White Paper

Operator safety in biopharmaceutical manufacturing:

The role raw material suppliers can play in contributing to a safer production environment

Proper handling of commonly used chemicals in bioprocessing is critical to maintaining a safe working environment as well as operational efficiency. Chemical mishandling can also lead to failed batch processes, quality issues, lost time and resources. As new technologies designed to help mitigate these safety risks become available, biomanufacturers have more opportunities to ensure their production environments are safe.

As a raw materials supplier, we believe there is a critical role for suppliers to play in terms of providing product and packaging solutions designed to minimize chemical handling risks.

Introduction

Chemical usage is ubiquitous in many upstream and downstream biomanufacturing operations. Risk anticipation, recognition and control is key to reducing potential injury and the associated costs that result from spills and chemical exposures.

Workplace Risks

Accidents and subsequent OSHA citations stemming from the mishandling of chemicals used in pharmaceutical manufacturing operations have been well documented. While the causes of these accidents vary, it is imperative for biopharmaceutical manufacturers to identify the appropriate engineering controls to effectively contain materials during process development. This necessitates close cooperation and collaboration among everyone involved in the process, including site EHS, process engineers, line management as well as suppliers.

Common examples of chemicals used in biomanufacturing processes and associated health hazards [1]

Chemical	Classification	Common Uses in Biomanufacturing	Hazards
Sodium Hydroxide (NaOH)	Strong base	Cleaning / Sanitization, pH adjustment in buffer preparation	Causes skin and eye irritation Concentrated solutions can cause severe burns and eye damage, and in extreme cases, blindness
Hydrochloric Acid (HCl)	Strong Acid	pH adjustment in buffer preparation	Causes skin and eye irritation Direct contact with aqueous solutions of hydrogen chloride can cause severe chemical burns
Ethanol (C_2H_6O)	Organic Solvent	Component in cleaning and storage buffers	Highly flammable liquid and vapor Causes serious eye irritation
Triton X-100 ($C_{14}H_{21}(C_2H_4O)_nOH$)	Nonionic Surfactant	Cell lysis and protein extraction	Causes serious eye damage
Sodium caprylate ($C_8H_{15}NaO_2$)	Medium chain fatty acid	Partitioning agent and stabilizer for plasma proteins such as albumin and fibrinogen	Causes skin and eye irritation

1) Information sourced from material safety data sheets (MSDS), the Agency for Toxic Substances and Disease Registry website (www.ATSDR.CDC.gov) and the Centers for Disease Control and Prevention (www.CDC.gov)

Figure 1:
The encoded Quick Connector for safe handling of liquid chemicals.

Figure 2:
The Quick Connector is connected to the top of a pre-installed dip tube by screwing it together.

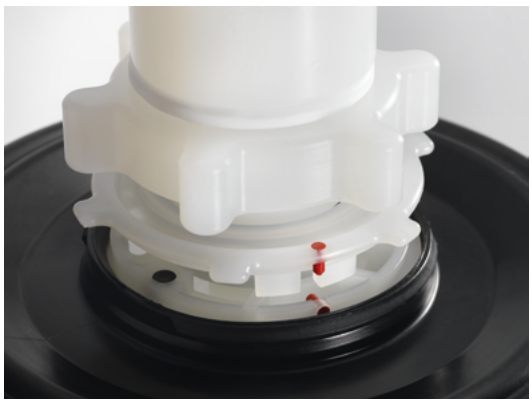

Figure 3:
Connected dispense head and dip tube showing coding pins and Quick Connector fit.

Bulk Chemical Handling Technologies

User safety is of prime importance as is continuing to improve raw material packaging and handling characteristics, keeping in mind that they may be used in a large-scale facility.

In a production environment, hazardous raw materials may be used to prepare numerous buffers for upstream and downstream unit operations. In a large scale biomanufacturing facility, this could represent substantial volumes of these materials being routinely handled (transport, dispensing and storage). In a typical monoclonal antibody production process, for example, the total buffer volume used per batch could be 2-10 times the batch volume itself (assuming an mAb titer of 1-5g/L, respectively) depending on antibody concentration and the number and types of buffers required. For a large scale production facility, this could equate to upwards of 1-2 million liters of buffer annually.[2]

Below are commonly encountered chemical hazards for liquid and dry chemicals and examples to highlight our efforts as a supplier to improve user safety by providing built in engineering controls.

