

**SOLIDS HANDLING
IN A
MODERN BULK
PHARMACEUTICAL
FACILITY**

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“Cone Valve” IBC System providing “Validated” transfer of intermediates on “feeder floor” down to Reactor below.

INTRODUCTION:

With the FDA (US Food and Drug Administration) becoming increasingly involved in the manufacture of bulk pharmaceuticals and fine chemicals, for subsequent use in finished pharmaceutical, food and oral hygiene products, the requirement to introduce and follow “good manufacturing practices” enabling process steps to be validated, is now of paramount importance.

This now also relates to the inter-process activities, the movement of materials (solids and liquids) from one process to another.

Due to the batch processes involved, “Bulk Solids Handling” to the bulk pharmaceutical industry usually means the transfer of batches of 1000kg or less from one process to another.

Methods of transfer employed by other industries (e.g. mechanical or pneumatic conveying) cannot usually be considered because requirements for cleaning, batch integrity, hygiene and containment cannot be met. Also the difficulty in handling the generally poor flowing, cohesive solids are a problem.

Therefore, traditionally the bulk pharmaceutical industry has used drums, kegs or big bags as the means of transferring batches of solids from process to process.

This is very labour intensive and requires the operator to be “suited up” when handling potent or toxic products. More importantly, it is also totally “operator reliant” on the batch being transferred to the process and not spilt on the floor. Obviously this method cannot be considered good G.M.P. and cannot provide batch traceability. Also open transfers to and from kegs will not comply with international regulations governing dust control (C.O.S.H.H., O.S.H.A., etc).

Rigid stainless steel Intermediate Bulk Containers or IBC’s have been used successfully for many years in the secondary pharmaceutical industry for inter-process batch transfer. However, their introduction into the process chain has historically followed the granulation process, where the powders are free flowing and create few problems of discharge from the IBC.

In the past when these traditional IBC’s, usually fitted with butterfly valves at their outlet, have been introduced into bulk or primary pharmaceutical production, they have generally failed to consistently discharge the more difficult flowing, cohesive solids found in this industry.

This paper will show how the introduction of “Cone Valve” IBC’s to the Bulk Pharmaceutical Chemical Industry enables the transfer of intermediates from process to process to be carried out in a contained, traceable manner, with discharge of even cohesive centrifuged/filter press type solids. Validation of the batch transfer with corresponding documented evidence now becomes a reality.

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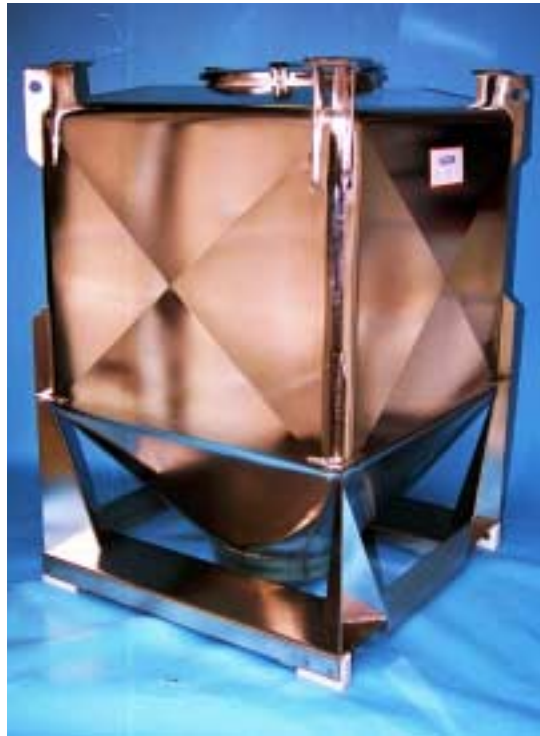
1.0 IBC DISCHARGE

The principle and various methods of discharge of the “Cone Valve” IBC System are further described below.

