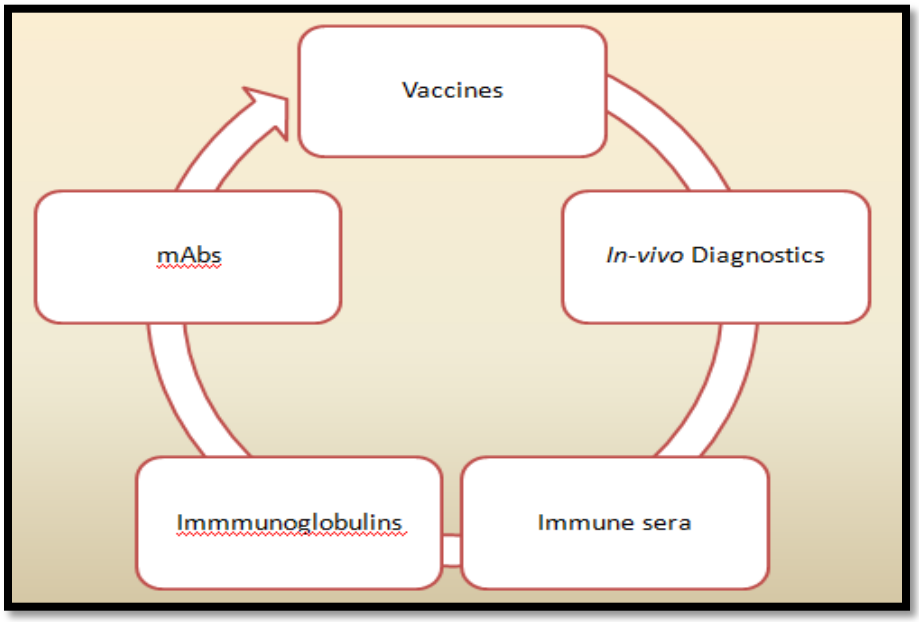
IMMUNOLOGICAL PRODUCTS:

Group of pharmaceutical preparations with diverse origins but a common pharmacological purpose: Modification of the Immune status of a recipient, either to provide immunity to infectious diseases or to aid in the detection of such diseases.

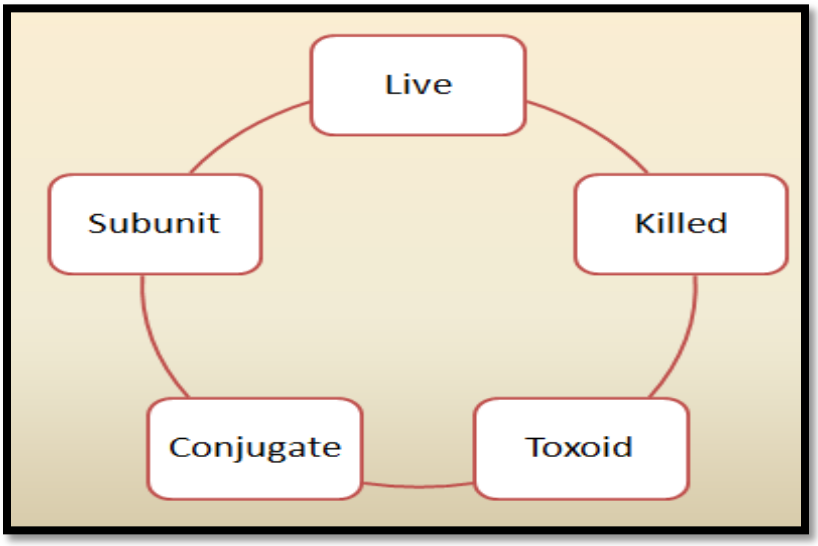
Types of Immunological Products



VACCINES

- Vaccine is a biological preparation that consists of either a whole organism or a part of it against which immunization has to be achieved.
- Vaccines provide active immunity as they stimulate the immune system of the recipient to produce T cells or antibodies that impede the attachment of infectious agents and promote their destruction.

Types of Vaccines:



I. Live Vaccines:

- These are preparations of live bacteria, viruses or other agents which, when administered by an appropriate route, cause subclinical or mild infections. In the course of such an infection the components of the microorganisms in the vaccine evoke an immune response which provides protection against the more serious natural disease.
- Examples: Vaccinia (Smallpox), BCG (TB)

II. Killed Vaccines:

- Killed vaccines are suspensions of bacteria, viruses or other pathogenic agents that have been killed by heat or by disinfectants such as phenol, ethanol or formaldehyde.

Killed organisms cannot replicate and cause an infection. Thus every dose of killed vaccine must have an antigenic material to increase the immunogenic response

- Since all the components of the micro-organism are present, it may be toxic to the body. Thus it is recommended to divide the vaccine into booster doses which may be given at regular intervals of time.
- Examples: Polio, Typhoid, Pertussis, Cholera, Plague, Rabies.

