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How are vaccines produced in the Biologics Manufacturing Centre?

A Biologics Manufacturing Centre expert conducting analytical tests in the quality control laboratory.

The Biologics Manufacturing Centre is designed to produce cell based vaccines and other biologics, including viral vector, protein subunit, and virus-like particles and other recombinant proteins.

What does all that mean?

Vaccines trigger an immune response without actually causing the illness. The key ingredient that makes a vaccine work is something called an antigen, which is a protein or group of proteins that causes an immune response in the body. The antigen used by most COVID-19 vaccines is called a spike protein.

The vaccine works by introducing safe amounts of the antigen into the body. The body doesn't recognize the antigen, considers it foreign, and tells the immune system to produce other proteins (called antibodies) that attack and neutralize the antigen. If the same antigen appears again as the actual virus, these antibodies will recognize it, and are ready to protect you from illness.

Using cells to produce the antigen

Since it's the key ingredient, clearly a large quantity of the antigen is needed to make millions of doses of a vaccine. But antigens don't grow on trees. And you can't buy them in the grocery store. So where do they come from?

In this type of vaccine, biomanufacturing experts introduce genes that carry antigen-producing information into cells. When the cells multiply, they act like microscopic factories producing large quantities of the antigen needed to manufacture the vaccine.

At the Biologics Manufacturing Centre, the cells are grown in bioreactors, where the growing conditions like nutrients, temperature, pH and oxygen levels are controlled to provide optimal conditions. The mixture inside the bioreactors is called a cell culture. The cell culture can be scaled up to larger volumes by transferring it from small-scale vessels to successively larger bioreactors.

The specific cell growth process may vary slightly depending on the type of vaccine being produced. In general, growing the cells and producing the antigen is called upstream processing and can take several days or weeks.

Separation and purification

When enough of the antigen is produced, the cell culture needs to be separated and purified. This removes impurities (called cell debris) and other substances that are required during cell growth, but aren't part of the final vaccine.

The process of separation and purification of the vaccine is called downstream processing and could take 3 to 5 days, depending on the specific process.

Once the downstream processing is complete, the result is the purified, concentrated, biologically active ingredient, called the drug substance.

A member of the Biologics Manufacturing Centre's production team testing a 2500 L mixer used during separation and purification in downstream processing.

Formulation

During formulation, the drug substance is diluted in a neutral solution to the exact concentration needed for final use. If the vaccine contains an adjuvant, which enhances the body's immune response and makes the vaccine more effective, this is also added during formulation.

Fill and finish

In the fill-and-finish area, the production team fills individual sterile vials using specialized machinery called aseptic filling equipment that ensures the final product is sterile and safe.

Once formulation is complete and the vials are filled, the result is the drug product, or the final vaccine.

Quality assurance

Once they are filled, each vial is carefully inspected before being labelled, packaged and put into cartons. The vaccine is then stored at a specific temperature until the quality assurance team confirms it meets all requirements and releases it for shipping.

Compliance with good manufacturing practices (GMP) is an integral part of the operation of the Biologics Manufacturing Centre. Quality assurance teams and quality control teams conduct constant testing and verification to ensure this compliance, which is supported by solid documentation at each step in the vaccine production process. GMP compliance and exhaustive quality assurance protocols are essential to ensure the products produced in the Biologics Manufacturing Centre consistently meet the required quality specifications and are safe for human use.

In addition to demonstrating that the production of each batch of vaccine is GMP compliant, as a new facility, the Biologics Manufacturing Centre must also demonstrate its overall compliance with GMP before being granted a drug establishment licence to allow vaccine production at all.

To that end, our teams have been working since June 2021 on the commissioning, qualification and validation process for more than 50 rooms and 250 pieces of equipment.

Current production process

The basic production process to make cell based vaccines is fairly consistent: grow cells to produce the antigen; separate and purify the drug substance; stabilize and formulate it; and fill vials to create the final drug product.

It may seem simple, but in reality, there is nothing simple about this process. Each vaccine has a unique production process and every facility is a little bit different. So even for biomanufacturing experts, the production process is like a whole new ball game every single time.

Teams from the NRC have been working with the facility's first vaccine sponsor, Novavax Inc., since March 2021 on the technology transfer for the Novavax COVID-19 vaccine. Technology transfer for small-scale batches is now complete. Engineering runs are planned for later this year to test and confirm that the process will produce the expected results at full commercial scale.

Read the other stories in this series to learn more: https://nrc.canada.ca/en/research-development/nrc-facilities/readying-biologics-manufacturing-centre

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