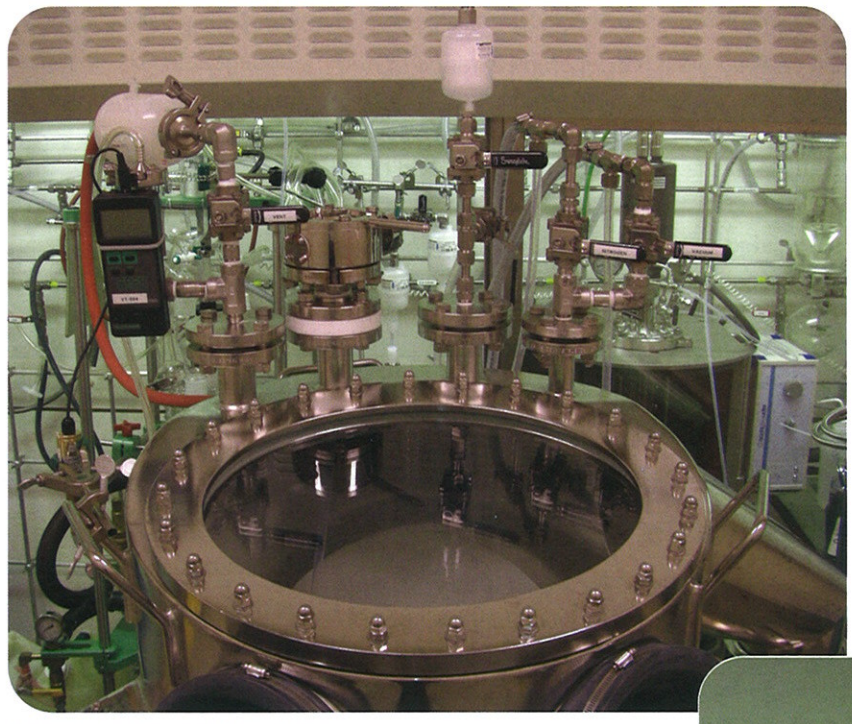
ICMS
Ingredients and Contract Manufacturing Solutions

Bridging the Gap Between HAPI Production and Material Science

Hovione New Jersey offers Larger Scale HAPI and Intermediate Drug Product Manufacturing

Over the past decade, API (Active Pharmaceutical Ingredient) manufacturers have seen an explosion in the number of potent compounds. Thus, to afford pharmaceutical companies the opportunity to reduce time to clinic, API manufacturers had to expand and or install capabilities to handle potent compounds. These active compounds are of great interest for physicians and patients, but cannot be made in standard plants because of the potential danger to operators and the environment in the event of exposure. Facing this challenge, pharmaceutical CMOs (Contract Manufacturing Organisations) must adapt by introducing the adequate equipment and controls to assure staff safety.



Picture 1: Aurora filter dryer.

Picture 2: Operator charging reactor using flexible containment during processing.

Doug Hecker, Global Business Director — Particle Design, Hovione, and Filipe Tomás, Head of Process Engineering, Hovione.

Hovione has been installing new facilities where enhanced containment is designed from the start up and retrofitting existing facilities with the necessary engineering controls to handle potent compounds.

A methodical approach is applied to each project to assess the potency, toxicity and other associated hazards. Hovione determines what level of containment is required at each operational stage. Based on the toxicological data available, the product is classified into one of the categories in Table 1 by Hovione's Health, Safety & Environment department.

While it is common for the compound classification system to differ between pharma companies and independent health and safety consultant companies, the intent of the systems is the same — to determine the handling procedures required to handle each compound depending on its category. The band system is of great importance especially at the start of a product lifecycle when insufficient data is available.

When handling potent compounds, all aspects of manufacturing are important. Hovione has focused primarily on facility design, isolation and containment. The necessary attention has been given to personnel protective equipment and personnel controls, but as a secondary layer of protection.

The selection of engineering controls takes into account performance, suitability and cost. The number and types of cost-effective containment solutions is increasing. The key and last piece of evidence in accepting a containment solution (engineering control) is based on performance qualification done by IH (Industrial Hygiene) monitoring.

Utilising this approach, Hovione has recently upgraded its FDA inspected facility in New Jersey, a VPP star facility by OSHA, to safely handle category 3a products in all production areas. The facility does not handle compounds that are β-lactams, penicillin or hormonal steroids.

In 2005, the TTC (Technology Transfer Center) was challenged to start manufacturing highly potent compounds. Hovione engaged with SafeBridge Consultants, Inc. to assess the capabilities of the site and perform an extensive analysis to confirm the safe operations. The production was done by using containment filter dryers, double a/b butterfly valves and reactors up to a maximum of 20 l.

In 2007, the site was subjected to a Pre-Approval Inspection by FDA (no FDA Form 483 issued) by FDA and received the VPP Star Award by the Occupational Safety and Health Administration (OSHA).

