



**Torsten Belger**  
*General Sales Manager, Powder Systems Limited*



**John Hanna**  
*European Director, Engineered Technologies Corporation*

# **A Brief Introduction to API / HAPI Plant Design & Validation for Potent Compounds Manufacture**

## ***Introduction***

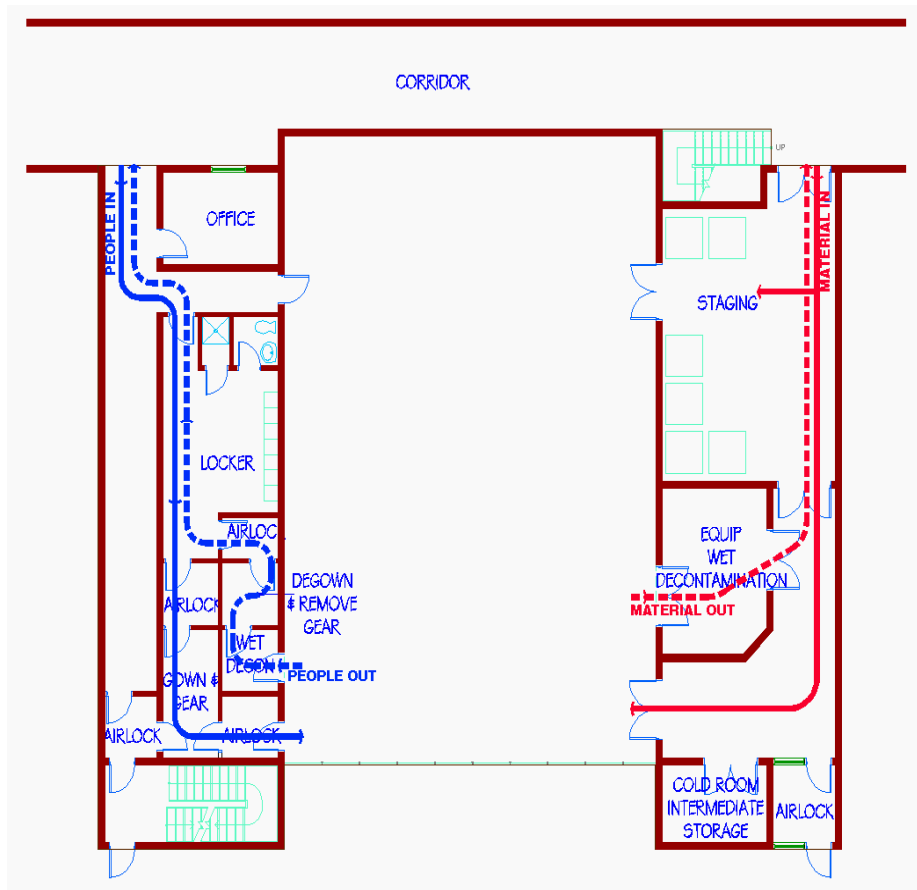
Currently some 5-10% of Pharmaceutical Drugs on the Market contain highly potent compounds. It is estimated that some 25% of the 6,500 drugs currently being developed, contain highly potent compounds. As a result of this a “class” of pharmaceutical manufacturing facilities, often referred to as Highly Active Pharmaceutical Ingredient (HAPI) facilities need to be developed to meet the specific challenges associated with the handling of such compounds. This article aims to outline the demands placed upon those involved in the specification, engineering and operation of such facilities and to provide some practical guidance on the measures need to address these demands. Comparisons, where possible, are drawn between conventional Active Pharmaceutical Ingredient (API) manufacturing facilities and HAPI facilities with differences highlighted. The handling of HAPI, affects in a much greater way than anticipated, the designs and “norms” that have been developed for API facilities.

Such effects include building layout, building ventilation and effluent handling. There are also specific effects on configuration and specification of the processing equipment itself with a typical equipment configuration such as a reactor-condenser-receiver becoming more complex since it has many more subsystems. The handling of HAPI involves the supply of “contained” solutions and readers should rest assured that there is considerable expertise and many practical existing engineering solutions already available. Each of these areas is investigated further below.

## *HAPI Plant Characteristics*

Conventional API facilities have Ventilation systems with air and room pressure regimes where the principal aim is the protection of the API from contamination introduced from adjacent areas to the processing area. This is achieved often by having processing areas operating at positive pressure to the surrounding areas. HAPI facilities conversely have pressure regimes where the emphasis is to ensure that adjacent areas do not become contaminated with the HAPI. These facilities typically have processing areas with high rates of air change. Such rates provide assurance that in the event of an unexpected release of HAPI into this immediate processing environment operator exposure will be minimized.