III. Toxoid Vaccines:

- Toxoid vaccines are preparations derived from the toxins that are secreted by certain species of bacteria.
- In the manufacture of such vaccines, the toxin is separated and treated chemically (Formaldehyde) to eliminate toxicity but not immunogenicity.
- This process is called as toxoiding and the end product is termed as Toxoid or Formol toxoids.
- Examples: Tetanus, Diphtheria, Botulism, Clostridial infections of farm animals.

IV. Cell components or Subunit Vaccines

- Instead of using whole cells which may consist of undesirable reactogenic components, vaccines are prepared from purified protective components.
- Such vaccines is that they evoke an immune response only to the component, or components, in the vaccine and thus induce a response that is more specific and effective.

- Examples: Hemophilus influenzae type b, Neisseria meningitidis ACWY, Hepatitis b etc.

V. Conjugate Vaccines

- Some antigens which are used to prepare vaccines are less immunogenic and do not give appropriate responses.
- Such antigens are conjugated to certain immunogenic carriers which improve the immunogenic response.
- Example: Glyco- Conjugate Vaccine of Neisseria meningitidis with carrier protein is CRM_{197}

VI. Adjuvants

- Heterogeneous collection of substances which enhance the immune response.
- Examples: Aluminium hydroxide gel (hydrated aluminium oxide) and aluminium phosphate are the only ones in general use in human vaccines.
- A much wider range of substances including oily emulsions, saponin, immune- stimulating complexes (ISCOMS), monophosphoryl lipid A and others are used in veterinary vaccines and some are under investigation for use in human vaccines

❖ QUALITY CONTROL

- Mainly to provide assurances of both the probable efficacy and safety of every batch of every product.
- There are two ways
  - **1. In-process control**
  - **2. Final product control**
    - **i. Assays**
    - **ii. Safety tests**

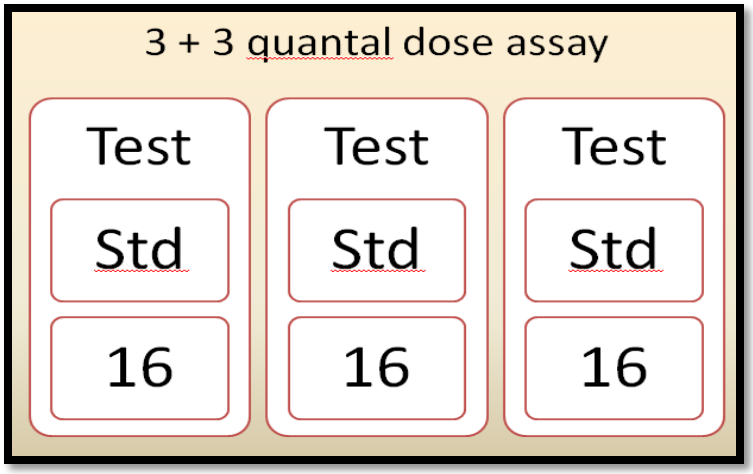
1. In-process Control

- In-process quality control is the control exercised over starting materials and intermediates.
- The toxoid concentrates used in the preparation of the vaccines have been much diluted and, as the volume of vaccine that can be inoculated into the test animals (guinea-pigs) is limited, the tests are relatively insensitive. In-process control, however, provides for tests on the undiluted concentrates and thus increases the sensitivity of the method at least 100-fold.

2. Final Product Control

i. Assays:

- Vaccines containing killed microorganisms or their products are generally tested for potency in assays in which the amount of the vaccine that is require to protect animals from a defined challenge dose of the appropriate pathogen, or its product, is compared with the amount of a standard vaccine that is required to provide the same protection.



