MATCON®

ISPE
The Society for Pharmaceutical and Medical Device Professionals

'Solids Handling'

THE 'MISSING LINK' IN ACHIEVING CONTAINMENT

M:\sempapers\papers\the missing link.cdr

THE PEOPLE . THE TECHNOLOGY . THE SOLUTION

1.0 INTRODUCTION: CONTAINMENT AS PART OF A PROFITABLE BUSINESS

This paper deals broadly with ‘containment’ of potent compounds. It may seem obvious, however it is easy to forget that the only reason that ‘containment’ is on anyone's agenda is because there is a business requirement to process potent or potentially harmful materials. The key words here are 'business' and ‘process’. The only way that pharmaceutical business can successfully continue is through ‘processing’ materials. The challenge is how to achieve the most efficient and economic processing methods which accommodate the multiple constraints that face today's pharma business.

Containment is just one of those constraints and it is forever being balanced against all the others. In itself ‘containment’ is just a ‘means to an end’ and as in so many other aspects of life it is necessary to ask – does the ‘end’ justify the ‘means’. If the achievement of containment means that it is not possible to carry out a profitable business then it is necessary to change something. Those of us involved in Pharmaceutical Processing must assess this balance on every project and implement solutions that fit the ‘big picture.

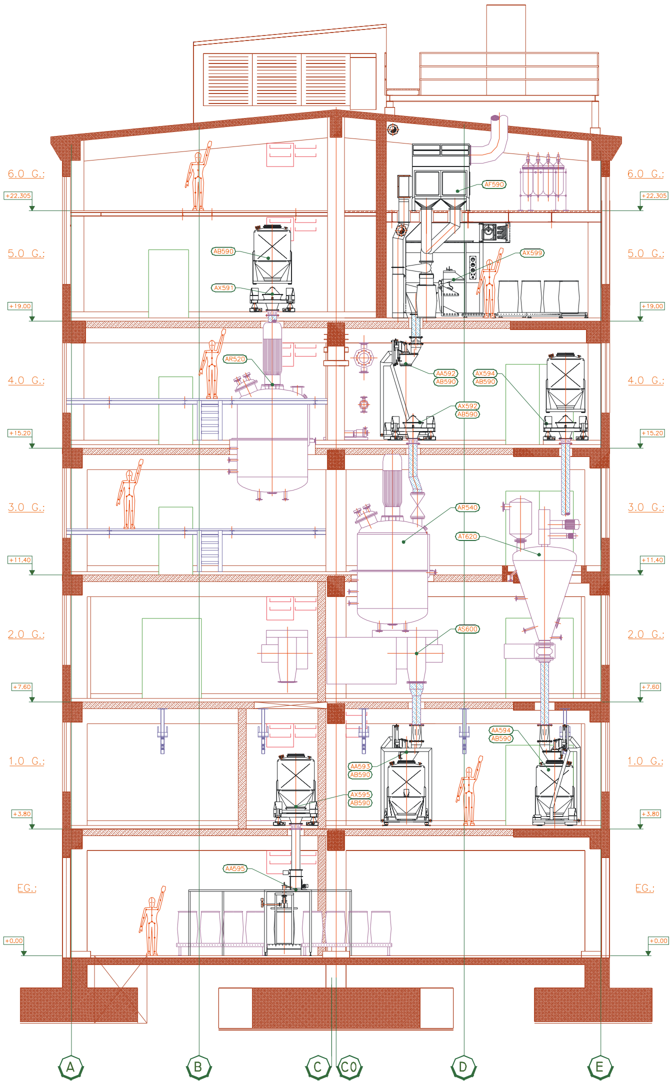

Fig. 1 – Typical Bulk Pharmaceutical Facility

2.0 SOME BUSINESS TRENDS AND RISKS

Before getting into the ‘technical’ aspects of containment, let us consider a few of the main business trends and risks that influence the subject.

- **Speed to market –** minimising lead-time between ‘concept’ and ‘production’ to take full advantage of market potential. It's obvious that pre-engineered, modular solutions can be deployed much faster than bespoke systems. And yet many plants apply bespoke ‘containment’ methods – especially to the ‘interface’ points which involve different vendor packages and services.

- **Risk management -** minimising the exposure on investment in plant and facilities before regulatory clearance. This usually means that commitment to full-scale production facilities is delayed till the last minute so that expensive capital equipment is not lying idle. The downside of this is that there is usually precious little time allowed to optimise ‘bespoke’ interfaces and often too much optimism on how well ‘things will work together’.

- **Flexible manufacturing methods –** catering for multiple products in one facility and being ‘battle-ready’ for tomorrows products and processing methods. One of the most significant aspects of flexible manufacturing is the ‘de-coupling’ of process modules that were traditionally linked, to allow more efficient campaign production. A good example of this would be discharging a dryer to an IBC which will be packed off later, rather than packing direct from the dryer as is very common, or discharge of intermediates from <u>ANY</u> dryer to <u>ANY</u> reactor using IBC's (not in line vertical processing) providing total flexibility of processing throughout the facility. Another example would be the storage of intermediates in IBC’s following centrifugation and their subsequent charging to dryer. The risk here is that a solution is implemented which works fine with today's products but not when a new process or product comes on stream. And of course, its impossible to conduct meaningful tests with a product that does not yet exist…… or is it ??