1.1 “Cone Valve” IBC - Principles of Operation and Discharge

The “Cone Valve” IBC System consists of two major components; the IBC, which is transportable, and its Discharge Station, which is usually permanently fixed above a process.

The IBC can be positioned on its Discharge Station by stacker truck, overhead hoist or A.G.V. System, enabling large numbers of IBC’s to be discharged by one or more Discharge Stations to individual processes.



“Cone Valve” IBC

The IBC is square in cross section with a square to round transition hopper ending in a circular outlet, in which is located an inverted cone with an integral edge seal. This becomes the “Cone Valve” and gives a dust tight seal under all conditions of full or empty IBC’s, and during any form of transportation of the IBC’s. The latest design can incorporate a further sealing arrangement which gives high containment of powder and dust whilst being stored, transported or discharged for high potency products where minimum operator exposure levels are required.

The IBC Discharge Station

The IBC Discharge Station consists of square frame with corner guides to ensure that the IBC is automatically positioned centrally on the Discharge Station. The cone valve remains fully closed and the IBC hopper section engages a lip seal on the Discharge Station to give an automatic dust tight seal between the two units each and every time.



The system is fully automatic. When the "on" signal is received, a probe within the Discharge Station rises and locates into the underside of the cone valve. An inflatable seal positioned within the hygienic probe cover is interlocked to inflate and totally seal the top of the probe to the inside surfaces of the IBC cone valve before the cone valve is opened. This "alpha/beta" seal ensures the bottom of the cone valve and the top of the Discharge Station probe are sealed together during transfer of powder, therefore when the IBC is eventually removed from the station these "open" surfaces are clean).

After this operation is complete, the probe/cone valve assembly continues to lift, raising the cone and creating an annular gap through which material can flow. The lift height is totally adjustable to vary flow and accommodate different materials with varying flowability.

A pneumatically operated vibrator is built into the probe and this combination of lifting and vibrating probe/cone valve assembly is very effective in discharging and controlling the flow of cohesive to flushing materials.

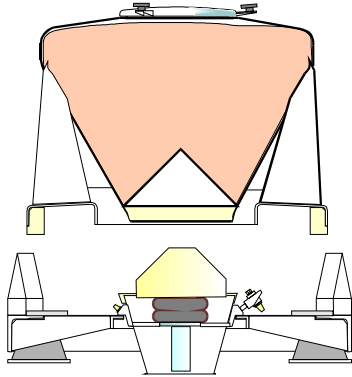


**“Cone Valve” IBC being located onto
Through Floor Reactor Feed Discharge Station**

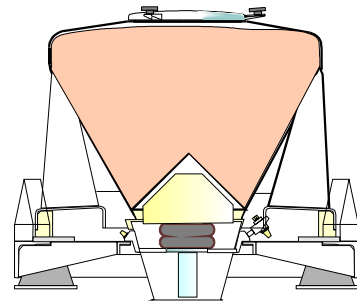
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This controlled feed principle is ideal for feeding directly to process and weighing systems where control of discharge and accurate shut off are required. It ensures that material is always presented in a consistent form, is not overworked, compacted or segregated when discharged to the process.

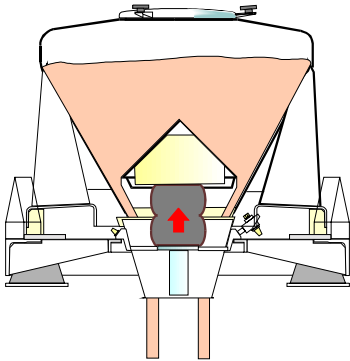
For extremely poor flowing solids, external vibrators are used in sequenced operation with the lifting/vibrating cone to discharge wet cake, centrifuged type solids.



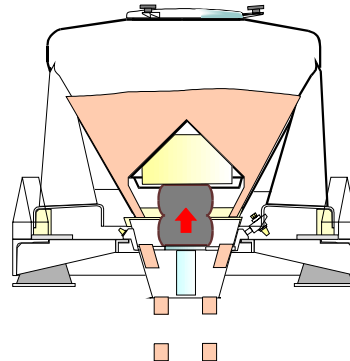
IBC Positioned over station by fork truck or overhead hoist.



