

# The evaluation and safe handling of ADCs and their toxic payloads: Part 2

The handling of antibody-drug conjugates (ADCs) in R&D and manufacturing environments requires careful examination of potential health effects that may be caused by occupational exposure and the control measures needed to protect workers from these effects. In this second article of a two part series, **John Farris** and **Robert Sussman**, SafeBridge Consultants, cover safe handling of ADCs

**A comprehensive programme required to proactively** establish that ADC materials are handled safely and that employees are properly protected from exposure should include the following:

- Employee selection
- Employee training
- Work practices, process designs and engineering controls
- Personal protective equipment (PPE)
- Cleaning and waste disposal (routine)
- Spill response (emergency)
- Industrial hygiene monitoring
- Medical surveillance (including reproductive and developmental issues)
- Record keeping
- Transportation

Written procedures for handling payloads, payload-linkers, and ADCs should be established for each unit operation including specific information on the appropriate precautions and controls for each activity.

The process designs for each facility handling payloads and ADCs should include effective strategies for process containment and enclosure, ventilation and PPE to assure worker protection. Appropriate use of these strategies will also reduce the risk of a significant spill or upset, and may prevent the loss of valuable materials, production setbacks or impairment of an employee's health. Key steps in the pharmaceutical processes require particular attention and include operations where powders are handled. Liquid handling steps are also a concern and must be controlled where the potential for creation of liquid aerosol droplets exists.

For many unit operations, good work practices by employees are critical in controlling chemical exposure. Individual workers, whether they are in the lab, production, QA/QC, packaging, shipping and receiving, and regardless of their age or experience can positively or negatively impact their exposures. The proper use of engineering controls, correct work practices and procedures, and of PPE can enable the employee to limit their exposure to hazardous materials.

## Powder handling

To prevent contamination and overexposure, powders should not be handled in the open. Operations, such as sampling, and weighing and dispensing should only be carried out in a closed containment system such as an isolator unless air monitoring data indicate that an equivalent ventilated containment system (such as a ventilated balance enclosure) is effective. If powders are to be transferred outside of containment, they should be put into solution or into a closed and sealed container.

## Solution handling

Solutions containing the payload, ADC, or both should only be handled inside a containment system or with local exhaust ventilation during procedures unless there is high degree of certainty that there will be no potential for aerosolisation. If the procedures have the potential for producing an aerosol (e.g. vortexing, pipetting, transfer under pressure), solutions must be handled in a chemical hood, biosafety cabinet or other effective containment system (such as a glove bag). Closed in-line sampling devices for solutions are strongly recommended (for batch processes as applicable). At a minimum, liquids should be sampled in a chemical hood or biosafety cabinet for laboratory sampling operations. All liquid and powder residues must be cleaned up promptly to reduce the opportunity for subsequent airborne and skin exposure.

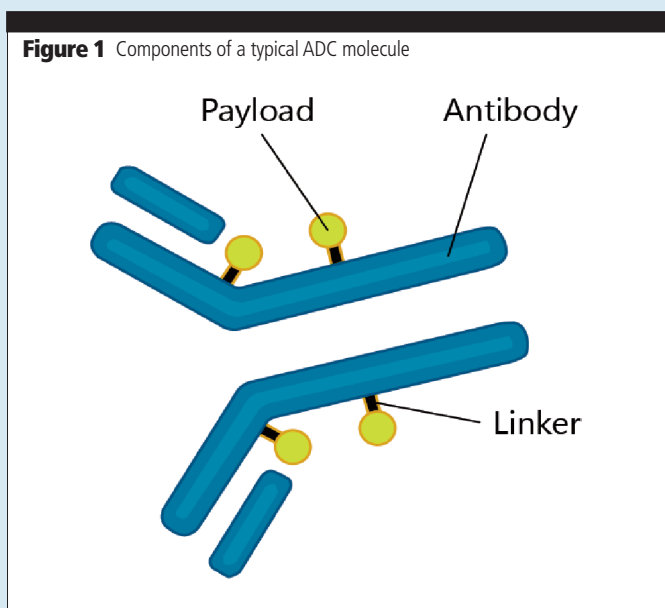
## Facility features and engineering controls

Facility features can present a challenge depending on the other operations in a given facility. Where powders are handled and the primary concern is potential occupational exposure to extremely toxic materials one set of recommendations may apply. Once powders are in solution and antibodies are introduced to complete the conjugation reaction, GMP-related concern regarding protection of the purity of the product will drive the recommendations. The following facility feature recommendations apply primarily to the areas where powder handling will take place. The solution handling areas should follow guidance for typical sterile pharmaceutical production.

**HVAC and air pressure relationships:** A separate and dedicated heating, ventilation, and air conditioning (HVAC) system is recommended. A negative differential air pressure relative to surrounding areas should be established in processing areas. Room air locks/anterooms are recommended to create buffer zones for a means of establishing air pressurisation differentials and to be used as gowning and degowning areas. An alarm or monitoring system should be in place to alert operators in the event of failure of the air pressurisation system. Unidirectional personnel traffic flow (i.e. separate entry and exiting) is preferred with a separate material airlock for movement of equipment and processing materials.

