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Application of QbD to Influenza Vaccines

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ABSTRACT

The vaccine is a biological preparation that is used as a preventive inoculation to confer immunity against a specific disease, usually employing an innocuous form of the disease agent; as killed or weakened bacteria or viruses, to stimulate antibody production. Nowadays there has been vast research in the field of different subspecialties of Vaccines such as Human Vaccines such as Qbd to Influenza Vaccine, Immunology, Quality by design (QbD) is an essential part of the modern advance to pharmaceutical quality. QbD is the best key to build a quality in all pharmaceutical products. The base of Quality by design is ICH Guidelines Q8 for Pharmaceutical for development, Q9 for quality risk management, Q10 for pharmaceutical quality systems.

INTRODUCTION

Quality

In Quality by Design, Quality is an important word. So Quality is 'Standard or suitability for intended use.' This term includes attributes such as the identity, potency, and purity.

Quality by Design

Pharmaceutical industries are alert to product quality, safety, and efficacy. Product quality has been increasing by implement scientific tools such as QbD (Quality by Design). Scientific approaches will provide the clear and sufficient knowledge from product development to manufacturing. These QbD tools will minimize the risk by increasing the output and quality. Nowadays, QbD approach has been successfully implemented in common formulation development. USFDA has released specific QbD guidance for the immediate and extended release of drug products as well as biotechnological products. Regulatory authorities are always proposing the implementation of ICH quality guidelines Q8 to Q11 [3]. According to ICH Q8 guidelines, QbD is defined as 'A systematic approach to development that begins with predefined objectives & emphasizes product, process understanding & process control, based on sound science & quality risk management'.[4] It means, to design & develop the formulation & manufacturing process to make sure predefined quality product. It requires an understanding of how product & process variables influence product quality. It is a systematic process to build the quality into the final product. QbD requires identification of all critical quality attributes and process parameters as well as determining the level to which any variation can impact the quality of the final product.

Target Product Profile (TPP)

Under this title Target is an important word. Target is nothing but a result that we try to achieve. So, in this, we target the drug profile or product which ensures desired quality, safety & efficacy. [10] TPP is defined as, 'A prospective summary of the quality characteristics of the drug product that ideally will be achieved to ensure the desired quality, taking into account safety & efficacy of drug product.'(ICH Q8) Target product profile should include.

- Dosage form

- Route of administration
- Dosage strength
- Pharmacokinetics Stability.

The TPP is a patient & labeling centered concept because it identifies the desired performance characteristics of the product related to the patient's need & it is organized according to the key section in the drug labeling. [11] Pharmaceutical companies will use the desired labeling information to construct a target product profile. The TPP is then used to design the clinical trials, safety & ADME studies as well as to design the drug product i.e. The QTPP.

Critical Quality Attributes (CQAs)

A CQA has been defined as 'a physical, chemical, biological or microbiological property or characteristics that should be within an appropriate limit, range or distribution to ensure the desired product quality'. Identification of CQAs is done through risk assessment as per the ICHQ9. Critical Quality Attributes are generally associated with the drug substance, excipients, intermediates and drug product. Critical Quality attributes include the properties that impart the desired quality, safety and efficacy. CQAs for biotechnological products are typically those aspects affecting product purity and stability. Drug product CQAs can be identified from the Target Product Profile. Use of strong risk estimation methods for identification of CQAs is new to the QbD standard.

Material Attributes

Material attributes can be an excipients raw material, drug substances, reagents, solvents, packaging & labeling materials. Material attributes can be quantified & typically fixed but sometimes can be changed during further processing. e.g. Impurity profile, porosity, specific volume, sterility.

Application of QbD to Influenza Vaccines

Vaccination

The word 'Vaccine' originates from the Latin Variolae vaccine (cowpox), which Edward Jenner demonstrated in 1798, could prevent smallpox in humans. Today the term 'vaccine'

applies to all biological preparations, produced from living organisms, that enhance immunity against disease and either prevent (prophylactic vaccines) or in some cases, treat disease (therapeutic vaccines). Vaccines are administered in liquid form, either by injection, by oral or by intranasal routes. Vaccination is the phenomenon of protective immunization. In modern concept, vaccination involves the administration (injection or oral) of an antigen to obtain an antibody response that will protect the organism against future infections.[8] Attenuated viruses are the genetically modified pathogenic organisms that are made nonpathogenic & used as vaccines. Attenuated strains of some pathogenic organisms were prepared by prolonged cultivation for weeks, months or years. Due to this, the infectious organism would lose its ability to cause disease but retains its capacity to act as an immunizing agent. The flu vaccine is the best protection against flu & its complications. Flu vaccine also helps to prevent spreading flu from person to person. The flu vaccine can not prevent all cases of flu, but it is the best protection against the acute respiratory diseases

Some people should not get this vaccine

1) If they have any severe, life-threatening allergies. E.g: Allergy to gelatin, antibiotics or eggs, you may be not to get vaccinated.