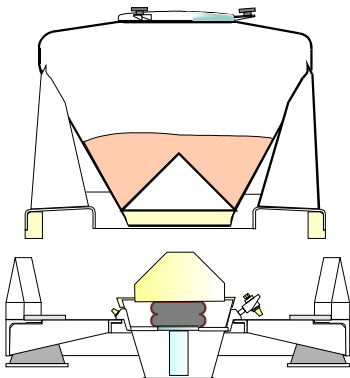
IBC lowered and docked with Matcon discharge station.



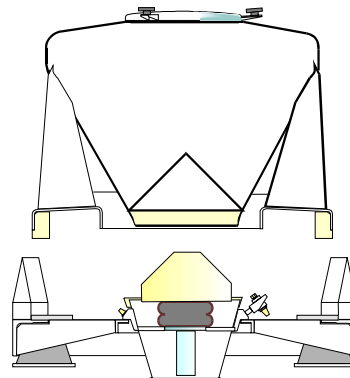
Station probe lifts and vibrates discharging product in continuous mode.



Station probe lifts and vibrates product discharging in pulse mode.



Part empty IBC removed from station.



Empty IBC removed from station for washing and refilling.



**“Cone Valve” IBC providing
controlled volumetric feed to Reactor**

1.2 Volumetric Dosing (controlled Feed by Volume)

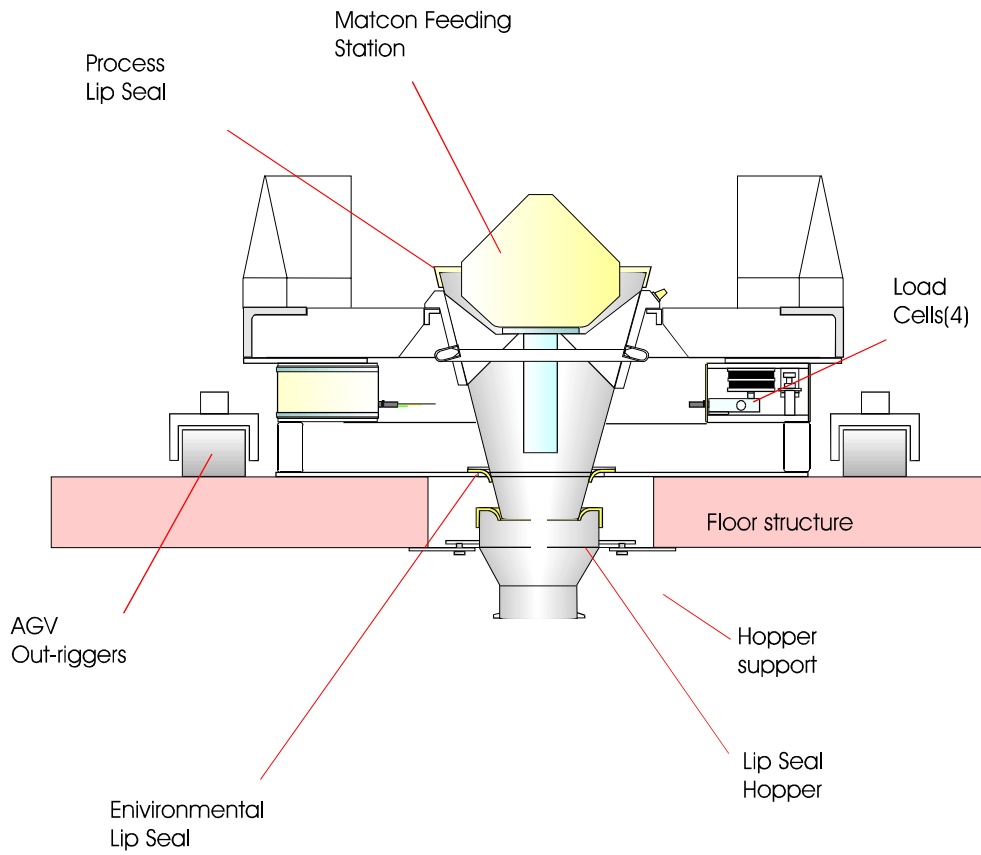
In applications where batches are pre-weighed into IBC's and are then required to be completely discharged into process (i.e. reactor feeds), it is usually an advantage to provide a controlled feed rather than a flood feed.