**Air changes and airflow:** Air changes must meet local building code occupancy class and must be maintained as appropriate for comfort. Airflow (distribution) should minimise air currents in the room and turbulence at open-faced hoods. Supply air should be delivered through perforated ceiling panels (or equivalent) rather than vane style air diffusers.

**Recirculation and filtration of room air:** The recirculation of room exhaust air is not recommended to



prevent the reintroduction of particles to the work environment in the event of undetected filter breach. HEPA filtration of room exhaust air is required for manufacturing areas prior to discharge to atmosphere. Recirculation of air from control devices is not recommended as this may also reintroduce particles into the work environment in the event of undetected filter breach. Safe change (i.e. bag in/bag out) exhaust air filtration systems are required on facility exhaust and on the exhaust of control devices to prevent exposure during filter change and other maintenance activities. Air purifying respirators and chemical protective clothing should be used during these operations.

**Changing areas:** Separate and dedicated changing facilities are not necessarily required for laboratories; however, laboratories should be equipped with areas to safely store, put on and take off PPE. The use of an airlock leading to the laboratory is preferred. For clinical and commercial manufacturing operations, adjoining gowning areas are required. A separate adjoining degowning area is required (by use of the room airlock). Misting water showers are recommended for personnel decontamination based on laboratory activities and are required for clinical and commercial manufacturing activities. Air showers are not recommended for personnel decontamination.

**Designated areas:** An area designated for handling pharmaceutical compounds is required. Work surfaces should be easily cleanable and free from cracks, crevices, and hard-to-clean designs or surfaces. Access to the area should be restricted to those properly training with a business reason to enter.

### Specific operational guidance

**Payload synthesis:** Procedures involving work with powders should be performed in isolators. Procedures with liquids should also be performed inside isolators, unless properly designed industrial hygiene air monitoring studies have demonstrated that there is little or no potential for aerosolisation of liquids and that open-faced ventilation controls such as chemical hoods or other well-designed ventilated enclosures are appropriate.

Chemical synthesis (including additions, reactions, heating, reflux, cooling, work ups, separation, liquid/liquid and liquid/solid extraction, filtration) should be carried out using good lab practices in an isolator or other ventilated containment system verified for effectiveness by industrial hygiene monitoring.

Processes using organic solvents should be handled in a chemical hood or other ventilation system verified for effectiveness. The open charging of vessels should be avoided and materials should be handled in solution when possible. Rotary evaporation must be carried out in a chemical hood using closed transfer techniques.

Laboratory scale drying must be carried out within an appropriate control system verified for effectiveness (laboratory bench hood, ventilated enclosure or isolator) or in a lab scale contained filter dryer. Clinical or commercial scale drying must be carried out within an isolator.

Milling and size reduction are not recommended for these powders. If required, size reduction operations should be carried out in an isolator.

Conjugation Procedures involving powders (weighing & solubilisation) must be carried out in isolators.

**Purification and filtration:** Liquid conjugation reactions, filtration, purification, etc. must be done in a chemical hood or biosafety cabinet at a minimum. Work should be carried out behind sashes and sashes should be completely closed for operations left to run. All equipment should be double contained and liquid transfer lines double clamped (particularly for transfer lines under pressure) or, at a minimum, single clamped when luer fittings are used.

**Filling:** Laboratory procedures involving manual liquid filling should be performed within a biosafety cabinet at a minimum. Clinical and commercial procedures involving manual or automated filling must be done in an isolator.

**Lyophilisation:** Lyophilisation control requirements should be assessed based on the physical nature of the ADC after it is freeze dried. The physical form can range from light fluffy electrostatic powders to hard cakes. The light powders are significantly more difficult to control and can require the lyophiliser to be integrated into an isolator. Controls should match the exposure risk. Lab scale lyophiliser faces, at a minimum, should be equipped with custom designed (engineered) local exhaust ventilation (LEV) and with exhausted air filtered and discharged out of the facility, utilise automated loading and unloading or integrated and/or contained within an isolator system depending on the scale of the equipment. Clinical and commercial scale lyophiliser faces must be equipped with engineered LEV, utilise automated loading and unloading, or integrated and/or contained within an isolator system.

**Cleaning:** The high toxicity and uncertainty of exposure potential means that other ancillary activities such as cleaning may lead to exposure to trace levels of residues. This exposure can occur during manual cleaning of contaminated equipment and may be significant. Cleaning techniques that avoid contact with contaminated surfaces, are effective at removing the contaminants and prevent inadvertent spreading of residues should be developed.

