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Batching and storage of bulk biological products

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BATCHING AND STORAGE OF BULK BIOLOGICAL PRODUCTS

BATCHING AND STORAGE OF BULK BIOLOGICAL PRODUCTS

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DEFINITION

BIOLOGICAL PRODUCTS

The term “biological product” means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Section 351, Public Health Service (PHS) Act

42 U.S.C. § 262(i)

BIOLOGICAL PRODUCTS

Biological products, or biologics, are medicinal products.

Biological products could be made of

Sugars

- Proteins, or nucleic acids or complex combinations of these substances, or
- living entities such as cells and tissues.

Like drugs, biological products are used to either:

✓Treat or cure diseases and medical conditions,

✓Prevent diseases, or

✓Diagnose diseases

DEFINITION – BATCH NUMBERING

Batch means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

A batch therefore is a specific amount of an API or other material that is processed in one or more ways so as to demonstrate homogeneity of the product.

Batch Number: A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificate of analysis, etc.

BATCHING

Biological products can be manufactured in sublots and pooled as one batch, thus bulk batch can be packed in different presentation or packs in terms of volume or concentration.

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IMPORTANCE OF BATCH NUMBERING

IMPORTANCE OF BATCH NUMBERING

- Recording of the batch and batch number typically starts at the manufacturing plant. Batches should be maintained and recorded according to:
- Quantity
- Manufacturing Date
- Expiry date
- Strength of the active ingredient and purity
- Excipient(s)

Complete production history must be able to be traced back through the batch number.

BULK BATCH NUMBERING

BULK BIOLOGICAL PRODUCT – NUMBERING

- Simple is beautiful
- Traceability to best possible extent for quality specifications of sub lots and starting materials
- Traceability to best possible extent for Finished product specifications
- When Stored should be easily differentiated from other batch numbers and from batches of other bulk products.

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CASE STUDY

CASE STUDY – 1

Reprocessing of Vaccine bulks – Challenges and QRM?

Every 5th sub lot of bulk does not meet purity criteria, thus has to be reprocessed. The manufacturer makes 20 sub lots per month. Each bulk batch consists of 4 sub lots. How should the reprocessed sub lots be handled to make a bulk batch.

QUALITY RISK MANAGEMENT – BATCH NUMBERING

QUALITY RISK MANAGEMENT – BATCH NUMBERING

- Execute the batch numbering SOP on theoretical basis and identify the risks of inadequate numbering, traceability and mix ups.
- Assign clearly differentiable batch numbers to bulks of multiple products or combination products.
- Identify similar looking batch numbers or names and adequately segregate them for storage.
- Calculate risk scores for each batch numbering system.
- Mitigate the risk by re-numbering for further differentiations.
- Re-write draft SOPs and execute on work shop floor level before final approval.

CRITICAL AND MAJOR OBSERVATIONS DURING WHO INSPECTIONS

CRITICAL AND MAJOR OBSERVATIONS DURING WHO INSPECTIONS

- Traceability of finished product from bulk batches and sub lots
- Consistency of bulk batches and sub-lots vis a vis batch numbers
- Trending of quality parameters for bulk batches and sub-lots
- Assigning shelf life to bulk batches
- Stability Studies of bulk biological products in actual container or in same material of construction
- Media Simulation studies for aseptic processes followed for bulk biologicals production
- Bulk Manufacturing intermediate stages are not considered in APQR

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STORAGE OF BULK PRODUCTS

STORAGE MANAGEMENT SYSTEM

Primary Container – Similar to finished product:

- Should protect the bulk from external environment.
- Should be of appropriate material and compatible, i.e leachability study.
- Bulk should be stable in it.

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STORAGE MANAGEMENT SYSTEM

STORAGE MANAGEMENT SYSTEM CONT...

Hold Time/Storage Stability Study

- Relevant temperature and other conditions including any short-term excursions or elevated conditions to simulate the real storage condition.
- The container and its size used for hold time study should be of the same Material of Construction/Size in which the actual bulk is stored.
- Storage conditions should be continuously and online monitored.

STORAGE MANAGEMENT SYSTEM CONT…

Storage locations

- Appropriate storage locations to ensure that adequate controls are in place.
- Locations include buildings and facilities:
  - ✓ Warehouse
  - ✓ Storage or hold area in manufacturing facility
  - ✓ Original manufacturer's warehouses
  - ✓ Contractor warehouses

STORAGE MANAGEMENT SYSTEM CONT...

Storage in buildings and facilities

- Required to maintain the product temperature between the limits as defined on the product label based on stability study.
- Ware-housing, storage, and/or holding of product areas should be of adequate size for their intended use.
- Adequate to prevent overcrowding.

STORAGE MANAGEMENT SYSTEM CONT...

