CHAPTER 18

IMMUNOLOGICAL PRODUCTS

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Abstract

Immunological products represent a specialized category of pharmaceuticals designed to stimulate, suppress, or modulate the immune system. This section explores various types of immunological products, including vaccines, immunoglobulins, and monoclonal antibodies. The principles of immunology underlying these products, such as antigen-antibody interactions and immune response mechanisms, are discussed. Vaccine development and production processes, including live attenuated, inactivated, and subunit vaccines, are examined in detail. The formulation considerations for immunological products, such as adjuvant selection, stabilization, and preservation, are addressed. Manufacturing processes specific to immunological products, including cell culture techniques, purification methods, and fill-finish operations, are explored. Quality control measures for immunological products, including potency assays, identity tests, and safety evaluations, are detailed. The challenges in developing and manufacturing immunological products, such as cold chain requirements and stability issues, are discussed along with mitigation strategies. Regulatory considerations specific to immunological products, including lot release requirements and post-marketing surveillance, are highlighted. Recent advancements in immunological product development, such as DNA vaccines and therapeutic cancer vaccines, are briefly explored to provide insight into future directions in this field

Keywords: *Vaccines, Antibodies, Immunomodulation, Adjuvants, Biological manufacturing, Potency assays*

Learning Objectives

After completion of the chapter, the student should be able to:

- Define immunological products and their role in healthcare.
- Classify different types of vaccines and their mechanisms of action.
- Explain the production processes for various types of vaccines.
- Discuss the formulation considerations for immunological products.
- Describe the quality control tests specific to vaccines and immunologicals.
- Outline the storage and handling requirements for immunological products.
- Analyze the challenges in developing and manufacturing new vaccines.

Immunity

Immunity can be natural or artificial, innate or acquired =adaptive, and either active or passive.

Active natural (contact with infection): develops slowly, is long term, and antigen specific.

Active artificial (immunization): develops slowly, lasts for several years, and is specific to the antigen for which the immunization (Vaccine) was given.

Passive natural (transplacental = mother to child): develops immediately, is temporary, and affects all antigens to which the mother has immunity.

Passive artificial (injection of gamma globulin): develops immediately, is temporary, and affects all antigens to which the donor has immunity.

Innate Immunity

The innate immunity system is what we are born with and it is non-specific; all antigens are attacked pretty much equally. It is genetically based and we pass it on to our offsprings.

Adaptive or Acquired Immunity

Lymphocytes come in two major types: B cells and T cells. **B cells** are produced in the **stem cells** of the bone marrow; they produce antibody and oversee humoral immunity. **T cells** are non-antibody-producing lymphocytes which are also produced in the bone marrow but sensitized in the **thymus** and constitute the basis of cell-mediated immunity.

There are two fundamental adaptive mechanisms: cell mediated immunity and humoral immunity.

Cell-mediated Immunity

Macrophages engulf antigens, process them internally, then display parts of them on their surface together with some of their own proteins. This sensitizes the T cells to recognize these antigens.

T cells are primed in the thymus, where they undergo two selection processes. The first *positive* selection process weeds out only those T cells with the correct set of receptors that can recognize the MHC molecules responsible for self-recognition. Then a *negative* selection process begins whereby T cells that can recognize MHC molecules complexed with foreign peptides are allowed to pass out of the thymus.

Cytotoxic or **killer T cells** (CD8+) do their work by releasing **lymphotoxins**, which cause cell lysis.

Helper T cells (CD4+) serve as managers, directing the immune response. They secrete chemicals called

lymphokines that stimulate cytotoxic T cells and B cells to grow and divide, attract neutrophils, and enhance the ability of macrophages to engulf and destroy microbes.
Suppressor T cells inhibit the production of cytotoxic T cells once they are unneeded, lest they cause more damage than necessary.
Memory T cells are programmed to recognize and respond to a pathogen once it has invaded and been repelled.

Active Immunity (Vaccines)	**Passive Immunity (Anti Sera/ Immunoglobulins)**
Slowly develops but long lasting effect	Quickly develops and immediate effect or temporary
Antigen containing preparation	Antibody containing preparation
Immunological memory present	No memory
Used mainly for Prophylaxis	Used for treatment
Both cell mediated and Humoral Immunity take part	Exclusively humoral immunity involved
Effective after a lag period	Immediate effect

Humoral Immunity

An immunocompetent but as yet immature B-lymphocyte is stimulated to maturity when an antigen binds to its surface receptors and there is a T helper cell nearby (to release a cytokine). This **sensitizes** or **primes** the B cell and it undergoes **clonal selection**, which means it reproduces asexually by mitosis. Most of the family of

clones become plasma cells. These cells, after an initial lag, produce highly specific antibodies at a rate of as many as 2000 molecules per second for four to five days. The other B cells become long-lived **memory cells**.