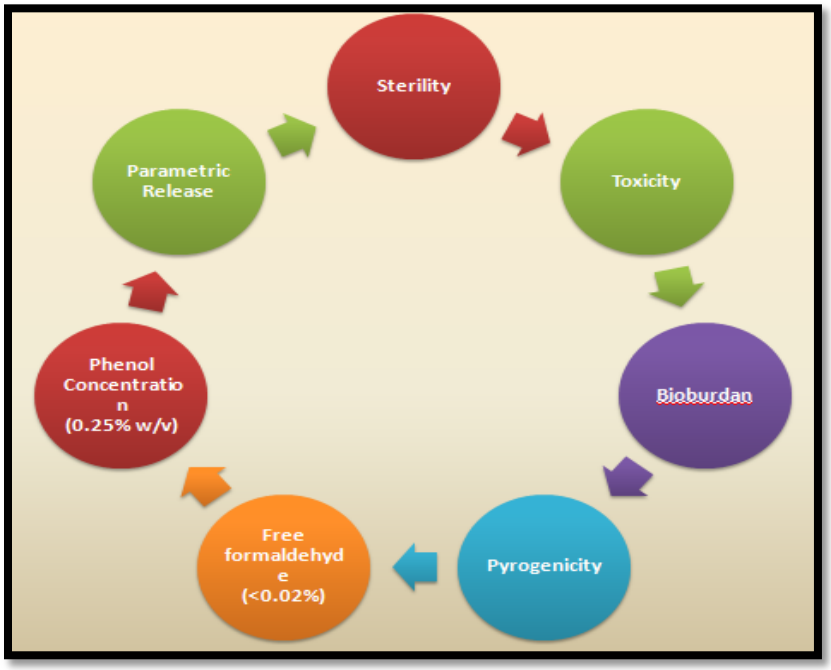
- The number of survivors in each group is used to calculate the potency of the test vaccine relative to the potency of the standard vaccine by the statistical method.
- The potency of the test vaccine may be expressed as a percentage of the potency of the standard vaccine
- Vaccines containing live microorganisms are generally tested for potency by determining their content of viable particles.
- Example: In the case of BCG vaccine, dilutions of vaccine are prepared in a medium which inhibits clumping of cells, and fixed volumes are dropped on to solid media capable of supporting mycobacterial growth. After a fortnight the colonies generated by the drops are counted and the live count of the undiluted vaccine is calculated.

ii. Safety Tests

- Bacterial vaccines are regulated by relatively simple safety tests. Those vaccines composed of killed bacteria or bacterial products must be shown to be completely free from the living microorganisms used in the production process.

- Those vaccines prepared from toxins, for example, diphtheria and tetanus toxoids, require in addition, a test system capable of revealing inadequately detoxified toxins.
- This can be done by inoculation of guinea-pigs, which are exquisitely sensitive to both diphtheria and tetanus toxins.
- A test for sensitization of mice to the lethal effects of histamine is used to detect active pertussis toxin in pertussis vaccines.
- With killed vaccines the potential hazards are those due to incomplete virus inactivation and the consequent presence of residual live virus in the preparation.
- With attenuated viral vaccines the potential hazards are those associated with reversion of the virus during production to a degree of virulence capable of causing disease in recipients

❖ Tests of general Applications



a. Bioburden

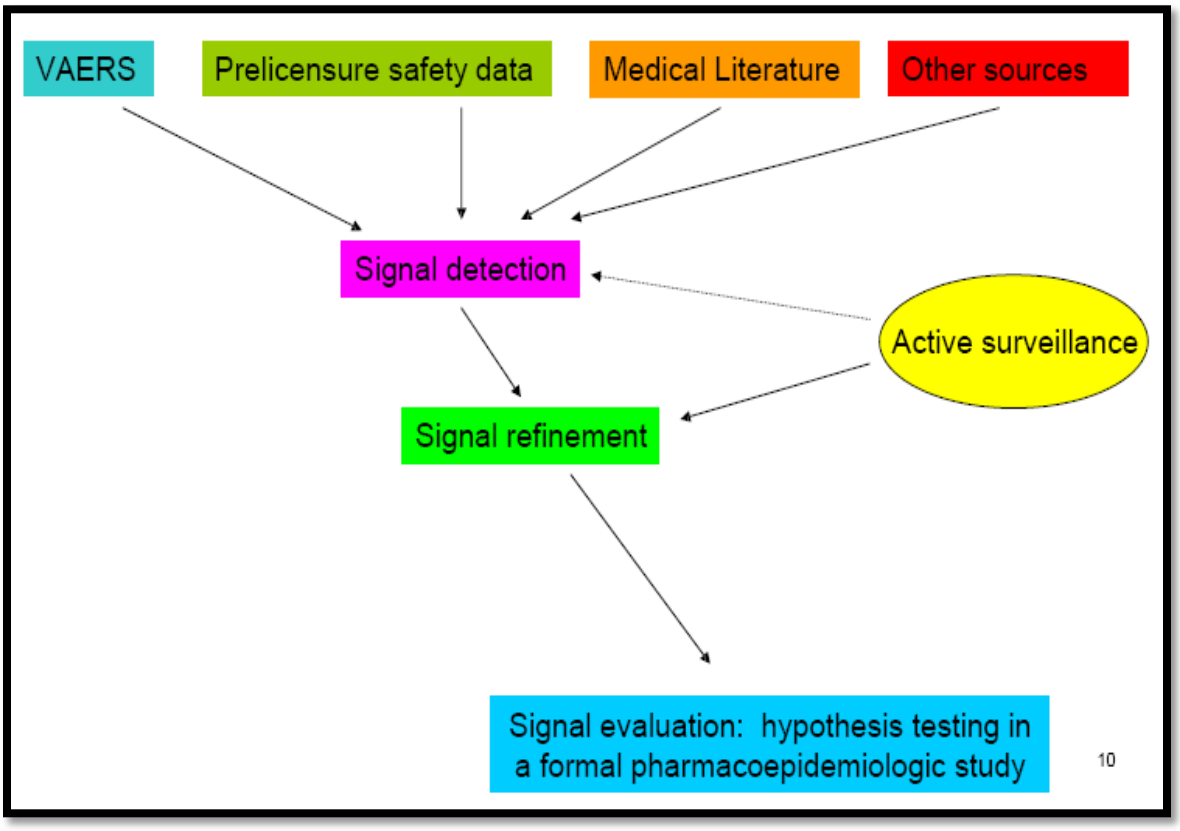
- A successful sterilization process is dependent on a product having a low pre-sterilization bioburden. Sterilization should be considered as the removal of the bioburden.
- This will also be true of the individual ingredients, which must have low levels of microbial contamination or else there is a danger that the contaminants will find their way into the final product or be a source of pyrogens.
- The bioburden is an estimate of the total viable count of microorganisms present pre-sterilization, and a knowledge of the resistance characteristics of these organisms is often an integral part of the sterility assurance calculation.
- Sterilization process should be chosen in such a way that all micro-organisms are highly resistant.

