U.S. ARMY PUBLIC HEALTH CENTER

TIP No. 98-131-0121

Preventing Occupational Exposure While Compounding Monoclonal Antibody Therapy

PURPOSE

To discuss potential occupational exposure from pharmacological preparations of monoclonal antibody (mAb) treatments and describe controls which can be implemented to prevent such exposures, as related to novel mAb treatments for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), the cause of Coronavirus Disease 2019 (COVID-19).

INTRODUCTION

The COVID-19 pandemic has encouraged many pharmaceutical companies to research and develop novel treatments for use against SARS-COV-2. Approaches have ranged from investigating new uses for existing approved pharmaceuticals to developing new pharmaceuticals and biologics. Under normal circumstances, the pharmaceutical companies developing new drugs would utilize a standardized research and development process—normally taking years to accomplish, followed by a lengthy, U.S. Food and Drug Administration (FDA)-mandated clinical study prior to the issuance of a Use Authorization. However, due to the wide impact of COVID-19, the FDA has utilized the Emergency Use Authorization (EUA) for a number of treatments for SARS-COV-2 (FDA, 2020). These include two new mAb treatments, Bamlanivimab® and Casirivimab®/Imdevimab® cocktail, developed by Eli Lilly and Regeneron Pharmaceuticals, respectively (FDA, 2021).

BACKGROUND

Monoclonal antibodies are laboratory-produced molecules that act as substitute antibodies and can restore, enhance, or mimic the human immune system's destruction of harmful cells, both native and invasive. The clinical use of mAb treatments was first introduced in in the United States in 1992, when the FDA approved muromonab-CD3 to prevent rejection of transplants. Between 1992 and 2015, the FDA approved 37 additional mAb to be used clinically. Initially, the National Institute for Occupational Safety and Health (NIOSH) determined that all mAb treatments should be classified together and handled as hazardous, but in 2014 NIOSH removed nearly all the mAb treatments from its listing of hazardous drugs (Kirsa, 2016). This was done due to a further refinement and study of the classes of mAb treatments. Since 2015, the FDA has approved over 68 new mAb for therapeutic use (Cai, 2020), and most of those drugs have not yet been evaluated by NIOSH to determine if they should be handled as hazardous drugs.

OCCUPATIONAL EXPOSURE POTENTIAL

The limited research regarding occupational exposure while compounding and delivering mAb treatments indicates the risk of exposure is minimal, but not zero (Graham, Hillegass and Schulze, 2020). The occupational exposure potential specific to compounding Bamlanivimab® and Casirivimab®/Imdevimab® has not been determined. Since the risk is unknown the prudent course of action would be to assume the greatest risk until further information is available. The following discussion on potential occupational exposure is based on general mAb treatments and not specifically on mAb treatments for SARS-COV-2.

Due to the mechanisms of compounding mAb, the two primary routes of exposure are dermal and inhalational.

Potential Dermal Exposure Route

The risks presented from dermal exposure to mAb are primarily localized and are generally not systemic. Compounds that can cause a systemic reaction must penetrate the dermal layer of the skin in sufficient quantity to elicit a response. It is generally accepted that compounds that are larger than 0.5 kilodaltons (kD) cannot sufficiently penetrate the dermis to create a therapeutic level in the blood (Bos and Meinardi, 2000). Based on the average mAb weight, in the range of 10-100 kD, it has been assumed that they pose no dermal penetration risk since they will not reach therapeutic levels in the body. More recent research suggests that the 0.5 kD assumption may be inaccurate, and small quantities may traverse the dermis, which could result in detectable sub-therapeutic levels (de Lemos, 2018). The greater dermal risk presented by exposure to mAb is localized irritation.

Potential Inhalational Exposure Route

The potential for inhalation of mAb treatments during compounding poses the greater risk for systemic effects from exposure. If inhaled, the majority of the treatment will be absorbed and enter the blood stream. Although the risk for systemic effects is greater via inhalation, the overall risk of occurrence is still low. When compounding is conducted correctly, ideally no drug is aerosolized. However, even when following standard compounding routines, aerosolization can occur and result in an occupational exposure if no controls are in place.

OCCUPATIONAL EXPOSURE CONTROL MEASURES

Controlling occupational exposures is best described in NIOSH’s Hierarchy of Controls. The hierarchy describes five descending levels of control, each of which is more dependent on the user and therefore less desirable. The first two levels of controls cannot currently be used with mAb, as eliminating their use and substituting something else in their place is not acceptable. The remaining three controls—Engineering, Administrative, and Personal Protective Equipment (PPE)—can all be used to help reduce and potentially eliminate exposure to mAb while compounding.

Engineering Controls

Bamlanivimab and the Casirivimab/Imdevimab cocktail require compounding utilizing aseptic techniques (Eli Lilly and Company, 2020 and Regeneron Pharmaceuticals, 2020). The use of aseptic techniques often requires the use of engineering controls, not to protect the individual compounding, but to protect the product from adulteration. The specifics for aseptic compounding are defined by the United States Pharmacopeia (USP) General Chapter <797>, Pharmaceutical Compounding – Sterile Preparations (2008).

Although the engineering controls that are required for aseptic compounding are intended to protect the product, certain pieces of equipment will afford the worker protection as well. Examples include Biological Safety Cabinets (BSC) and Compounding Aseptic Containment Isolators (CACI). All of these controls will help capture any potentially airborne mAb that may be generated during the compounding process, thereby reducing the potential inhalation risk.

Administrative Controls

Administrative controls include, but are not limited to, warning signs, training, and limiting the workforce to authorized personnel. Warning signs and hazard training both notify the workforce of potential hazardous processes occurring and provide the knowledge required for the workforce to take measures to avoid exposure. Specific training on proper handling and proper risk communication will also reduce the potential for worker exposure. By limiting the work of compounding mAb to occur only within the engineering controls and limiting access to the area to authorized personnel only, the potentially exposed workforce is significantly reduced.

Personal Protective Equipment

Using PPE is the least desirable control as it is completely dependent on the worker. Again, the aseptic technique required for compounding Bamlanivimab and the Casirivimab/Imdevimab cocktail require the use of certain PPE. The gloves and gowns required, although intended to keep the mAb pure and unadulterated, also serve to protect the worker who is conducting the compounding from unintended dermal exposures.

RECOMMENDATIONS

The risk of occupational exposure to Bamlanivimab and the Casirivimab/Imdevimab cocktail during compounding is unknown, due largely to their minimal time on the market. However, by utilizing proper aseptic techniques, the risk from dermal and inhalational exposure is minimized (Kirsa, 2016). Until more is known about the potential effects of occupational exposure to these products, measures to reduce exposure should be employed, including:

1. Prepare mAb treatments using engineering controls that protect the product as well as the worker (i.e., BSCs or CACIs)
2. Post warning signs and limit access to authorized personnel only.
3. Provide job-specific training and risk communication.
4. Utilize proper PPE (as outlined in the product insert).

POINT OF CONTACT

The U.S. Army Public Health Center point of contact is the Industrial Hygiene Field Services Division of the Occupational Health Sciences Directorate; Commercial: 410-436-3118, or DSN: 584-3118.

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Dated: January 2021

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