This enables venting of the process below to be controlled (avoiding solvent gases/fumes rising from the reactor into the IBC) and providing gradual dispersion of the solid into the reactor where exothermic reactions are possible.

Volumetric Dosing from the "Cone Valve" IBC with reasonably consistent flowing solids is achieved by pulsing the cone valve up and down continuously using "pulse timers" to control the throughput.

Two sets of pulse timers are used, one to control the length of "on" time (cone valve up and vibrating), the other to control the length of "off" time (cone valve down and sealed). These are adjusted to provide the volumetric dosing required.

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Gravimetric Discharge Stations

1.3 Gravimetric Dosing (controlled Feed by Weight)

The "Cone Valve" principle of discharge enables a PLC or Weigh Controller to control and vary the throughput from the IBC System by weight (on a continuous or batch basis). The IBC Discharge Station is positioned on a four-load cell weighing system, which enables discharge from the IBC to be monitored and controlled by the Weigh Controller on a "loss-of-weight" basis.

Continuous Feeding to Process

Accurate feeding to processes requiring a true continuous feed i.e. sieving, milling, reactor feed and microniser is achieved by "pulsing" the IBC "Cone Valve" up and down and measuring each slug of material discharged.

The weigh controller monitors and compares each slug discharged to a pre-set slug weight and adjusts the next pulse "on" time accordingly. This enables the weigh controller to "self learn" to the varying flowability of the material as it is discharging from the IBC.

The "off" time between pulses is also adjusted to achieve the required continuous discharge rate.

Batch Weighing (Proportional Feeding)

Proportional feeding to processes requiring a weighed sub batch to be discharged from the IBC (i.e. 200 Kg aliquots to reactor from 800 Kg IBC) is achieved by raising/vibrating the cone valve in the IBC and discharging material continuously, with the weigh controller monitoring the discharge to an adjustable weight set point (approximately 95% of the sub batch) when the IBC cone valve will be interlocked to close and shut off material flow.

The weigh controller will then pulse the cone valve up and down, measuring each slug discharged and incrementally reducing each subsequent slug until the final pulse is provided to "top up" the sub batch within the required tolerance.

Where very high accuracies are required, a secondary dosing valve is fitted to the outlet of the Discharge Station. This valve opens fully when the bulk of the batch is being discharged and does not interfere with powder flow. When the "topping up" procedure is initiated, the valve is sequenced to close allowing a small amount of solid to rest on top of the valve. The valve is then proportionally opened and closed with the fast acting, knife type valve providing very accurate dosing.

The small residue of solid left on top of the valve after dosing is complete, is automatically discharged when the next batch discharge is initiated and the valve fully opened.

1.4 Containment

The primary containment achieved by the “Cone Valve” IBC System can be expected to provide compliance to international regulations such as C.O.S.H.H., O.S.H.A. etc.

Secondary containment options are added to the system to provide Operator Exposure Levels to single figure microgramme per m³ levels when dealing with highly toxic/potent solids.

Cleaning-in-Place options are also available (usually very important in containment projects).