- **Increasing potency**. Put simply, this means that it's possible to achieve more value per cubic meter of production. The risk is that processes which were suitable for one product may be poor or unusable for another.

- **Optimising batch sizes –** cutting down on sampling, cleaning, inter-process handling, manual intervention – non-value added operations. If you can process twice the volume, then you can cut many of these operations in half. However, in some cases, the bigger the batch volumes the bigger the challenge for containment.

- **Remove inefficient manual operations (drums) -** Provide totally 'closed' systems with single batch transfer wherever possible. For example: one IBC filling operation and one IBC emptying operation drastically reduces number of containment connections and risk.

3.0 CONSTRAINTS

Manufacturing in the most technically efficient manner is **not** always possible. Sometimes there are certain constraints that apply.

- Processes must be controllable and validated. How often have we seen process improvements that cannot be applied because the existing method is validated and cannot easily be changed?

- Material loss through spillage, retention, contamination, production inconsistencies.

- Non value-added time – operation failure, cleaning or planned maintenance

- Safety and occupational hygiene issues - including containment. This may mean that cumbersome methods and procedures have to be implemented. Often even the operators don't appreciate the need for these and may have a tendency to disregard safety in their desire to do a better job – climbing on frameworks, failing to connect earthing straps, handling potentially harmful materials etc.

- Regulatory compliance – FDA, EPA, COSHH etc.

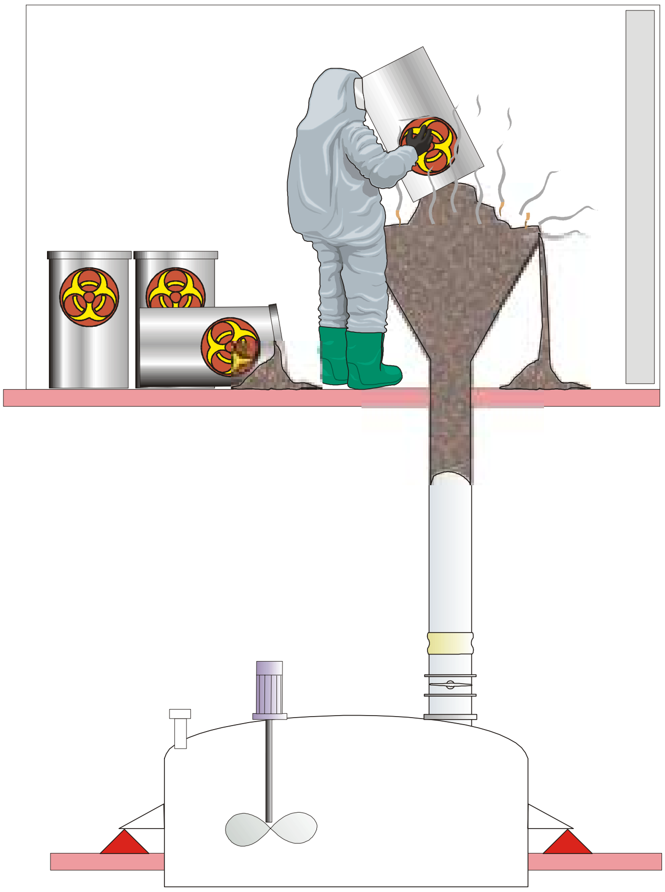

Fig. 2 – The wrong way to handle solids!!

4.0 SOLIDS HANDLING FIRST – CONTAINMENT SECOND

Containment of potent compounds is pretty easy during processing. The challenge really arises during the transfer of materials to and from the process into mobile batch vessels – usually IBC's or drums.

Designing systems requires a thorough understanding of Solids Handling issues. Here are some that need to be considered.

- **No-Flow**:

Materials always behave predictably on P&I diagrams however the reality in solids handling is quite different. Materials often don't just flow because a valve is opened. Problems such as compaction, bridging, adhesion are frequently encountered and some materials need extensive agitation, manipulation or vibration in order to make them flow at all. They may also need large clear openings for passage of materials. Damp cake from centrifuges or filter dryers fall into this category but so too do many compressible, fine chemicals. Any containment system that does not accommodate or provide for such flow assistance will not suffice. When problems occur, people often take extraordinary and sometimes desperate measures to try to achieve flow – hammers, paddles, shaking, air jets etc. Such measures often totally undermine all containment planning that has gone into the system design.

- **Too Much Flow**:

Allowing materials to 'dump' into or out of process, or choking feed chutes or valves increases the risks of breaching containment by straining flexible couplings, seals etc. The ability to control flow between processes is a key element in optimising containment.

