Gene Therapy Risk Assessment

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Background

Luxturna (voretigene neparvovec-rzyl) is a gene therapy medication used to treat patients with inherited retinal disease due to a mutation in their RPE65 gene. It is a one-time gene therapy treatment that has the potential to restore vision. Luxturna was approved for use in Canada in March 2022; Alberta Health Services (AHS) received a request to compound Luxturna for a patient shortly after.

Gene therapy is a relatively new and rapidly evolving treatment. Gene therapy clinical trial processes do not include an assessment or any clear information on the potential risk to the health care setting or health care personnel. Legislation and compounding standards have not yet caught up to the practice which has resulted in incomplete information regarding minimization of exposure and reduction of risk.

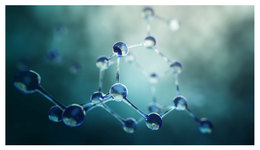
Pharmacy Services is left to develop their own polices and procedures for safe compounding practices. In order to develop these policies and procedures, Pharmacy Services required a resource to assist in the risk identification.

Understanding Biologics

Biologic medications, including gene therapy medications, are typically larger and more complex than chemically produced pharmaceutical medications. In Canada, biologic medications are listed in Schedule D of the Food and Drugs Act.

Biologic medications come from living organisms or their cells and are often made using advanced biotechnology processes. They are used to treat diseases and medical conditions, including but not limited to:

- anemia
- diabetes
- psoriasis
- genetic conditions
- hormone deficiency
- rheumatoid arthritis
- some forms of cancer
- inflammatory bowel disease



Biologic medications are also used as replacement therapies for blood proteins and vaccines to prevent bacterial and viral infectious diseases.

The type and level of risk associated with a biologic medication varies.[1] The biosafety risk level of biologic medications differs from the National Institute for Occupational Safety and Health (NIOSH) hazardous medication classification. “NIOSH criteria can be used to identify drugs with mutagenic, carcinogenic, or teratogenic properties, it falls short of identifying biologic drugs as hazardous.”[2]

Process

To support safe handing and compounding practices Pharmacy Services needed a way to identify the possible risks and resulting mitigation strategies, specific to gene therapy. A tool that would assist in this process was developed, in a similar fashion to a hazardous medication risk assessment, with the assistance of the Canadian Biosafety standards, and guidelines for handling of biologic material in a laboratory setting.

Step 1. Identify Risk Group

The risk group identifies the likelihood to cause human or animal disease, and to what degree. Each of the four risk groups has a resulting biosafety containment level, which outlines the containment parameters required when handling the medication.

Risk Group 1 (RG1)

- Low individual and community risk
- Unlikely to cause human or animal disease

Risk Group 2 (RG2)

- Moderate individual risk, low community risk
- May cause human or animal disease but is unlikely to be a serious hazard to personnel, the community, or the environment
- Exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited

Risk Group 3 (RG3)

- High individual risk, low community risk
- Causes serious human or animal disease but does not ordinarily spread from one infected individual to another
- Effective treatment and preventive measures are available

Risk Group 4 (RG4)

- High individual risk, high community risk
- Causes serious human or animal disease that can be readily transmitted from one individual to another, directly or indirectly
- Effective treatment and preventive measures are not usually available

Step 2. Review Exposure Risk

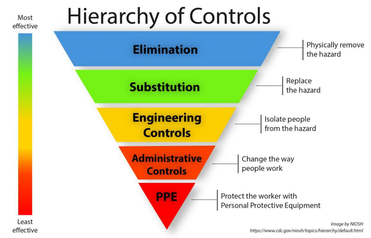
Identification of what type of exposure risks could exist needed to be identified to support appropriate mitigation strategies.

Common routes of possible exposure include:

- Accidental injection (needlestick injury)
- Eye contact
- Aerosol generation/ inhalation risk
- Spill risk
- Skin contact
- Accidental ingestion
- Mucus membrane
- Inhalation

Step 3. Assess Options for Risk Mitigation

Appropriate risk mitigation strategies are required for the exposure risks identified. Risk mitigation strategies should take into consideration the Hierarchy of Controls as outlined by NIOSH[4]:



It is unlikely that we will be able to eliminate or substitute the hazard, as the medication is required by patients. We can ensure secondary engineering devices and appropriate infrastructure are in place, that appropriate deactivation agents are used, and that appropriate personal protective equipment (PPE)requirements are outlined.

Step 4. Summarize Assessment

A final assessment summary is provided indicating detailed information on the risk and resulting risk mitigation recommendations. The appropriate controls that will be required to support safe compounding practices
will be outlined.

Agent Specific Toolkits

Biologic medications usually require specific storage, shipping, and handling. They also require specific compounding processes and risk mitigation strategies. To simplify processes and ensure information was available for personnel, agent specific toolkits were developed. Product monographs, company facilitated product specific training, and resources provided by the company were used to support the creation of the toolkit.

The toolkit includes the following information:

- Risk group level
- Containment level
- Medication
- Receiving
- Safe handling
- Storage
- Disposal
- Transportation
- Exposure
- PPE
- Spill management

Conclusion

The world of medicine is constantly evolving, and with that Pharmacy practice also continues to evolve. Safe handling and compounding processes within Pharmacy Services are essential for the protection of both personnel and patients. In order to ensure we have safe practices, we need tools, policies and procedures to align with current practices.

The Canadian Biosafety Standards and Guidelines outline safe practices in laboratory settings for the handling of biologics such as gene therapy. These standards are less detailed than pharmacy legislative standards such as United States Pharmacopeia (USP) <800> and the National Association of Pharmacy Regulatory Authorities (NAPRA) model standards for pharmacy compounding of Hazardous Sterile Preparations.

Although not as detailed, Pharmacy Services can overlay the Canadian Biosafety Standards with USP and NAPRA standards to:

- develop polices and procedures
- evaluate infrastructure requirements
- develop risk mitigation strategies

References

1. Health Canada- Biologics, radiopharmaceuticals, and genetic therapies, [cited 2021-September- 10] available at: Biologics, radiopharmaceuticals and genetic therapies - Canada.ca
2. Blind JE, McLeod EN, Brown A, Patel H, Ghosh S. Biosafety Practices for In Vivo Viral-Mediated Gene Therapy in the Health Care Setting. Appl Biosaf. 2020 Dec 1;25(4):194-200. doi: 10.1177/1535676020942195. Epub 2020 Dec 1. PMID: 36032390; PMCID: PMC9134634.
3. Health Canada- Canadian Biosafety Guidelines Pathogen Risk Assessment{cited 2023-June-13} available at: Canadian Biosafety Guideline Pathogen Risk Assessment - Canada.ca
4. Hierarchy of Controls | NIOSH | CDC