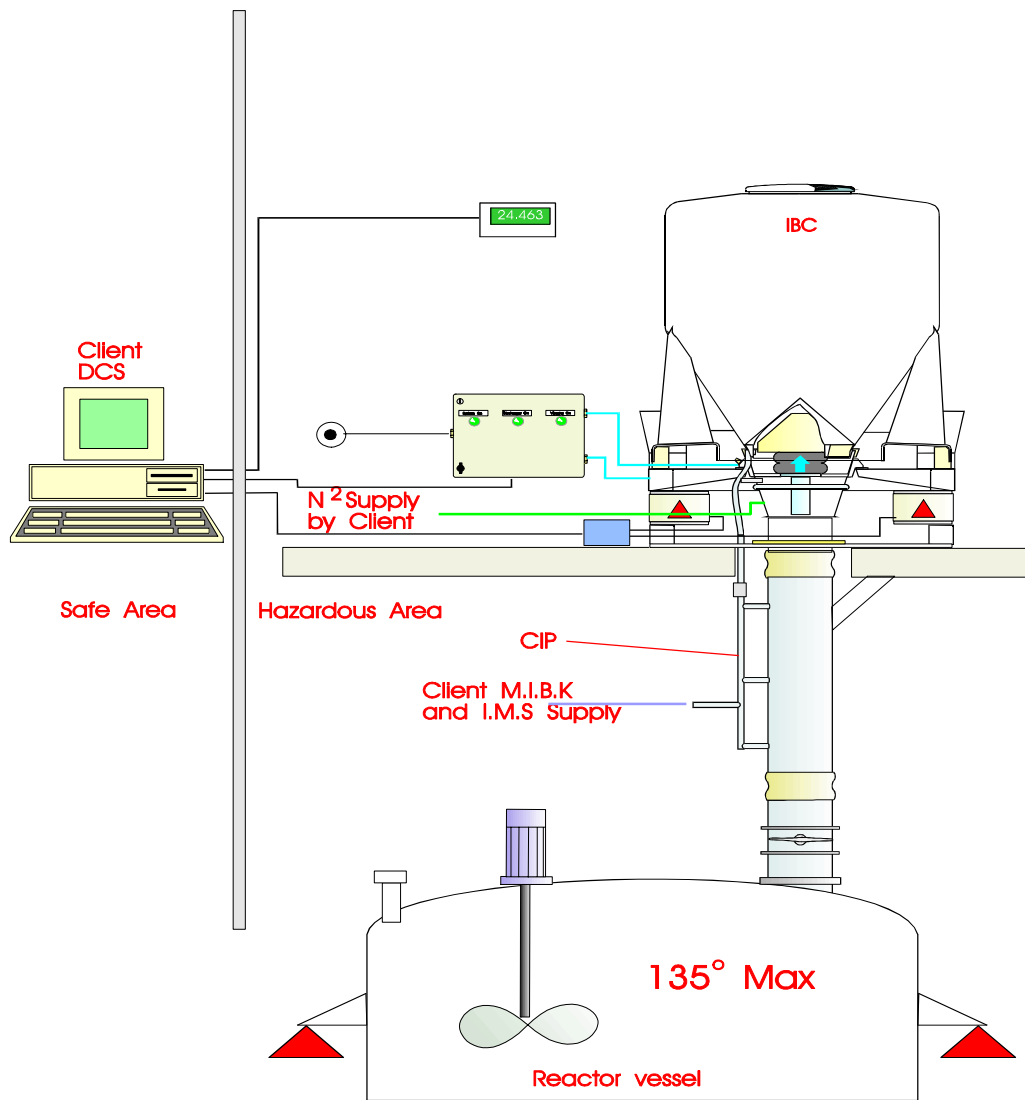
1.5 Applications (Automation/Validation of Discharge)

In any modern Bulk Pharmaceutical Facility there is a G.M.P requirement for traceability of the batch inter-process movements and to prove or validate that the correct batch has been transferred to the correct process.