A possible HAPI facility layout is detailed in Fig 1. Separate gown/de-gown areas into the processing areas are required. Separation of personnel access from raw materials and finished product access should also be considered as good practice with appropriate differential pressure regimes as previously described.

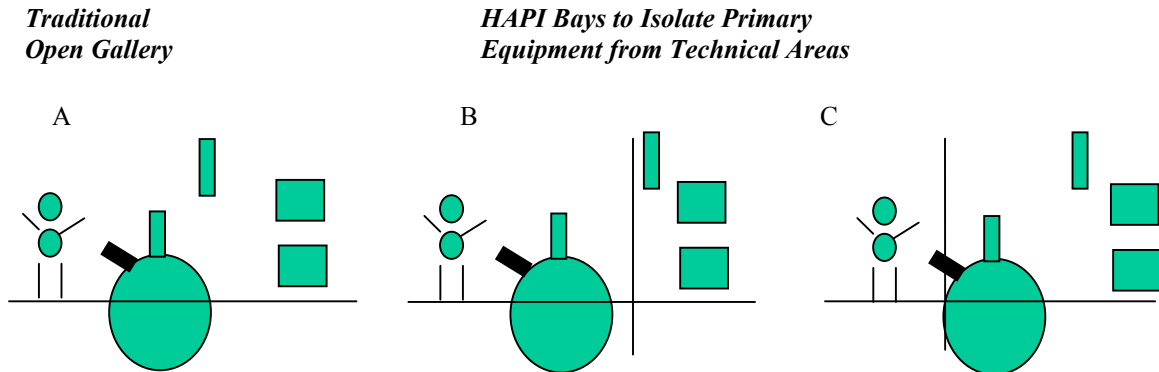


**Fig 1.**  
*Typical layout of HAPI facility*

## ***HAPI Processing Equipment and Equipment Configuration***

API facility design began with designs where reactors and processes were in “open galleries” as shown in Fig 2. Over time these designs evolved into separate processing bays. HAPI bay designs are a variation on this theme. Whilst HAPI facilities use processing bays with the bays acting as secondary containment, the primary containment for operations such as charging and discharging into and from the primary process equipment is achieved using proven equipment designs. Such equipment includes glovebox isolators, split butterfly valves, airlocks, rapid transfer ports etc.

A further aspect of HAPI bay design is that the amount of equipment, piping etc. in the HAPI bay should be minimized as indicated in Fig 2B and should be segregated from adjacent “technical areas.” Ancillary process equipment is located in these so-called “technical areas” and segregation is provided by a wall/partition. Such a design facilitates cleaning in the event of any unexpected release from the primary containment. A photograph of a plant with this design is shown in Fig 3. A further variation on this HAPI bay arrangement is shown in figure 2C where the only equipment that is not behind the wall is the primary containment equipment.



***Fig .2***  
***Bubble diagrams depicting a reactor condenser distillate receiver process group. The purpose of the diagram is to indicate the transition from open gallery processing suites for conventional API manufacture to HAPI processing suites where equipment in the bay is minimized.***

**Fig 3**

***Typical equipment Bay with segregating wall between primary process equipment and ancillary process equipment***



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Although facilities for HAPI tend to be smaller in scale, since the increased product potency allows for smaller batches to meet dosage demands, they are much greater in complexity due to the number of added systems, refined features and more physical congestion. Space available on the smaller reactors being used to process these reduced batches becomes limiting since the piping and instrumentation components do not shrink in the same proportion as the batch reactor size

### ***Features of HAPI processing equipment***

In general, HAPI facilities require processing equipment which is inherently cleanable. Components typically should easily dis-assemble for the cleaning operation and for the verification of the cleaning regime. Just as in API facility design cleaning of the equipment is a critical aspect of HAPI facility design with “cleaning downtime” directly affecting productivity due to its impact on batch cycle time. Maintenance of HAPI facilities is also severely affected by inefficient cleaning regimes caused by inadequate design.

HAPI facilities have increased controls and automation. Automation and controls systems should be used to maximize the extent of remote and non-intrusive process operations e.g level and weight determination systems. Sampling systems for in-process operations are also required to be closed and cleanable.

