Chapter 7

Special Considerations in Compounding Biologicals

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Introduction

Biological agents are used for the prevention, treatment, and cure of disease in humans. *Biological therapy* is sometimes referred to as *immunotherapy*. The term *biological* is used to distinguish agents isolated from natural sources and laboratory-produced versions of natural sources from chemically produced low molecular medications. Biological agents are difficult to identify or characterize, resulting in rigorous production processes. Robust oversight of the manufacturing of biological agents is required because standard chemical and molecular biology techniques may not detect changes to the biological molecule that could significantly alter the safety or efficacy profile. Within the U.S. Food and Drug Administration (FDA), the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) regulate the development, manufacturing, approval, access, and the safe and effective use of biologics within humans. The CDER regulates monoclonal antibodies (MABs), cytokines, immunomodulators and proteins, including recombinant versions. The CBER regulates vaccines, cellular products, gene therapy, allergenic extracts, antivenins, blood, and blood components.[1] These agents represent an array of products with many applications in medicine including cytokines, gene therapy, MABs, and the immunomodulator bacillus Calmette-Guérin (BCG).

The scope of this chapter encompasses the safe handling of commonly prepared therapeutic biological agents within an institutional or specialized compounding pharmacy.

Biological Agents

Vaccines

Vaccines are biological agents that strengthen the immune system to target certain infectious causes of disease. Vaccines have been developed against both viral and bacterial

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causes of infection. Vaccines that target specific viruses have proven to reduce the risk of certain types of cancer (e.g., Human Papillomavirus 9-valent Vaccine, Recombinant).[2] In 2010, the FDA approved the first vaccine therapy, sipuleucel-T, for the treatment of metastatic prostate cancer. This vaccine is designed to stimulate the T-cell immune response to an antigen highly expressed in prostate cancer cells.[3] Other vaccines targeting various aspects of cancer propagation are presently being studied.

Cytokines

Cytokines are proteins produced by white blood cells (WBCs) that are involved with signal transduction pathways within the human body.[4] There are three types of therapeutic cytokines: interferons, interleukins, and hematopoietic growth factors. Interferons and interleukins activate specialized WBCs to enhance the body's natural immune response.[4] Hematopoietic growth factors stimulate the proliferation of the bone marrow in the setting of neutropenia and anemia.[5] Cytokines are used therapeutically in the treatment of cancer, hepatitis, neutropenia, anemia, and multiple sclerosis.

Monoclonal Antibodies

MABs are used to treat cancer, autoimmune, cardiac, neurological, and infectious diseases. MABs are not conventional cytotoxic agents because they do not damage the genetic material of cells directly or indirectly. MABs have several mechanisms of action. In general, these agents typically bind a specific antigen, and the effect may be either an enhanced or suppressed immune response. In targeted therapy, MABs interact with specific molecules that interfere with tumor growth and progression. For example, MABs like rituximab stimulate an immune response by targeting proteins present on the surface of cancer cells that are not present on healthy cells. Other MABs suppress immune response by binding to proinflammatory agents, thereby disabling receptor binding and the subsequent downstream response.[6]

MABs' low risk of occupational exposure is attributed to their large molecular structure and poor absorption via dermal, mucosal, and inhalation exposure.[6] Nonconjugated MABs, with the exception of pertuzumab, have been excluded from the NIOSH 2016 hazardous drug list and can be handled as nonhazardous agents.[7] MABs, when coupled with a chemotherapeutic agent (e.g., ado-trastuzumab emtansine) or a radioactive substance, must be handled as hazardous drugs. MABs developed in the future must be assessed for potential risk of occupational exposure.

Gene Therapy

Gene therapy is the introduction of genetic material into an individual or modification to an individual's genetic material to achieve a therapeutic outcome.[8] Gene therapy research encompasses the investigation of treatments for a diverse range of diseases including cancer, acquired immunodeficiency syndrome, cystic fibrosis, Parkinson disease, cardiovascular disease, and arthritis. Gene therapy uses viral and nonviral vectors to recognize certain cells and insert genetic material into the cells. Viral vectors are predominately used in research for intracellular delivery. Oncolytic viruses (OVs) are made from many different DNA and RNA viruses. OVs' mechanism of action begins by specifically infecting tumor cells, replicating, and destroying cancer cells while leaving the normal cells undamaged. In addition, OVs also create an immunological response to both itself and the infected tumor.[9] The drug, talimogene laherparepvec, is an oncolytic herpes virus for the treatment of advanced, inoperable melanoma.

Immunomodulators

BCG is an attenuated strain of *Mycobacterium bovis*. It was originally developed as a vaccine for the prevention of tuberculosis and is now an agent that is approved for cancer therapy. BCG is instilled intravesically for the treatment of bladder cancer, and it has a stimulatory effect on the immune system. The beneficial effect of BCG is believed to begin with a cascade of immunologic events causing the activation of T-cells, B-cells, macrophages, dendritic cells, and natural killer cells.[10]

BCG has a high risk for transmission. To avoid cross-contamination, other compounded sterile preparations (CSPs) should not be prepared in