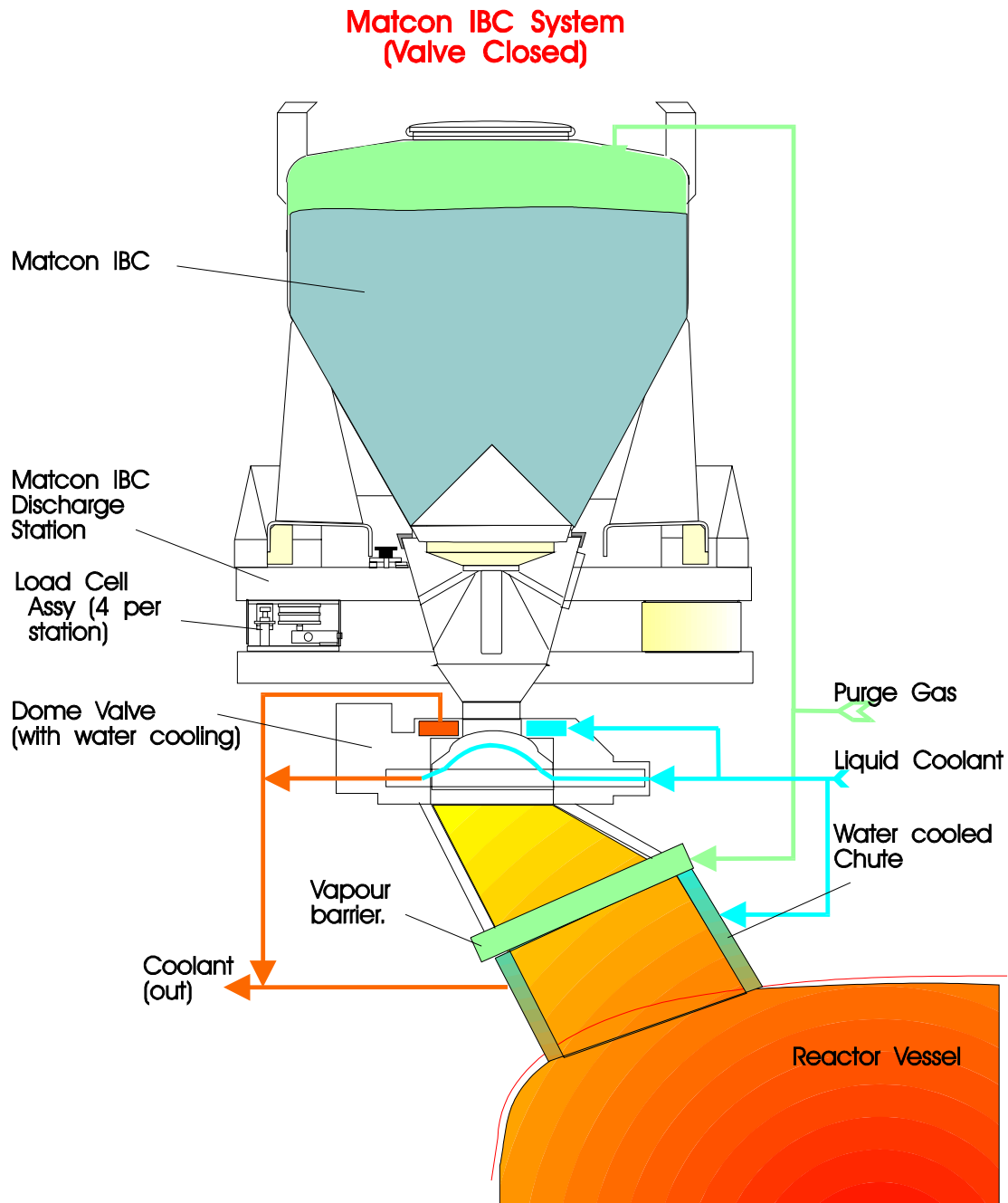
By their very nature, inter-process IBC Systems lend themselves to ease of product traceability. More often than not, a single batch may be stored in a single IBC, which may be uniquely identified. In the most modern facilities, these single batch (or multi-batch) IBC's may be “traced” using a unique bar code or electronic tag device on the IBC, to feed data to a central processing unit. This provides “proof” of inter-process and process activities, giving fully validatable operation.