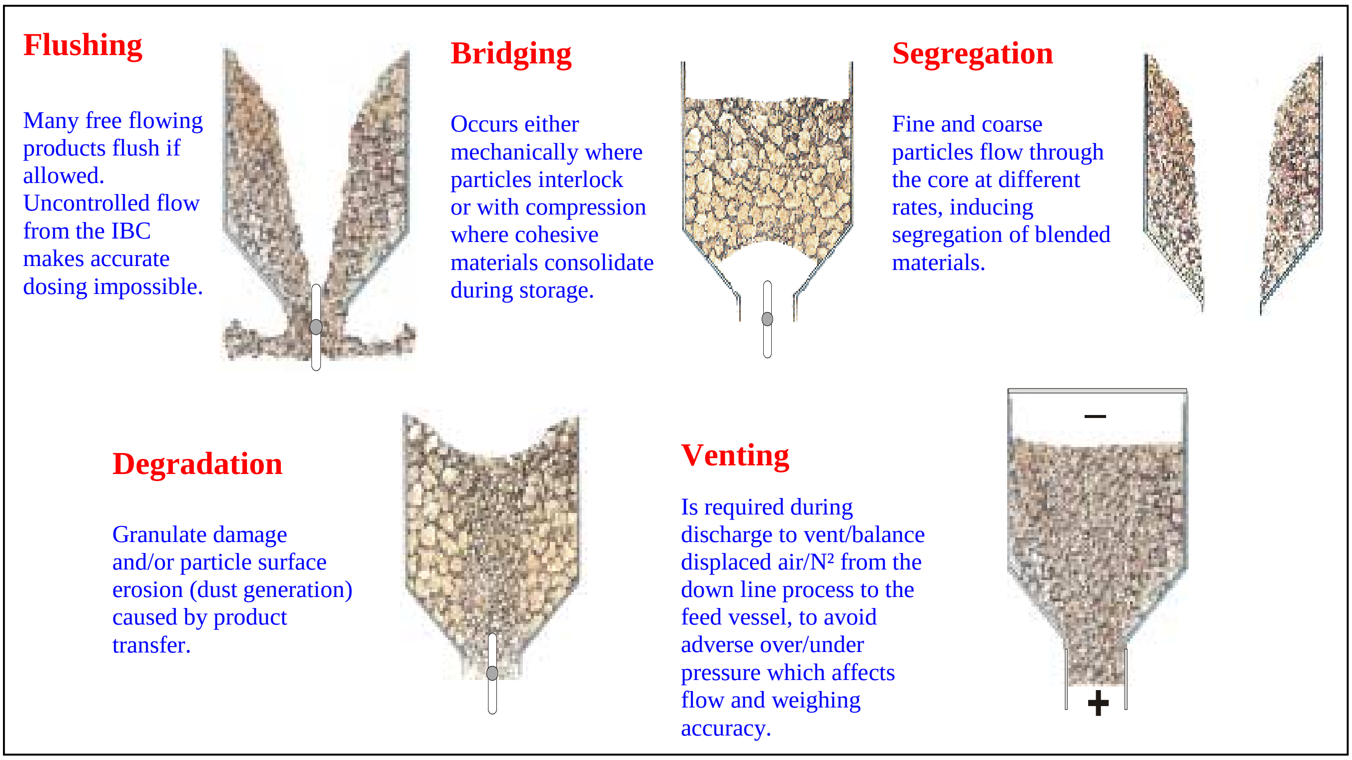

Fig. 3 - The 'usual' Solids Handling Problems

- **Purging, Airwashing, Extraction & Venting**:

It is essential to consider the complete system process flow in order to achieve containment. The movement of air or nitrogen is critical to this. Failure to achieve balanced, controlled venting in a system before, during or after material transfer can result in a serious breach of containment. Air being pulled into a reactor headspace due to residual vacuum as a bin is dis-engaged could allow a solvent explosion. Dust extraction systems pulling against closed volumes can collapse flexible connections and actually cause a breach which later allows material to escape outwards. Conversely, a puff of overpressurised nitrogen from a purging operation could potentially carry potent dust straight out into an operators face when a bin is disconnected from a filling system.

- **Impracticality**:

It is no use providing a system that works in laboratory scale but is not capable of full scales industrial application. If bulk production cannot be accommodated then its precious little use to the manufacturer of today. Containment devices can sometimes be completely bypassed by well-meaning production teams that simply want to be more efficient.

- **Over Sensitive engagement**:

High accuracy tolerances which are difficult or impossible to achieve on day one and impossible to maintain over time. If a device requires very high accuracy coupling but there is no practical means of achieving that in a full scale, manufactured IBC system then it is of limited practical use.