## ***Process Equipment Cleaning***

The effectiveness of cleaning systems for typical HAPI reactor system is influenced heavily by the choice of piping design. Joints in piping systems are particularly difficult to clean and the consequent need to minimize piping joints tends towards the use of special alloy metal piping systems as opposed to borosilicate glass, glass lined or PTFE lined. A well designed HAPI facility reactor-condenser-receiver piped system can have as few as 15 mechanical joints. This is in contrast to some 100 joints in a similar glass or PTFE lined piping system which could be used in an API facility. Although such systems should maximize welded designs, they cannot be fully welded since there is a need to verify the cleanliness of the HAPI piping system by an intrusive technique such as swabbing. HAPI piping designs have many similarities with “aseptic” piping systems. They are characterized by pocket free fittings, cleanable valves, polished interior finishes and with pipelines which are free draining. Reactor designs are also affected with the preference being pad as opposed to flange mounted nozzles to ease cleaning. Reactor interior finishes also are typically polished.

### ***CIP systems***

CIP systems in HAPI facilities generally rely on the “wetting” of surfaces with cleaning solvent. Within reactors this often requires the use of more than one spray device per vessel to avoid washing “shadows” typically created by items such as the vessel agitator affecting spray dispersion. This requirement for two or more spray devices results in reactor nozzles being occupied. With the number and size of nozzles decreasing due to smaller reactors being used in HAPI facilities, designers must alter piping layouts to configurations which can be accommodated on more shared nozzles.

Piping at less than DN80 nominal bore should be cleaned by in-line flow of liquid through it. Designers should be aware of the hazards of static build-up when using certain solvents. One means of reducing static build up is the restriction to pipeline flows which are less than 2 m/s. At DN 80 nominal bore and above high in-line piping flowrates are impractical since they require too large volumes of cleaning fluid. Consequently , DN 80 and greater nominal bore pipe is cleaned with spray devices which are integral to the piping.

Equipment spacing is also affected by CIP requirements in HAPI facilities. Long unwieldy charge chutes and processing lines should not be used since they result in inefficient cleaning regimes. Consequently where possible processing operations should be performed in combination equipment items such as filter/dryers, reactor-filter-dryer, centrifuge dryer, isolator-slurry vessel.

The quantity of CIP fluid should be minimized in order to reduce effluent. Recirculation of the CIP fluid through a filter is possible provided the filter can be removed and disposed of in a contained manner.

Spill containment is critical in all API facilities and especially in HAPI plant. Designers should provide collection points that facilitate the contained removal of liquids that contain HAPI. Designers should also address the containment and disposal of fire water containing HAPI.

### ***Specification of HAPI facilities***

In the specification of HAPI facilities two areas require specific consideration. Firstly, should an equipment supplier demonstrate the effectiveness of their CIP system and if so how? Secondly, should the equipment supplier demonstrate the effectiveness of the containment of their equipment and if so how?

In terms of demonstrating effectiveness of the CIP system, one means of doing this is to coat all surfaces which are to be cleaned by the CIP with a solution of Riboflavin in water at a concentration of 0.2 grammes/litre. The CIP system sprayballs and spray rings etc. can then be tested with water and it is recommended that inlet pressure, flow and duration of cleaning are recorded in a formal procedure. On

completion of CIP testing the surfaces which have been coated with Riboflavin and subsequently cleaned should be checked with a UV light source. Any remaining Riboflavin appears to fluoresce and is noticeable under this light. Acceptance criteria must be pre-defined to determine whether the CIP testing is acceptable and these should be defined on a system by system basis since equipment suppliers may provide additional systems such as flexible hoses or they may supply jacketed vessels with heating/cooling fluid, which allows the setting up of internal refluxing within the vessel to be cleaned.

## ***Selection of suitable Solids Containment Equipment***

When selecting suitable containment equipment for new or existing HAPI Processing Plant it is important to carefully assess all aspects of the process and to fully understand its materials flow. Failure to do so will ultimately result in the wrong containment philosophy and equipment being selected and the end user of the plant cannot will not achieve the desired containment results.

In order to maximise the achievable containment levels for any engineered solution, actual operator intervention in handling solids needs to be minimised as much as possible, after all, if no-one has to get near the hazardous substance, then no-one will be exposed to it. It is, therefore, important to spend an appropriate amount of time and money in the design of any equipment required to aid solids flow of the hazardous substances. Of course, as in many solids dispensing and container emptying applications, complete exclusion of manual intervention with the hazardous substance is not always possible. In cases like that, a specialist Containment Engineer with significant relevant experience should be involved in the project. Containment Engineers can be specialists from Equipment Manufacturers, Consultants or Engineering Companies and some of the larger Pharmaceutical Companies even have their own in-house personnel specifically dedicated to addressing these types of issues.