Storage in buildings and facilities

- Designed to control environmental conditions with easily cleanable materials.
- Sanitation and pest control procedures, indicating frequency of cleaning and the materials and methods used.
- Orderly storage and segregation of approved, quarantined, rejected, returned, or recalled materials.

STORAGE MANAGEMENT SYSTEM CONT...

Receiving and transferring

Storage of a product includes also time spent at the receiving bay area. The material should be

- Transferred as quickly as possible to a designated storage or within a time period.
- Time spent in a transport vehicle is considered to be part of the distribution process and is not a storage location.
- Loading and unloading docks for receipt and distribution of products, should be clean, cleanable, and free from pests.
- The incoming receiving area should limit access to authorized persons.

STORAGE MANAGEMENT SYSTEM CONT...

Receiving and transferring cont..

- Delivery vehicle/container should be examined before unloading.
- Adequate precautions should be taken to prevent theft.
- Appropriate delivery records checked, for example
  - ✓ Transport vehicle movement papers
  - ✓ Receiving/delivery records
  - ✓ Data logging records
  - ✓ Temperature recorders and similar devices.

STORAGE MANAGEMENT SYSTEM CONT...

Refrigerators and freezers

- Operating procedures and maintenance protocols should be in place.
- Product stored in the units in a manner that allows adequate air flow to maintain the specified conditions.
- Units should be positioned in the facility so that they are not subjected to environmental extremes that could affect their performance.
- Recording systems to log and track temperatures.
- Alarm systems should be an integral part of the monitoring system.
- While automated systems monitor units continuously, manual checks should also be performed.

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DISTRIBUTION MANAGEMENT SYSTEM

DISTRIBUTION MANAGEMENT SYSTEM

Packaging for the distribution and transportation processes

- Package performance testing and evaluation for factors such as:
  - ✓ Shock
  - ✓ Vibration
  - ✓ Pressure
  - ✓ Compression
  - ✓ Other transit events
- The type, size, location, and amount of the temperature stabilizers required to protect the product should be based on documented studies.

DISTRIBUTION MANAGEMENT SYSTEM CONT...

Validation and thermal performance qualification for transport systems

- Transport systems should be continuously monitored by calibrated monitoring systems.
- Shipping systems should be qualified and based on historical data relative to the process.
- Studies should reflect actual load configurations, conditions, and expected environmental extremes.
- Testing should be performed on both active and passive thermal packaging systems.

ENVIRONMENTAL MANAGEMENT SYSTEM

ENVIRONMENTAL MANAGEMENT SYSTEM

Temperature monitoring

- Temperatures should be tracked using monitoring system.
- Monitoring devices should be under calibration and/or preventive maintenance schedule.
- The monitoring devices used should provide an alert mechanism.
- Appropriate number of temperature monitors.
- Chemical temperature indicators may be used as appropriate during transportation.
- Plan of action in the event of an unacceptable excursion.

ENVIRONMENTAL MANAGEMENT SYSTEM CONT…

Temperature mapping

- A temperature mapping study should be designed
  - ✓To assess temperature uniformity across a three-dimensional space.
  - ✓Stability over time.
- Temperature mapping should begin with an inspection of the facility, equipment and/or vehicle and should be re-evaluated as appropriate.

ENVIRONMENTAL MANAGEMENT SYSTEM CONT…

Facility temperature mapping

The following factors may contribute to temperature variability:

- Size of the storage space
- Location of controlling unit i.e conditioner
- Sun Facing wall
- Low ceilings or roofs
- Airflow inside the storage location
- Temperature variability outside the storage location
- Workflow variation
- Loading or storage patterns of product
- equipment capabilities e.g., defrost mode, cycle mode

RISK MANAGEMENT SYSTEM

QUALITY RISK MANAGEMENT

Risk Management System strategies should ensure but not limited to the following:

- Nature of the drug product.
- Distribution requirements on the readable container labelling.
- Exposure to adverse environmental conditions.
- Number of stages/receipts in the supply chain.
- Drugs at risk from freezing (vaccines, insulin, and biological products).

RISK MANAGEMENT SYSTEM CONT...

Examples of risks

- Vibration
- Temperature excursions
- Loss of container–closure integrity during storage and in transit
- Ingress of water or oxygen

CRITICAL & MAJOR OBSERVATIONS DURING WHO INSPECTIONS

CRITICAL & MAJOR OBSERVATIONS DURING WHO INSPECTIONS

Examples:

- Reject material stores for bulk products, sub-lots or intermediates
- Inadequate hold time studies for bulk materials
- Temperature monitoring and excursions in bulk storage areas
- Temperature mapping of the storage area
- Mix-up of bulk batches
- Label compatibility to storage temperature
- Loss of container–closure integrity during storage and in transit
- Inadequate studies on container-closure systems for bulks

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THANKS