Hazard Type: Liquid Chemical Spillage

Case Study 1: Liquid sampling of hazardous chemicals from large tanks

One common liquid chemical operation is to draw analytical samples or use a smaller amount of liquid from large chemical containers. Discharging liquid chemicals from the bottom of bulk containers, such as solutions of sodium hydroxide, hydrochloric acid and acetic acid can present a significant spillage risk due to the high amount of pressure that can be exerted as they exit the container.

The **Quick Connector** system makes the discharging process safer, faster and cleaner. Suitable for use with 950-liter Intermediate Bulk Containers (IBCs) and 200-liter drums, the system is comprised of a **Quick Connector** screwed to the top of a pre-installed dip tube. The **Quick Connector** extracts chemicals from the top of the container using a closed system and dry coupling. This sealed environment and top positioning allow for safer withdrawal of liquids without introducing excessive amounts of pressure, reducing the risk of accidental discharge. In addition, a sophisticated encoding system avoids potentially dangerous and costly product mix-ups ensuring easier handling by employees.

(2) Xenopoulos, A., 2015. A new, integrated, continuous purification process template for monoclonal antibodies: Process modeling and cost of goods studies. J. Biotechnology 213, 42–53.

Hazard Type: Dust Generation from Dry Powder Handling

Case Study 2: Modified formulation to minimize dust during transfer and dissolution of dry powdered cell culture media

With dry powdered formulations, dust generation during and after bulk dispensing into large mixing tanks can cause a significant respiratory hazard as well as an environmental contamination risk. Even powdered preparations of cell culture media, although not considered to be toxic, can still cause irritation of the upper respiratory tract if inhaled.

Dry compaction is one way of helping to address chemical dust inhalation/exposure risks. This method results in a significant reduction in dust formation as well as improved handling and cleanliness in the production area. One example of this is the dry compaction of powdered cell culture media.

Figure 4:
Dry compacted DMEM cell culture media

Currently available compaction methods vary, but a recently developed technology called **Dry Compression** provides the unique advantage of being water- and additive-free. Compression force is applied to highly homogenous dry powdered media, fixing that homogeneity in place and creating granules several millimeters in size. The process does not alter the media's amino acid or vitamin composition, and leaves intact the physio-chemical parameters of dissolved media and feeds, preserving the media's ability to support cell growth and productivity.

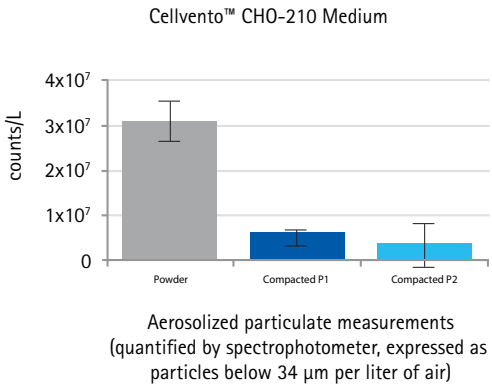

Figure 5:
Comparative dust measurements in samples of non-compacted versus compacted cell culture media

Figure 5 clearly demonstrates the reduction of dust in dry compacted cell culture media. Jars containing non-compacted (left-hand in each image) and dry compacted (right-hand in each image) cell culture media are both shaken three times. Afterwards, dust is clearly visible in the jar containing the non-compacted media. Comparative measurements showed a 13-fold reduction in aerosolized particulates present in the compacted media jar.

Case Study 3: Dust containment during dispensing of powdered raw materials into large mixing tanks

For improved handling and cleanliness, the **Mobius® Powder Delivery System** was developed to allow users to safely and easily dispense powder on-site into a compatible stainless steel or single-use vessel. The system includes a hoist, fill stand, support bracket and single-use powder container. The patented single-use asymmetric container (Figure 6) minimizes clumping and blockage providing optimal flow into a mixer. A manually controlled butterfly valve allows users to control the speed and quantity of powder dispensed. This system is ideally suited for the preparation of buffers, media, APIs, and other applications - the powder container is compatible with the majority of process containers that feature a 4-inch port. The use of a closed connection to the mixer eliminates dust in the production area in addition to increasing chemical stability by reducing exposure to humidity and minimizing product oxidation.

Figure 6:
Mobius® Dry Powder Delivery Container in Fill Stand

Figure 7:
Caked material often needs to be broken up manually prior to mixing.