- **Cleaning and Cleanability**:

This is such a sensitive and mis-understood subject that it is often more convenient to avoid it at the early stages of a project only to see it re-emerge later to cause great problems or ultimately compromise. People have very different expectations and understanding of equipment cleanability and in particular CIP. Some processes may require cleaning several times per week while others may be expected to operate for six months without cleaning. Equipment performance and even cleanability can vary enormously depending on the cleaning philosophy and practice that prevails in a specific plant – this is particularly true of containment systems.

Terms such as WIP (wet in place) and RIP (rinse in place) imply that manual intervention will be necessary for thorough cleaning although an end users expectation may be for fully automatic systems. Containment must be considered not only for normal operation but also for cleaning and maintenance.

5.0 KNOWLEDGE OF MATERIALS AND PROCESS FLOW.

When designing for containment, it is vital to appreciate the ‘form’ and ‘nature’ of the materials in question. Many projects go ahead with theoretical, chemical data on materials but precious little practical knowledge about what they look and feel like not to mention their ‘solids handling’ behaviour. In pharmaceutical processing there is a wide variety of material forms to consider and they need individual consideration. Here are some examples:-

- Raw materials in dispensary. Often fine powders which may be compressible and poor flowing when compacted. However, they may flush easily when aerated.

- Damp wet cake coming from a centrifuge. As the name suggests this may have awful flow properties and require serious agitation to move at all. The more vigorous the agitation the bigger the challenge to containment technology. The good news is that a damp material does not pose a high risk of dust emission. However such materials can stick firmly even to vertical walls and dry to a tough layer that presents interesting challenge to closure devices.

- Dry cake from a conical dryer. This may comprise a mixture of fine dry powder with agglomerated lumps. Again these lumps may block chutes and valves and invite rodding or hammering to free them.

- Granulation. Often delicate granules are prone to degradation if handled roughly.

- Direct blend. Can be highly prone to segregation during transfer to compression machines.

It is also critical to understand how materials are discharged from processes. For example the discharge from a conical dryer is quite different to that from a centrifuge. Containment is heavily dependent on having a clear understanding of the ‘in-process’ behaviour of the materials to be contained. It is also critical to address issues like vibrating or oscillating interfaces, which might make connection and containment impossible.

How are where venting of the complete system should take place will also vary from process to process. It is critical that the solution is agreed with all relevant parties to achieve optimum operation with no compromise to containment.

6.0 IBC'S

All of the above factors are particularly challenging when you are dealing with IBC systems. An IBC has to be coupled and uncoupled to a wide variety of process modules around a typical pharmaceutical plant. It thus encounters many different challenges in the form of materials, process interfaces, building constraints etc. Consider the following sample of applications:-

- Filling from a variety of dispensaries
- Filling from a variety of processes
- Movement by a variety of handling devices
- Movement between GMP and technical zones
- In-bin-blending – sometimes involving multi-titration
- Feed to bulk chemical processes
- Feed to secondary processing equipment
- Cleaning of bins and transfer equipment