Following are typical examples of Cone Valve IBC's in application:-

- Typical Primary Production Flow Sheets (2 off)
- Typical Reactor Feed Systems (2 off)



REACTOR FEED





Manual Lift/Lower IBC Filling Heads in operation

2.0 IBC FILLING

A common problem to all IBC's is how to fill them in the simplest and most effective method in keeping with the product and its environment. In most applications today, dust control and/or containment is becoming increasingly important.

In order to sell the MATCON IBC System, it is necessary not only to understand its discharging capabilities, but also the various ways it can and should be filled !

2.1 Manual IBC Filling Heads

These systems always involve the manual removal/replacement of the IBC lid before/after filling.

The filling head itself is suspended from the outlet of the preceding process or conveying system and can range from a simple flexible which is manually connected to the IBC inlet, to a pneumatically operated lift/lower double annulus filling head with dust extraction, which automatically lowers onto/into the IBC inlet.

These various filling heads, if fitted correctly, can usually provide dust free filling of the IBC's during the solid transfer into the IBC and if the venting of the displaced air in the IBC is adequate.

However, in all cases the actual connection or seal to the IBC is broken before the IBC lid is manually replaced.

Therefore containment is lost allowing any airborne dust or fumes from the filling head to escape to the surrounding environment. In the case of the more sophisticated double annulus filling head, dust extraction is used to pull the dust or fumes into the annulus during the raising of the fill head, thereby preventing the dust/fumes from becoming airborne and escaping into the environment. There is still a requirement for the operator to enter this extract flow to replace the IBC lid, therefore containment must be considered inconsistent and questionable for potent or toxic solids.

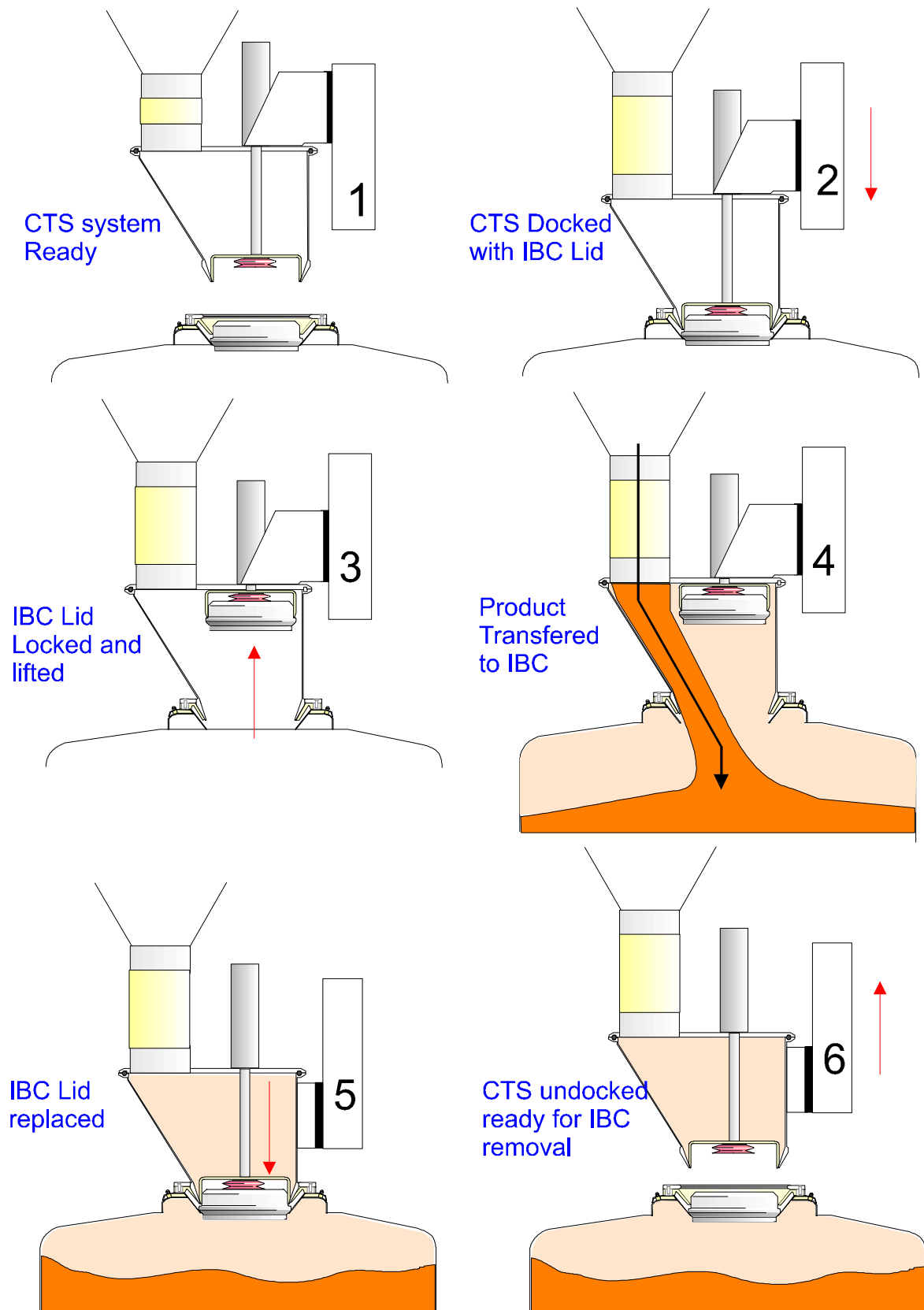
Automation and Containment of IBC Filling