2) If you are not feeling well, then also not to get vaccinated (Table No. 1)

Table No. 1 Quality target product profile

Parameter	**Description**
Mechanism of Action	Type A –VAX is a pentavalent vaccine containing the capsular polysaccharide of 5 serotypes, each linked to a recombinant non –infectious virus-like particle (VLP).Expected to produced enhanced cellular antigen-specific protective immunity
Indication	Active immunization of 2-60-month-old infants and children for prevention of disease-related illnesses due to causative agents.
Indication	Active immunization of 2-60-month-old infants and children for prevention of disease-related illnesses due to causative agents.
Primary Endpoints	70% reduction of confirmed disease within 1 year after dosing in the target population, safe and tolerable
Key Claims	Easy to administer, 0.5ml subcutaneous delivery in an outpatient setting using a 1ml syringe. Stability-2 years at RT

Table No. 2 Type of vaccines

Type of vaccine	Example
Live-attenuated	Measles, Mumps, Rubella, Varicella Zoster
Inactivated	Hepatitis A, Influenza, Pneumococcal polysaccharide
Recombinant sub-unit	Hepatitis B
Toxoid	Tetanus, Diphtheria
Conjugate polysaccharide-protein	Pneumococcal, meningococcal, Haemophilus influenza type b (Hib)

Why Get Vaccinated?

Influenza (flu) is a contagious disease that spreads around the United States every year, usually between October and May. Flu is caused by influenza viruses and is spread mainly by coughing, sneezing and close contact. Anyone can get flu. Flu strikes suddenly and can last several days. Symptoms vary by age, but can include:

- Fever/chills
- A sore throat
- Muscle aches
- Fatigue
- A cough
- A headache
- Runny or stuffy nose

Flu can also lead to pneumonia and blood infections and cause diarrhea and seizures in children. If you have a medical condition, such as heart or lung disease, flu can make it worse. Flu is more dangerous for some people. Infants and young children, people of 65 years of age and older, pregnant women and people with certain health conditions or a weakened immune system are at greatest risk. Each year thousands of people in the United States die from flu, and many more are hospitalized. The flu vaccine can:

- Keep you from getting flu,
- Make flu less severe if you do get it, and

- Keep you from spreading flu to your family and other people.

Inactivated and recombinant flu vaccines

A dose of flu vaccine is recommended every flu season. Children 6 months to 8 years of age may need two doses during the same flu season. Everyone else needs only one dose each flu season. Some inactivated flu vaccines contain a very small amount of a mercury-based preservative called thimerosal. Studies have not shown thimerosal in vaccines to be harmful, but flu vaccines that do not contain thimerosal are available. There is no live flu virus in flu shots. They cannot cause the flu. There are many flu viruses and they are always changing. Each year a new flu vaccine is made to protect against three or four viruses that are likely to cause disease in the upcoming flu season. But, even when the vaccine doesn't exactly match these viruses, it may still provide some protection.

The flu vaccine cannot prevent:

- Flu that is caused by a virus not covered by the vaccine
- Illnesses that look like flu but are not.

It takes about 2 weeks for protection to develop after vaccination and protection last through the flu season.

Some people should not get this vaccine

- If they have any severe, life-threatening allergies.
- If they ever had a life-threatening allergic reaction after a dose of flu vaccine, or have a severe allergy to any part of this vaccine.
- If they ever had Guillain-Barré Syndrome (also called GBS). Some people with a history of GBS should not get this vaccine. This should be discussed with the doctor.
- If they are not feeling well. It is usually okay to get flu vaccine when one has a mild illness.

Risks of a vaccine reaction

With any medicine, including vaccines, there is a chance of reactions. These are usually mild and go away on their own, but serious reactions are also possible.Most people who get a flu shot do not have any problems with it. Minor problems following a flu shot include:

- Soreness, redness, or swelling where the shot was given hoarseness
- Sore, red or itchy eyes
- A cough
- Fever
- Aches
- A headache
- Itching
- Fatigue

If these problems occur, they usually begin soon after the shot and last 1 or 2 days. More serious problems following a flu shot can include the following:

- There may be a small increased risk of Guillain-Barré Syndrome (GBS) after an inactivated flu vaccine. This risk has been estimated at 1 or 2 additional cases per million people vaccinated. This is much lower than the risk of severe complications from flu, which can be prevented by the flu vaccine.