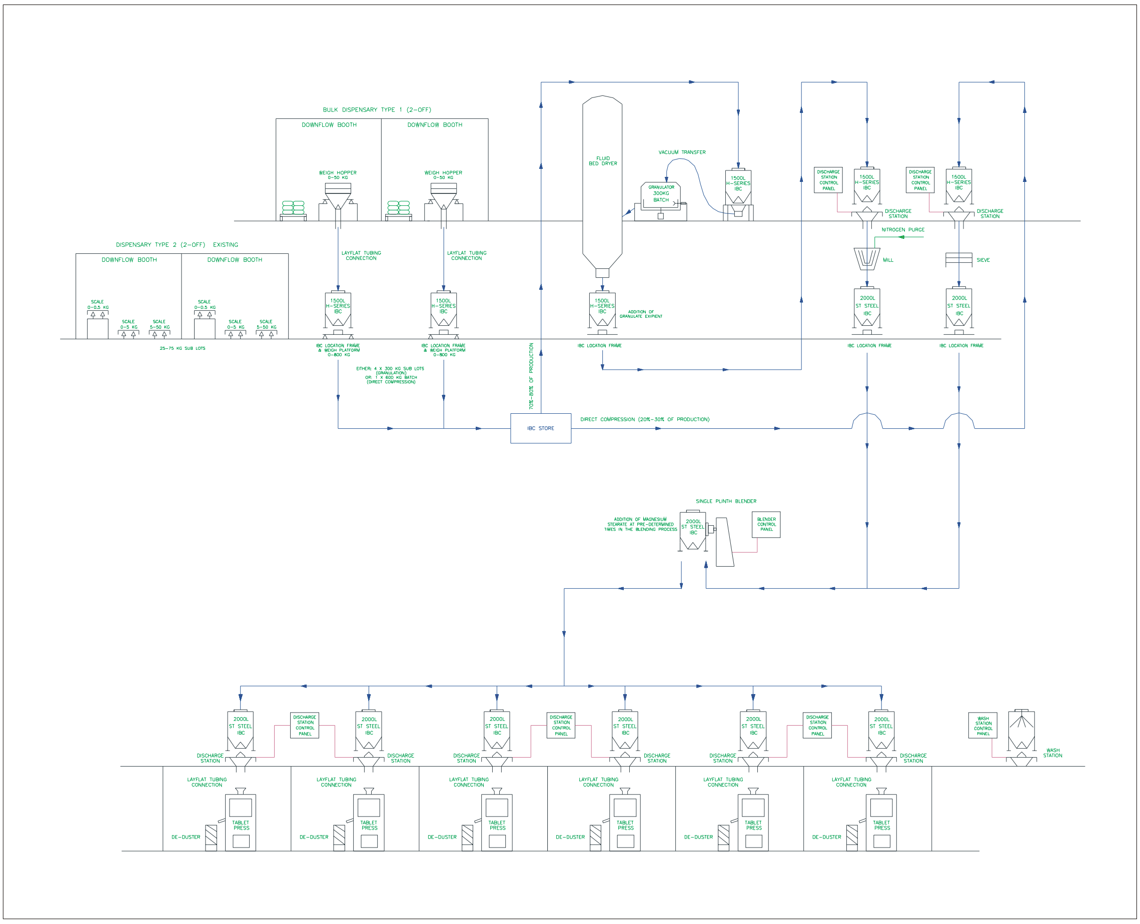

Fig. 6 – Typical IBC movement through a Solid Dosage Facility

7.0 IBC'S IN CONTAINMENT PROJECTS

It is imperative to design the system for solids handling first and then contain that system. If we have to 'rod' materials to obtain flow, then we will have lost containment and wasted our money.

There are many different technologies applied to provide containment 'connections' in IBC systems and each of these has its place in the market. It is critical to understand the differences in the technology however, because a technology which is perfectly suitable in one application may be totally incorrect in another. No one system can be expected to meet all requirements. Here are a few common examples of systems in use in modern bulk and secondary production facilities.

Fig. 7 - Containment IBC with split butterfly valve inlet and Cone Valve outlet.

Split Butterfly Valves

- These systems incorporate a 'passive half' of a Valve which is fitted to the inlet or outlet of an IBC. A corresponding 'active half' is attached to each process where a coupling is to be made. The bin and the process are offered together and the two halves of the valve wafer are pressed tightly together. The 'active' valve includes a rotary drive to turn the two halves to operate the classic 'butterfly' valve action. These systems can include airwash to assist in maintaining a clean interface when the two halves are separated. Several such devices are available on the market but there are many subtle design details that are important differentiators. The user must look to the detailed operation to know which is most suitable.

- Typical performance of the primary device itself can generally be expected to be in the range of 5-100 microgramme per cubic meter as an OEL, depending on circumstances.

- Secondary enhancements of air/water/solvent wash may be available to achieve containment levels of 1microgramme per cubic meter as an operator exposure level based in a time weighted average of 8 hours. However, this will obviously vary depending on number of disconnections per day.

Passive Valve

Active Valve

Fig. 8 - Split Butterfly Valve.

Glove Box Isolators with Alpha-Beta Ports

- Although Glove Box Isolators and Alpha-Beta ports (or Rapid Transfer Ports) are widely used to achieve high levels of containment with drums and drum handling equipment, they are very rarely coupled directly with IBC systems. One major reason for this is the need for very precise alignment and coupling of the Alpha and Beta ports – which is difficult with a large fabricated batch IBC.
- A further obstacle is the challenge of discharging potent materials with poor flow properties from an IBC through a Glove Box where it is almost impossible to apply vibration, agitation or manual intervention in the conventional way and relies on manual 'assistance'.
- There are distinct advantages in being able to overcome these obstacles and utilize Glove Box Isolator technology with IBC Systems to provide the best containment on the market, coupled with the operational benefits of a 'single batch' IBC System.
- Typical performance of Glove Box Isolators can be expected to be at nanogramme per cubic meter level as an OEL.