Antigen–Antibody Interaction

(a) **Complement fixation** (proteins attach to antigen surface and cause holes to form, i.e., cell lysis),
(b) **Neutralization** (binding to specific sites to prevent attachment—this is the same as taking their parking space),
(c) **Agglutination** (clumping),
(d) **Precipitation** (forcing insolubility and settling out of solution), and other more arcane methods.

Vaccines

1. Inactivated or attenuated microorganism
2. Subunit

Protein subunit–rather than introducing an inactivated or attenuated microorganism to an immune system (which would constitute a "whole-agent" vaccine), a fragment of it can create an immune response. Examples include the subunit vaccine against Hepatitis B virus that is composed of only the surface proteins of the virus (previously extracted from the blood serum of chronically infected patients, but now produced by recombination of the viral genes into yeast), the virus-like particle (VLP) vaccine against human papillomavirus (HPV) that is composed of the viral major capsid protein, and the hemagglutinin and neuraminidase subunits of the influenza virus.

3. Conjugate

Certain bacteria have polysaccharide outer coats that are poorly immunogenic. By linking these outer coats to proteins (e.g., toxins), the immune system can be led to recognize the polysaccharide as if it were a protein antigen.

This approach is used in the *Haemophilus influenzae* type B vaccine.

Valence

Monovalent (also called *univalent*) vaccine is designed to immunize against a single antigen or single microorganism.

Multivalent (also called *polyvalent*)–It is designed to immunize against two or more strains of the same microorganism, or against two or more microorganisms.

Type	**Live attenuated Vaccine**	**Killed vaccine**
Bacterial	Tuberculosis (BCG)	Cholera Typhoid Whooping cough
Viral	Small Pox Rubella Measles Yellow fever Mumps	Poliomyelitis Influenza Rabies
Rickettsial		Typhus
Toxoids	Diphtheria Tetanus	

Types of Vaccines	**Source**	**Storage and Route of Administration**
Cholera Vaccine	Vibrio cholera (2 strains-Inaba and Ogawa)	2-8°C and By Sub cutaneous route (S.C.)
BCG Vaccine (Freeze-Dried)	Bacillus of Calmette and Guerin strain of Mycobacterium tuberculosis var. Bovis.	2-8°C and by Intra cutaneous route
Small Pox	Vaccinia/Variola virus	2-8°C Puncture into skin

Types of Vaccines	Source	Storage and Route of Administration
(Freeze-Dried)		
Yellow fever vaccine	17 D strain of yellow fever virus	2-8°C and By Sub cutaneous route (S.C.)
Rabies vaccine (Freeze-Dried)	Rabies virus	2-8°C and By S.C. or I.M route
Typhus Vaccine	Rickettsia prowazeki	2-8°C and by S.C.
Polio Vaccine	Salk or inactivated/ dead polio vaccine pre- pared by three strains 1. Mahoney 2. MEF-1 3. Saukett. Inactivated by formalin	(Salk-parenteral) (Sabine-Oral)

Excipients

Beside the active vaccine itself, the following excipients are commonly present in vaccine preparations:

Aluminum salts (Aluminium Sulphate) or gels are added as adjuvants. Adjuvants are added to promote an earlier, more potent response, and more persistent immune response to the vaccine; they allow for a lower vaccine dosage.

Antibiotics are added to some vaccines to prevent the growth of bacteria during production and storage of the vaccine.

Egg protein is present in influenza and yellow fever vaccines as they are prepared using chicken eggs. Other proteins may be present.

Formaldehyde is used to inactivate bacterial products for toxoid vaccines. Formaldehyde is also used to kill

unwanted viruses and bacteria that might contaminate the vaccine during production.

Monosodium glutamate (MSG) and 2-phenoxyethanol are used as stabilizers in a few vaccines to help the vaccine remain unchanged when the vaccine is exposed to heat, light, acidity, or humidity.

Thimerosal is a mercury-containing preservative that is added to vials of vaccine that contain more than one dose to prevent contamination and growth of potentially harmful bacteria.

Sera

They immediately provide antibody for both prevention and treatment of established disease.

Horses are chief source for production but cattle, goats and sheep can be used.

Plasma is separated, diluted with water, digested with pepsin and fractionated with ammonium sulphate

Example–Botulinum anti-toxin, Diphtheria anti toxin, Gas gangrene (From Perfringens, Novyi, Septicum), Rabies antiserum, Tetanus anti-toxin

Toxoids

Prepared from Exo toxins which diffuse out from the cell during normal metabolic processes. Exo toxin produced from Corynebacterium diphtheria and Clostridium tetani.

They provide active immunity.

They are detoxified exo-toxins. Detoxification is done using Formaldehyde or Alum. Detoxification process removes toxicity but retains antigenicity.

END OF PREVIEW

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