In 2008, the handling of potent materials was extended to the spray dryer GEA Niro Pharmaceuticals Mobile Minor 2000. The unit dries material from both aqueous and organic solvent mixtures and is equipped with two atomisation systems (two fluid and pressure nozzles). The inherent nature of the product being produced and the operational aspects led to high-potential exposure by airborne particles. It was one of the most challenging areas to upgrade. The principle applied was the same as before; isolation and containment as a first line of defense and measurement by IH monitoring.

The flexible systems have many benefits as they: offer certification of containment levels based on extensive factory testing; are disposable, which eliminates the need to clean

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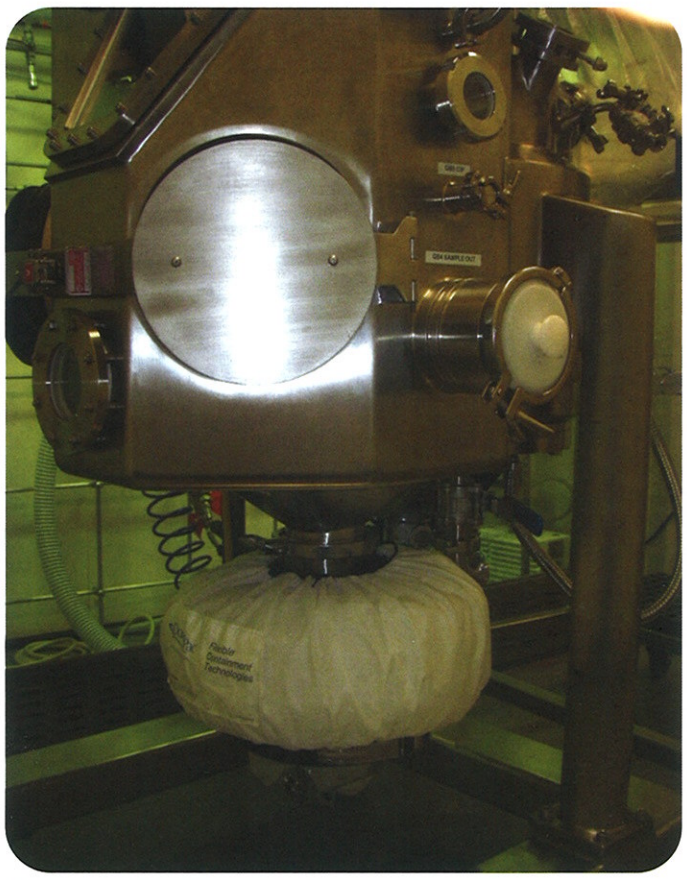

Picture 3: Filter Dryer discharge with continuous liner (flexible containment).

Picture 4: Operator charging reactor using flexible containment during surrogate testing.

and verify the enclosures; are easy to adapt and ergonomically friendly; and allow for unrestricted movement compared with fixed, hard-walled isolators. Hovione has demonstrated in all facets of its operations that disposable isolators meet customer requirements by utilising materials that comply with the requirements set forth by the GMP regulatory agencies and executing its performance qualification through surrogate testing.

In March 2010, all the remaining production areas were effectively equipped with the necessary engineering systems to allow the safe handling of potent materials to Cat 3a. These areas include hastelloy C-22 and glass line reactors from 100 to 800 l, capable of processing cryogenic and pressure reactions such as hydrogenations and carbonilations. They also include a variety of filters, including a filter dryer with hard wall isolator and different emission abatement systems options. The implementation of flexible containment systems in conjunction with the off-set design of the areas was a key aspect to the successful results on the surrogate testing. The following operations were tested: sampling, dispensing, charging, processing, filtration, drying, packing, cleaning, filter change and product discharge.

Retrofitting a facility to handle potent compounds requires a detailed assessment and careful consideration of all aspects. The growing number of APIs classified as highly potent is leading to an increase in the demand for API manufacturers to bring in new equipment and technologies. The qualification of containment systems is critical and should be the primary consideration for operations. Hovione, with its state-of-the-art facilities, can offer customers a multi-purpose, fully GMP kilo lab, pilot plant and spray drying units capable of handling highly potent compounds.

Table 1: Hovione product categories for potency and toxicity
(1) OEL stands for Occupancy Exposure Limits and is based on time weighed average (TWA) of 8h.