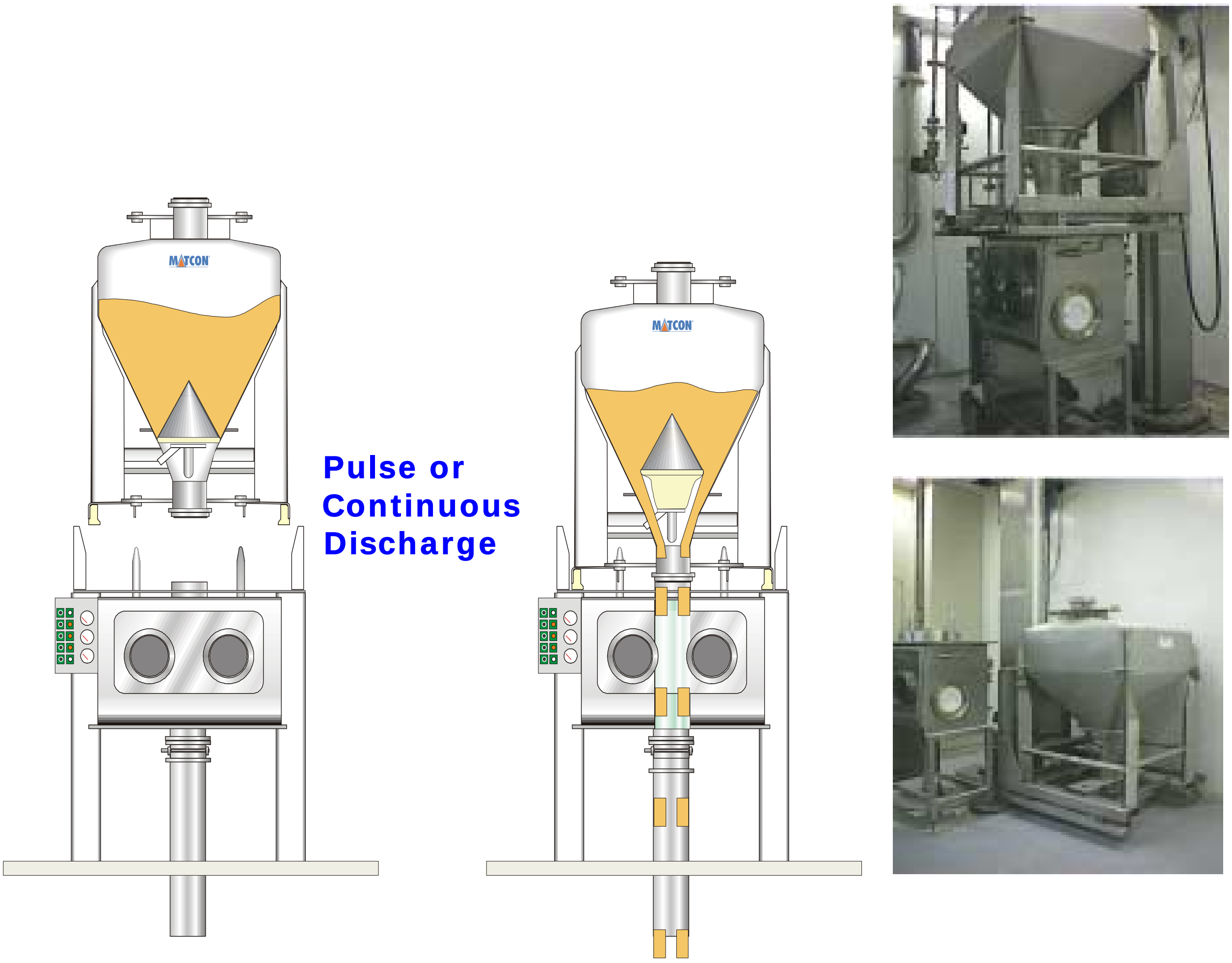

Fig. 9 - Contained Discharge Of 'Wet' Product From IBC With Glove Box Isolator.

Thru-lid IBC Filling Systems

- This system is similar in concept to the Alpha-Beta concept of the Glove Box except in this case the Beta port is actually a special lid in the IBC which is automatically lifted out of product flow ‘internally’ leaving a full bore port for passage of material with minimal risk to solids flow.
- Typical performance of the primary device itself can be expected to be in the range of 5-100 microgramme per cubic meter, as an OEL.
- Secondary enhancements of air flow and secondary covers will bring levels down to 1 microgramme per cubic meter as an OEL again dependent on number of disconnections per day.