Figure 8:
DRYPOUR™ drum and diagram showing unique inner Tyvek® liner (left) and outer PE liner with integrated desiccant packs (right)

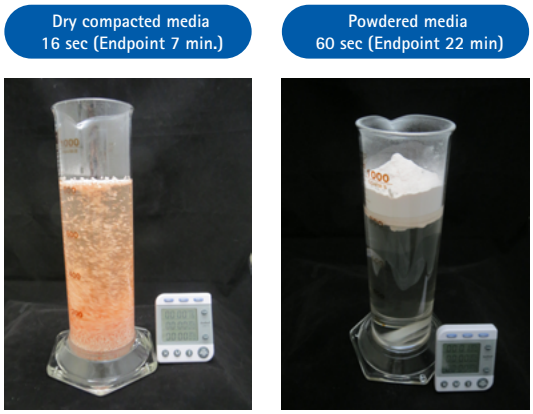

Figure 9:
Comparative mixing studies have shown a 3-fold reduction in preparation time using compacted media vs. non-compacted cell culture media.

Hazard Type: Ergonomic

Case Study 4: Caked powder transfer from large drums

A majority of raw materials used in biopharmaceutical operations arrive at the manufacturing plant in dry powder form shipped in large drums. These powdered raw materials may be used in upstream cell culture media, harvest, downstream purification or final formulation. Caked powders including hygroscopic salts often require use of manual methods (sledgehammers, picks, spades or other related implements – see Figure 7) to break up larger clumps into smaller pieces before weighing and transfer into tanks for mixing. This exposes employees to significant ergonomic risk factors such as high force and awkward postures.

To increase operator safety and reduce material preparation time, a new packaging technology called **DRYPOUR™** was recently developed at Merck Millipore. Inherent to this technology is a triple-layer of protection against moisture and outside contaminants in order to minimize the caking of hygroscopic salts. The system, which consists of a polyethylene drum with a tamper-evident seal, a polyethylene liner with integrated desiccant bags and a breathable interior Tyvek® liner, helps reduce the time and effort needed to break up heavily caked raw materials.

The drum and polyethylene liner prevent outside moisture from entering the product. Any water vapor in the product itself can permeate the interior, tear-resistant Tyvek® liner, migrate into the outer polyethylene liner and be absorbed by the integrated desiccant. Unlike other similar systems, the desiccant packs in the **DRYPOUR™** system are fixed to the perforated polyethylene liner, thus preventing contact with the product, so product quality is not compromised. For maximum effect, the desiccant packs are mounted in varying places on the liner (Figure 8). From a quality/process standpoint, the pre-mounted desiccant packs also make it easier to account for/reconcile their numbers during raw material transfer from the drum versus loose desiccant packs.

Beyond Safety – Other Considerations

Although safety is of primary concern, the benefits of safe chemical handling can also be seen in terms of improved process efficiency, product quality/consistency and regulatory compliance. Potential improvements in manufacturing operations following the implementation of these technologies include:

1. **Time savings** – resulting from the reduction and/or elimination of process steps that would otherwise be necessary to manipulate raw materials and provide adequate protection against potential hazards. For example, in addition to reducing dust, the use of dry compacted cell culture media can significantly reduce media preparation time. A 3-fold reduction in dissolution time during mixing can be observed when comparing dry compacted media to standard powdered media (Figure 9).

2. **Cost savings** - Clumping of powdered raw materials is not only an ergonomic safety hazard, but it may also result in additional capital cost. Evidence from a recent visit to a commercial production facility revealed that over time, clumps of hygroscopic salts had gradually scored the inner surfaces of their stainless steel mixing tanks. This resulted in the generation of metal particulates and the formation of minute crevices on surfaces in which dried materials and bioburden could accumulate. To address this issue, the drug manufacturer had to go through extensive new cleaning validation studies.

These situations may also require the eventual replacement of capital equipment.

3. **Reduced spillage and waste** – better OSHA compliance and less frequent need for hazmat/cleanup resources.

4. **Quality and consistency** – less moisture in raw materials and less opportunity for oxidation. Less opportunity for contamination.

Conclusions

Suppliers and drug manufacturers can take joint responsibility in creating safer manufacturing environments

We understand the challenges that must be overcome in order to create a safer manufacturing environment. By providing alternative formulations and packaging options, suppliers can improve the ways in which raw materials are typically handled in bioprocessing. And by working together, suppliers and drug manufacturers can take joint responsibility in creating a safer manufacturing workplace.

That's why we are committed to contributing to a safer manufacturing environment. Be part of the continuing conversation about chemical handling safety and what can be done to reduce hazard risks. Go to merckmillipore.com/safermanufacturing.

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