CATEGORY	PARAMETERS
1	**OEL(1) > 1000 µg/m³** OR; Effects at or above 500.0 mg/kg (human) OR; Therapeutic dose > 1000.0 mg/day (human ADI); Effects at or above 5.0 mg/Kg (animal) OR; Low acute or chronic system effects LD50 (oral-rat) > 2000.0 mg/Kg OR; LD50 (skin-rat) > 2000.0 mg/Kg OR; LC50 (inh-rat) > 2000 mg/m³ OR; $NOAEL_{28day}$ (oral-rat) > 500.0 mg/Kg OR; NOAELDermal (rat/rabbit) > 1000.0 mg/Kg OR; Reproductive = Negative Sensitisation = Negative, non-irritating Mutagenicity/Genotoxicity = Negative Carcinogenicity = Negative R Phrases = R36, R38 and all combinations
2a	**OEL(1) ▯ 1000 µg/m³ AND ▯ 100 µg/m³** OR; Effects at or above 50.0 mg/kg (human) OR; Therapeutic dose > 100.0 mg/day (human ADI); Low to Moderate acute systemic toxicity OR; Low to Moderate chronic toxicity LD50 (oral-rat) = 200.0 to 2000.0 mg/Kg OR; LD50 (skin-rat) = 400.0 to 2000.0 mg/Kg OR; LC50 (inh-rat) = 1000.0 to 2000.0 mg/m³ OR; $NOAEL_{28day}$(oral-rat) = 50.0 to 500.0 mg/Kg OR; NOAELDermal (rat/rabbit) = 100.0 to 1000.0 mg/Kg OR; Reproductive = Negative Sensitization = Negative, mild irritant Mutagenicity/Genotoxicity: Negative Carcinogenicity = Negative R Phrases = R20/21/22; R40/20/21/22
2b	**OEL(1) < 100 µg/m³ AND > 10 µg/m³** OR; Effects at or above 5.0 mg/kg (human) OR; Moderate to high acute systemic toxicity OR; Moderate chronic toxicity LD50 (oral-rat) = 50.0 to 200.0 mg/Kg OR; LD50 (skin-rat) = 50.0 to 400.0 mg/Kg OR; LC50 (inh-rat) = 250 to 1000.0 mg/m³ OR; $NOAEL_{28day}$ (oral-rat) = 5.0 to 50.0 mg/Kg OR; NOAELDermal (rat/rabbit) = 10.0 to 100.0 mg/Kg OR; Reproductive = some evidence in animals, Cat 3 Sensitisation = Slight dermal sensitiser, irritant Mutagenicity/Genotoxicity: AMES & WOE (-), Cat 3 Carcinogenicity = Some evidence in animals R Phrases = R48/20/21/22; R23/24/25; R34, R35, R36/37, R37/38, R36/37/38, R37, R39/23/24/25, R41, R43
3a Default (Potent from this point and below)	**OEL(1) ▯ 10 µg/m³ AND ▯ 1 µg/m³** OR; Effects at or above 0.5 mg/kg (human) OR; Therapeutic dose (human) > 10.0 µg/day OR; Severe acute systemic effects, irreversible LD50 (oral-rat) < 50.0 mg/Kg OR; LD50 (skin-rat) < 200 mg/Kg OR; LC50 (inh-rat) = 25.0 to 200.0 mg/m³ OR; $NOAEL_{28day}$ (oral-rat) < 5.0 mg/Kg OR; NOAELDermal (rat/rabbit) < 10.0 mg/Kg OR; Reproductive = Strong in animals, Cat 2 Sensitisation = LLNA +,potent response strong respiratory & dermal sensitiser, severe irritant Mutagenicity/Genotoxicity: AMES + in vitro & in vivo. Category 2 Carcinogenicity = known in humans, OSHA 13 R Phrases = R48/23/24/25; R26/27/28; R39/26/27/28; Carc Cat 3 - R40, R60, R61, R62, R63
3b	**OEL(1) < 1 µg /m³ AND > 0.03 µg/m³** OR; Effects at or above 0.01 mg/kg (human) OR; Therapeutic dose (human) > 1.0 µg/day OR; Severe acute systemic effects, irreversible LD50 (oral-rat) < 5.0 mg/Kg OR; LD50 (skin-rat) < 5.0 mg/Kg OR; LC50 (inh-rat) < 25.0 mg/m³ OR; $NOAEL_{28day}$ (oral-rat) < 5.0 mg/Kg OR; NOAELDermal (rat/rabbit) < 10.0 mg/Kg OR; Reproductive = Strong in animals, Cat 2 Sensitisation = Corrosive, can cause asthma, strong respiratory and dermal sensitiser Mutagenicity/Genotoxicity: AMES + in vitro&in vivo. Cat 1 Carcinogenicity = known in humans R Phrases = Mutagen Cat 1, R40, R42, R42/43, R45, R46, R49
4	**OEL(1) ▯ 0.03 µg/m³** OR; Effects below 0.01 mg/kg (human) OR; Therapeutic dose (human) < 1.0 µg/day OR; Life threatening, High level of medical intervention required; Severe, irreversible effects. May be delayed. Easily absorbed by all occupational exposure routes with little or no warning properties.

BIOGRAPHIES

Doug Hecker is currently Global Business Director — Particle Design at Hovione. He has over two decades of experience in GMP manufacturing for APIs, novel excipients and sterile drug products. Mr. Hecker had a primary role in establishing Hovione's contract GMP spray drying business.

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