- Young children who get the flu shot along with pneumococcal vaccine (PCV13) and/or DTaP vaccine at the same time might be slightly more likely to have a seizure caused by fever.

Problems that could happen after any injected vaccine

- People sometimes faint after a medical procedure, including vaccination. Sitting or lying down for about 15 minutes can help prevent fainting, and injuries caused by a fall. Tell your doctor if you feel dizzy, or have vision changes or ringing in the ears.

- Some people get severe pain in the shoulder and have difficulty moving the arm where a shot was given. This happens very rarely.

- Any medication can cause a severe allergic reaction. Such reactions from a vaccine are very rare, estimated at about 1 in a million doses, and would happen within a few minutes to a few hours after the vaccination. As with any medicine, there is a very remote chance of a vaccine causing a serious injury or death.

Which statement about inactivated viral vaccines is incorrect:

1. Chemicals can be used to inactivate infectivity
2. They do not replicate
3. They can be dangerous if inactivation is not complete
4. Antigenic variation can make them ineffective
5. None of the above are incorrect

Cell-Culture Based Influenza Vaccine Production

Objectives

1) The modern cell-culture technology potentially allows for quick, efficient production.

2) Production of cell-derived vaccine requires little-advanced planning & many provide the response in the event of the virus. The influenza vaccine production process involves 5 fundamental steps:

a) Cell propagation/Preparation of substrate.

b) Virus propagation

c) Purification

d) Inaction & Splitting

e) Blending, Filling, & Approval.

a) Cell propagation/Preparation of substrate: Take the frozen, preserved cell culture from WBC cell line & grown in an incubator at 37°c. Then these cells are first grown in the small volume of culture medium, due to this cells are grown & multiply. Then transfer into successively larger containers.

b) Virus propagation: Once a high number of cells have been produced, Add influenza seed virus obtained from WHO diagnostic laboratory into cell containing bioreactor (Fermenter) where the virus infects the cells & multiplies & produce the more virus particles. After several days viruses destroyed the cell in bioreactors. The virus is harvested by removing the waste made by the cells and made noninfectious.

c) Purification: Using a centrifuge or chromatography, the virus is then separated from the cells and removes from the solution

d) Inactivation and splitting: A chemical process is used to inactivate the virus, stripping it of its ability to infect, for that formaldehyde is used, this is called as splitting. Then the surface antigen is separated and extracted from the virus.

e) Blending, filling, and approval: Noninfectious solution is blended, concentrated and filled into the sterile syringe. By using QbD the following parameters should be controlled during vaccine production process.

1. Cell propagation: In this step, limiting concentration of nutrients may be helpful for optimal cell growth. If high nutrient concentration then it inhibits cell growth. For that to do online monitoring of the nutrients concentration.

2. Virus prorogation: The following variable parameters controlled during the fermentation process

- pH: for maximum effectiveness of fermentation can be achieved by continuous monitoring pH i.e. It required most favorable pH.

- Temperature: Temperature control is important for the good fermentation process. If the temperature is lower then it causes reduced product formation & if it is higher then it affects the growth of organisms. For avoiding this, bioreactors equipped with heating & cooling system as per the requirement to maintain the reaction vessel at optimal temperature.

- Dissolved oxygen: Optimal supply of nutrients & oxygen, due to this it prevents the growth of toxic

- Agitation: Good mixing also creates a favorable environment for growth & good product formation. If agitation is excessive then it damages the cells & increases the temperature of the medium. Metabolic byproducts.

- Foam formation: Avoiding this parameter antifoam chemicals are used such as mineral oils, vegetable oils which lower the surface tension of the medium & causes foam bubbles to collapse. Also, mechanical foam control devices fitted at top of the fermenter.

3. Purification: In this step check the purity by using ion exchange chromatography & remove the impurity.

4. Inactivation: Optimum concentration of formaldehyde is used for inactivation of viruses.

Flu is a communicable disease that spreads around the US every winter in Oct.

Symptoms:

- Fever/chills
- A sore throat
- Muscle aches
- Fatigue
- A cough
- A headache

CONCLUSION

One of the most important concerns of the pharmaceutical industry is the fact that its primary customer, the patient, inherently cannot discern, by observation or by use, the quality of a product. Therefore, a pharmaceutical manufacturer has a responsibility to produce a quality product that ensures safety, efficacy, and performance.

Nosocomial transmission of vaccine-preventable diseases can be avoided thanks to immunization. The ideal coverage is dynamic for each disease, depending on the effective reproductive rate, which itself varies with the level of herd immunity in the population (from vaccination and infection) and the density of contacts.

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