A good Containment Engineer should only require a certain minimum amount of initial information to successfully assess any particular project requirements and to make an initial proposal for possible containment strategies and possible solutions for any given issue. Of course, there should always be options presented for different philosophies. i.e. split butterfly valve technology, glovebox technology, Personal Protective Equipment, bag technology and so on (a selection of these options is shown in the sample pics below). After an initial understanding of the processes involved (i.e. vessel charging, vessel unloading, dispensing, etc.), then for most Solids Containment Applications, answers to the following questions should enable any experienced Containment Engineer to provide these initial strategies:

- What containment level is required?
- What quantities of solids are involved? What is the frequency/time scale of handling these solids?
- What types and size of containers will the solids be handled in?
- Where do the containers come from and where will they go to?

Following on from this initial, basic information being provided, a first list of possible containment strategies can be drawn up. It will then be necessary to look at specific issues for any specific application in more detail. This may involve special solvents being used, special atmospheric requirements, integration of special process equipment in the containment philosophy, weighing equipment accuracies required for dispensing and off-loading applications and so on.

Designing equipment or a process for contained handling of hazardous substances is not 'Rocket Science' and does not always need to involve elaborate, costly and time consuming design studies and optimum solutions can be found reasonably quickly and without significant cost expenditure in most cases by simply applying some common sense and by drawing from the experiences already gained in many similar applications from around the world. However, in some cases it will be beneficial to employ a Containment Engineer or a group of Containment Engineers to carry out a more involved design study of the problems in hand, but this should be confined to the larger and more elaborate containment projects only.

The purchaser (end user) of any containment equipment must also be clear about what is expected of the containment equipment in terms of usability, containment performance and its validation, as well as cleanability of the equipment. These performance criteria need to be defined right at the outset of specification process, as they may effect the design, leadtime and cost of any equipment being chosen. Cleaning validation of the equipment has already been discussed earlier in the article, but appropriate containment performance validation and the way of how any results gained from such performance validation are expressed is much more of a contentious issue and has been the subject of much discussion in recent containment seminars and in the press. One example of how this can be tackled in the case of split butterfly valves are the containment evaluation guidelines about to be published by the SMEPAC group of user, manufacturers and containment consultants. These guidelines aim to provide a common basis for manufacturers and users of how to perform the tests, how to analyse the results and of how to present the results and it is likely that these guidelines will be adopted universally for the performance testing of split butterfly valves. The SMEPAC guideline is likely to be published later this year under the auspices of ISPE.

Containment and Cleaning validation can be provided by most containment equipment manufacturers as part of their Factory Acceptance Testing (FAT) of the equipment, but this can rarely represent actual operating conditions on site and with the users of the equipment, which has to remain the ultimate performance verification for any such equipment.

One aspect that is often being overlooked by many companies is the early and detailed involvement of the eventual end user of the containment equipment. These are the people, who will be directly interfacing with the containment equipment and they can make either a complete success or a complete failure of any containment solution selected. Where these Operatives have been involved in the selection of the equipment (design meetings, reference visits, factory acceptance tests, etc.) from the start, then this installs a sense of ownership of the final solution and most of the time they will do everything they can to ensure that the equipment is used as intended and that resolutions are found to any eventual problems or failures of the equipment. Where these Operatives have not been involved in the selection of the equipment, then this usually installs a sense of strong initial scepticism and the attitude often is ‘well, we did not need this equipment before, why do we need it now...’ and every effort may be made to deliberately find faults with the systems and to find reasons for why it should not be used. Of course, this is not always the case, but it does happen....

### ***In summary:***

- The choice of handling method will greatly influence the system performance and design
- For best results, all powder handling operations should be kept to a minimum
- Successful high containment is achieved if the solids flow is predictable without the operator having to directly access the system
- Providing the right information at the start of the project will greatly improve the level of success of the project

*Some Examples of the Possible Solids Containment Solutions*



**DRUM EMPTYING GLOVEBOX**



**FILTERDRYER GLOVEBOX**



**SPLIT BUTTERFLY VALVE**



**DRUM FILLING FLOWBOOTH**

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