Using Bugs as Drugs: Compounding Viral Vectors in Cell and Gene Therapies

Cell and gene therapies (CGTs) represent a transformative advancement in personalized medicine, offering treatment options for previously untreatable conditions. With over 40 FDA-approved agents and an increasing number of therapies entering clinical trials, understanding safe compounding practices for CGTs is essential for healthcare providers and pharmacists.

What is Cell and Gene Therapy?

Cell therapy involves manipulating cells (autologous or allogeneic) to treat diseases. Notable examples include CAR T-cell therapy and NK cell therapy for cancers, and regenerative therapies utilizing stem cells to repair tissues.

Gene therapy includes editing or introducing genetic material to correct genetic diseases. CRISPR Cas9 and viral vectors (adenovirus, adeno-associated virus [AAV], lentivirus, retrovirus) are prominent gene therapy methods. Viral vectors deliver therapeutic genetic material directly into patient cells or modify cells *ex vivo* before reintroduction into the patient.

Manufacturing and Compounding Roles

Cell therapies typically involve direct cell handling, often bypassing traditional pharmacy compounding. Viral vectors, however, require compounding before administration.

Manufacturing of viral vectors (*e.g.*, AAV) involves highly controlled aseptic processes, utilizing stringent contamination control strategies. These vectors are then distributed to pharmacies in sterile, frozen forms for compounding and administration.

Risk Assessment for CGT in Pharmacy Settings

Overall, the risk of occupational exposure to CGTs is substantially lower than traditional chemical-based hazardous drugs (HDs):

- **Genetic Engineering**: Viral vectors (adenovirus, AAV, lentivirus, retrovirus) are engineered to prevent replication (adenovirus, AAV) and disease-causing capabilities of the native viruses.
- **Size and Exposure**: CGT agents are much larger molecules than most traditional NIOSH HDs, substantially reducing risks of dermal absorption. Primary risks are inhalation, mucous membrane exposure, ingestion, and accidental injection.

However, certain risks still exist:

- **Allergic Reactions and Seroconversion**: Exposure to viral proteins can trigger immune responses, potentially limiting future therapy effectiveness.
- **Replication Competent Contaminants**: Improper handling or manufacturing issues may lead to unintended replication.
- **Specific Biological Hazards**: Some biological-based therapies (*e.g.*, BCG) maintain infectious risks and require specific biosafety considerations.

Where Should Compounding Occur?

CGTs present unique hazards distinct from traditional NIOSH-defined HDs. The risks are classified through Biological Safety Levels (BSLs), with most CGTs classified at BSL-2 due to slight-to-moderate biohazard risks.

- **Recommended**: Compound CGT within a USP <800> compliant hazardous drug cleanroom. This strategy meets most of the criteria for handing BSL-2 agents.
- **Alternative**: A thorough risk assessment might justify compounding in a non-hazardous cleanroom environment, particularly with lower-risk therapies (*e.g.*, certain AAV-based vectors).

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Decontamination Practices for CGT

Decontamination recommendations depend on the therapy type:

- **Virucidal Agents**: Instructions commonly recommend chemical disinfectants proven effective against specific types of viruses or more robust organisms (*e.g.*, bacterial spores).
- **Specific Recommendations**: Some manufacturers of viral vectors specify the use of sodium hypochlorite or hydrogen peroxide with extended wet contact times.

Enveloped viruses (lentivirus, retrovirus) are generally easier to inactivate with chemical agents than non-enveloped viruses (adenovirus, AAV) and mycobacteria (*e.g.*, BCG).

- **EPA Registration and Compatibility**: Current IFUs and guidelines for CGTs rarely account for "musts" or "shoulds" in USP <797> or considerations such as material compatibility. Until more studies are available, it is recommended to use the strongest disinfectant in your rotation for decontamination after compounding cell and gene therapy. This will be sporicidal disinfectants like peracetic acid/hydrogen peroxide or bleach. One can also consider extending (*e.g.* double) the wet contact times prescribed for bacterial spores, especially in cases of a spill.

Final Recommendations and Considerations

- **Holistic Control Strategy**: Utilize multiple redundant contamination controls and comprehensive SOPs.
- **Biosafety Training and Spill Kits**: Specialized staff training, clearly defined SOPs for spill management, and biohazard-specific spill kits are critical.
- **Infrastructure**: Ensure adequate storage (ultra-low freezers), thawing conditions, time limits for administration, and waste management strategies aligned with biohazard disposal guidelines.

As the field evolves, pharmacists must remain informed through continuous education and clear communication with manufacturers and internal infection control teams.

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