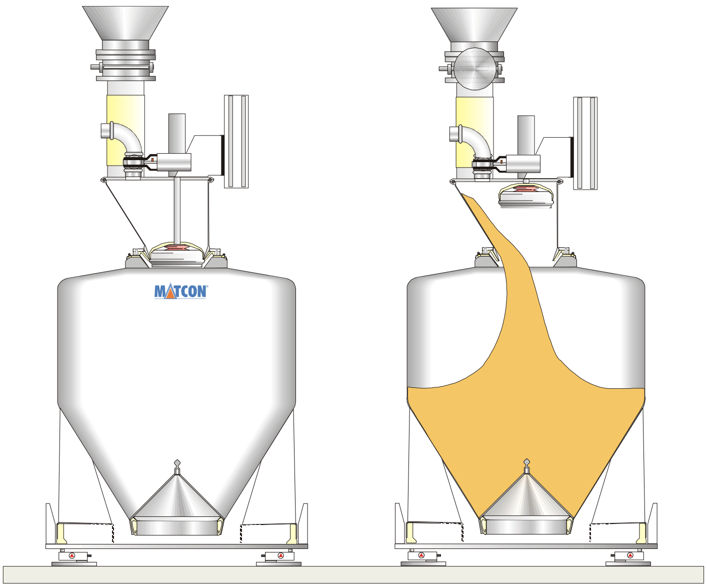

Fig. 11 - Contained IBC Filling

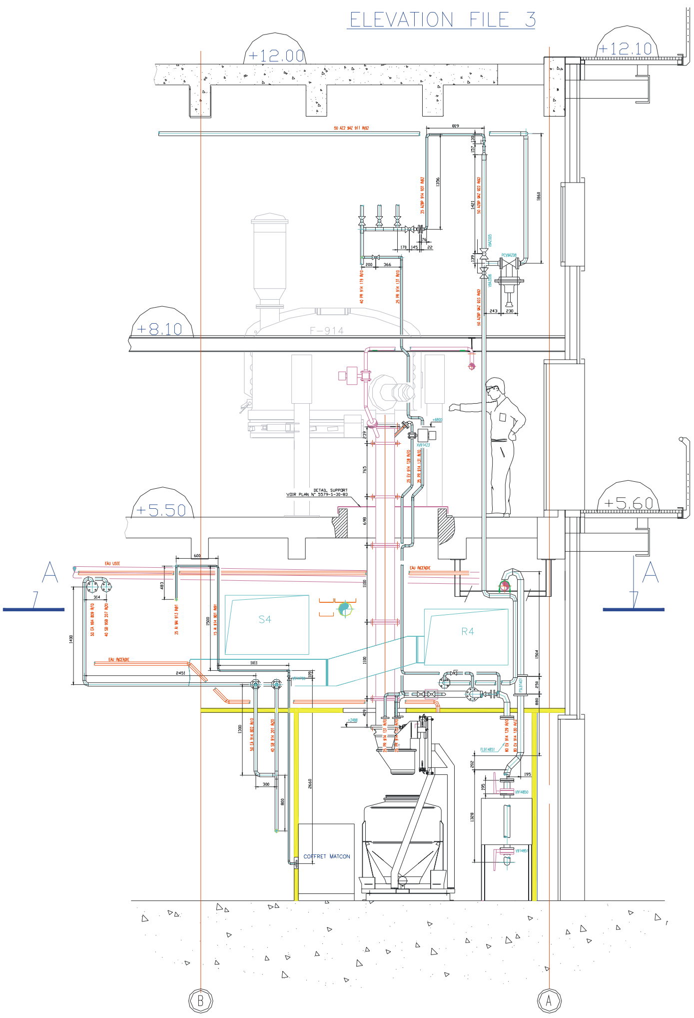

Fig. 10 - Contained Filling Of IBC From

Cone Valve Discharge Systems

- This system originally focussed primarily on the ability to consistently discharge materials, almost irrespective of flow characteristics. Developments in recent years have enabled enhanced containment performance through airwash (or nitrogen wash) and in some cases the use of automatically applied secondary covers.
- Typical performance can be expected to be in the range of 5-100 micgrammes per cubic meter as an OEL.
- Secondary enhancement of air flow and secondary covers will bring levels down to 1 microgramme per cubic meter as an OEL, again dependent on number of disconnections per day.

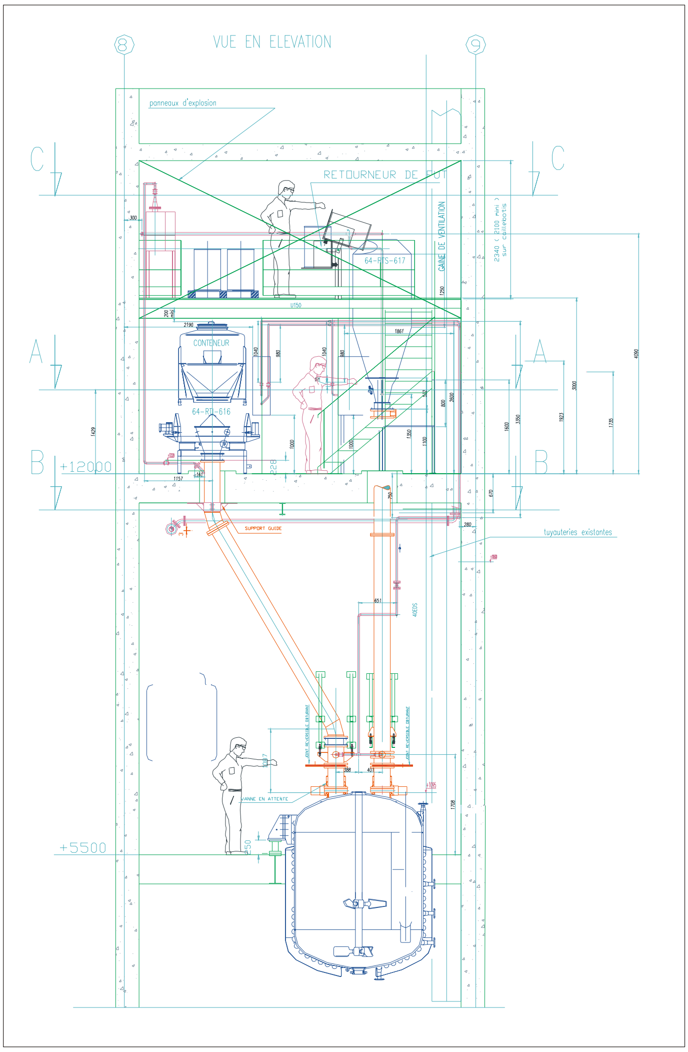

Fig. 12 - Contained Controlled Discharge From IBC to Reactor.