In any fully automated inter process IBC System, it is becoming necessary to automatically fill IBC's in a contained manner at every interface without operator intervention.

This means that not only is the operation easier to validate by removing any operator reliance on the integrity of the IBC filling operation, but also removing the operator from being exposed to that operation at all ! Therefore, when highly potent or toxic solids are being handled and operator exposure levels are minimal - the operator is not even there !

MATCON have developed a fully automatic "Through Lid" Containment Filling System for this very purpose.

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2.2 Containment Transfer System

The Through Lid Filling System enables the transfer of powders from process to IBC's while maintaining containment of the material from the outside environment. There is not even a momentary exposure of the inside of the IBC to the outside environment either before, during or after transfer.

The system is derived from the original alpha/beta mating flange system, but has the significant difference that the mating alpha/beta flanges are kept within the process vessel during transfer, so eliminating the need for an external containment chamber or glove box (which always fills with dust). This system is also totally automatic with no manual intervention whatsoever. The operator does not have to remove or replace a lid or operate a valve.

This system consists of:

- A flanged containment unit to bolt to the bulk store or process vessel outlets.
- A lift table situated below to locate and lift IBC's.
- A separate control cabinet.

In operation, the IBC to be filled is raised by a lift table to automatically engage its inlet lip seal to the containment unit outlet; simultaneously the alpha flange connects by suction cup to the IBC beta flange - thus sealing their mating surfaces from product contact.

The coupled flanges are then raised to create an annular flow path for product transfer.

After product transfer, the procedure is reversed. Thus, when the IBC lowers, the containment unit alpha flange and the IBC beta flange are both **already** closed, sealing the internal product areas **before** the IBC inlet lip seal disengages from the containment unit outlet.

The filled IBC can then be removed by A.G.V. (or stacker truck) and transported to the next process or stored until required.

Operator Exposure Levels can be expected to be in single figure microgramme per m³ levels.

Cleaning-in-Place options are also available.



Test/Demonstration System for:-

- **“Cone Valve” IBC Discharge with Containment (Volumetric and Gravimetric)**
- **IBC Automated Filling with Containment**
- **C-I-P of both systems.**