### Personal protective equipment (PPE)

Depending on the specific task to be performed, full-coverage protective clothing (sleeve covers, lab coats, disposable Tyvek® coveralls, nylon coveralls, etc.) may be required. Decisions regarding the types of protective clothing should be determined on a case-by-case basis after completing an activity-specific chemical risk assessment. Two layers of latex, nitrile or neoprene gloves should be used at all times when handling payloads and/or ADCs. Selection of gloves should be based on both reagent chemicals in use and the operations to be performed. During pilot scale operations and any operations where contact with the material and the wrists or forearms is possible, use gloves that cover the forearms or use disposable sleeve covers. Gloves should be changed and discarded any time

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glove puncture or abrasion is suspected. They should also be changed or cleaned thoroughly any time contamination is suspected and periodically during the activity regardless of whether or not there is any known contamination. If ADC materials are dissolved in organic solvents or if an organic solvent is used to clean contaminated process equipment, laboratory equipment or work surfaces, then the appropriate solvent resistant glove material should be selected. Gloves and sleeve covers should be removed 'aseptically' (inside out without touching the outer surface of the glove).

Effective eye protection should be mandatory for all laboratory and production activities. For some activities, safety glasses with side shields are sufficient protection. For other activities involving larger quantities of material or more potential for eye contact, chemical goggles or a face shield may be needed. Each task or work area should be evaluated to determine the appropriate level of eye protection.

Respiratory protection is a complex technical area and must be dealt with by trained professionals. The individual who was responsible for selecting respiratory protection and administering the respirator programme should evaluate the need for respirators when handling payloads and ADCs for each unit operation. A NIOSH rated powered air-purifying respirator (PAPR) with HEPA cartridges and a doubled-bibbed Tyvek® loose fitting face piece or a supplied-air respirator (SAR) should be worn until it has been confirmed that less respiratory protection is required. The air sampling of unit operations will help confirm appropriate respiratory protection requirements.

### Training

In accordance with OSHA's Hazard Communication standard, all employees should receive initial training in the toxicity and signs or symptoms of overexposure to the drugs and materials being handled. In countries outside the US, similar regulations apply. Training should include health effects applicable to the specific ADC and its payload. Many abstract concepts must be explained, such as the idea that unacceptable levels of these substances may be present in the working environment and may not be detectable by one's senses. Proper techniques and procedures when working with ADCs and their component materials should be covered and should be tailored to the specific tasks being performed and the specific equipment being used. Employees should report any signs or symptoms of possible overexposure to their supervisor, and health and safety personnel. There is a significant potential risk for developmental toxicity with many ADCs and pregnant employees should be informed as such. These issues should be handled according to the company's reproductive health policy.

### Industrial hygiene monitoring

Baseline industrial hygiene air monitoring should be performed for all activities involving the handling of payloads (and potentially ADCs) using validated air sampling methods. Sampling and analytical methods must be developed in advance of any monitoring survey by an industrial hygiene laboratory experienced and knowledgeable in pharmaceutical analysis. Where OELs are extremely low, effective analysis of these materials in the air may be difficult. Typically, analytical methods require levels of detection in the picogram range to achieve appropriate levels of sensitivity and precision required for useful in quantitative assessments.

In addition to air sampling, surface contamination should be evaluated routinely to monitor surfaces that are potentially contaminated with specific payloads and/or ADCs. It may help to determine whether: 1. Housekeeping measures are adequate (i.e. ADC materials are present or not, and, if present, whether they are accumulating over time); 2. Engineering containment



ADC isolator integrated with chemical hood via pass-through chamber:  
Photo courtesy of Howorth

approaches are adequate (i.e. whether ADC materials are found outside containment devices or areas); or 3. Whether ADC materials are present in areas of a facility where it should not be (i.e. lunch rooms or offices). The detection of ADC materials on surface samples in these areas or on the outside of packaging materials may help to identify how they are escaping the processing areas (e.g. ineffective containment, processing equipment, and/or work practice controls).

### Medical surveillance programme

It is recommended and often standard practice to have a targeted health surveillance of employees working in pharmaceutical laboratory and pilot plant operations. Health surveillance should be initiated prior to engaging in work with ADCs and should be continued periodically thereafter. Initial or baseline health surveillance of employees working with ADC materials should include a review of their medical history with a focus on the blood, gastrointestinal system, liver, and nervous system, and reproductive effects. Pregnancy status should be determined prior to working with the compound and aligned with the organisation's reproductive hazard policy. Medical surveillance should ideally be provided prior to or soon after (within days) beginning work in these areas. The results of the initial examination and the specific duties of each worker will determine the frequency and detail of follow-up examinations.

ADCs provide a promising future for the treatment of numerous tumour types using active ingredients previously investigated and determined to be too toxic to be administered on their own. However, the synthesis of these drug products still involves handling these highly potent genotoxic moieties and although the ADC provides a less toxic means to administer the active ingredient to the patient, little is known about the ability of the conjugated payload to have off-target effects in healthy individuals. The potential exists for occupational exposure to occur in workers in the R&D and manufacturing environments. As payloads being investigated get increasingly potent, the occupational exposure limits will become increasingly lower (below 10ng/m<sup>3</sup> as 8-hour time-weighted averages). Control and containment of these substances currently require the most advanced technology available in the industry. The challenges for maintaining higher levels of containment as OELs become lower will be significant.

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