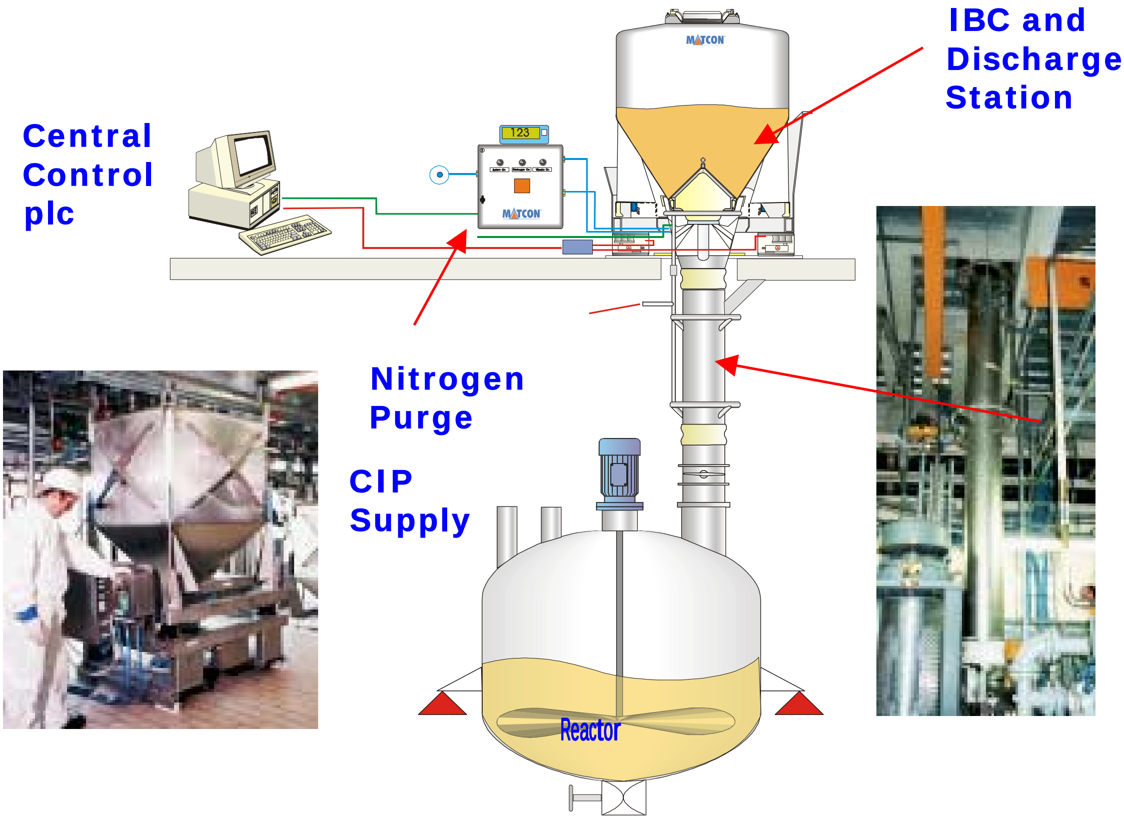

Fig. 13 - Contained Reactor Feed System.

8.0 CONCLUSIONS:

Containment is ultimately a responsibility not just for the supplier of containment equipment, but also for the Pharmaceutical Manufacturer and the Engineering Contractor.

Containment is not an 'off the shelf' item to be bolted in position. Achieving containment requires a marriage of equipment with operating and process philosophies that have to be fully understood by all parties to achieve optimum operation.

The issues of solids handling (material flow, bridging, flushing, segregation, venting) need to be fully understood and addressed or containment will always be compromised.

AUTHOR INFORMATION

Name:	Dave Drew
Company:	Matcon Group Ltd
Title:	Group Pharmaceutical Director
Address:	Matcon House, London Road, Moreton in Marsh, GLOS, GL56 OHJ, UK
Phone:	+44 1608 651666
Fax:	+44 1608 651635
E-mail:	**ddrew@matcon.co.uk**

BIOGRAPHY

Dave Drew is a mechanical engineer with 25 years extensive experience in the design and supply of Bulk and Intermediate Bulk Solids Handling Equipment and Integrated Process Systems.

He provides technical support for MATCON companies, licensees and agents worldwide, with specific interest in Primary and Secondary Pharmaceuticals.

He has worked extensively on the development of the MATCON “Cone Valve” IBC System for use in fully automated pharmaceutical facilities, with an emphasis on controlling solid flow from IBC’s to process, with containment of IBC filling and discharge.

He is also an active committee member of the central chapter of I.S.P.E in the UK.