b. Parametric Release

- As there are significant limitations with the test for sterility, many authorities place considerable reliance on the validation and reliable performance of sterilizers and their sterilization cycles.
- Parametric release takes this reliance a step further by allowing batches of terminally sterilized products to be released without being subjected to the test for sterility.
- Validation studies would include heat distribution, heat penetration, bioburden, container closure and cycle lethality studies.
- For a product to be subject to parametric release, pre-sterilization bioburden testing on each batch would be completed, and the comparative resistance of isolated spore-formers checked.

- In practice this requires confirmation that each part of the manufacturing process has been satisfactorily completed, the initial pre-sterilization bioburden is within agreed limits, that the controls for the sterilizing cycle were satisfactory and that the correct time cycles were achieved.
- Clearly reproducibility, regular monitoring and documentation are required

❖ Post Marketing Surveillance of Vaccines



❖ Vaccine Adverse Event Reporting System

- Co-administered by FDA and CDC
- Reporting by paper or electronic versions of a standard form
- – Serious AE reports are manually reviewed by medical officers to detect unexpected events
- – Nonserious reports assessed primarily through data mining

❖ Post-licensure Rapid Immunization Safety Monitoring System (PRISM)

- • Integral part of Mini-Sentinel dedicated to vaccine safety
  • 42 million individuals
  – 3 national health plans, 8 vaccine registries
  • Evidence reviews for key health outcomes underway
  • Developing methods
  – Identify signals without pre-specifying outcomes
  – Perform sequential regression using propensity scores

❖ Stability of Vaccines

1. **Choice of stability indicating parameters and frequency of testing**
2. **Cumulative age of an antigen in the final product**
3. **Stability of a final lot**

3a) Vaccine formulation

3b)Vaccine presentation, container and closure system

3c) Stability of freeze-dried vaccines

1. Choice of stability indicating parameters and frequency of testing

- Depending on the nature of the antigen and other components as well as on the manufacturing process, stability indicating parameters should be selected on a *case-by-case basis*. In the selection of stability indicating parameters, the potential clinical implications of the observed changes must always be considered. Ideally, stability indicating parameters should reflect the link between vaccine quality and efficacy or safety as demonstrated in clinical trials.
- For most vaccines, potency is considered as a stability indicating parameter that reflects potential impact of environmental conditions on the immunogenicity and subsequent protective efficacy of a vaccine.

2. Cumulative age of an antigen in the final product

The stability of the characteristics of a final product should be guaranteed during the whole shelf-life, irrespective of the age of the intermediates at the time they are used in the production process. Total age of all components at the end of shelf-life is considered as cumulative age of the product. In practice, stability data of the final product should include the data generated on the intermediates of different ages used in the final formulation

3. Stability of a final lot

Vaccine formulation:

- The stability of a final lot of vaccine depends of the stability of all intermediates as well as of the final formulation. Therefore, data on stability of the intermediates as well as stability data of the final formulation should be submitted to the National Regulatory Authority.
- In the case of combined vaccines, the stability of each component should be assessed and data included in the manufacturers dossier.

Vaccine presentation, container and closure system

- In addition to the data on stability of the final formulation, other factors that may affect vaccine stability during its use should also be tested in the stability study.
- Potential interactions between the vaccine and container and closure system are particularly important for vaccines in liquid form**.**

Stability of freeze-dried vaccines

- Data to support proposed use of vaccine after reconstitution, maximum storage period, and storage conditions should be generated as part of the stability study performed on the final lot. In the assessment of freeze-dried vaccines, residual moisture should be specified.
- Reconstitution period (time needed for reconstitution and appearance of reconstituted vaccine should be defined.