

Sustainable Production of Highly Active Pharmaceutical Ingredients (HAPIs)

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Abstract- This paper deals with the sustainable and best methods that should be employed in the production of Highly Active Pharmaceutical Ingredients (HAPIs). We start with a brief introduction of HAPIs, which includes their basic definition, market value and applications. We then study the conventional HAPI manufacturing process and its drawbacks. Finally we move on to propose some methodologies which, if practiced, would lead to better manufacturing standards in terms of safety, cost and sustainability.

Index Terms- Containment, Good Manufacturing Practices (GMPs), Highly Active Pharmaceutical Ingredients (HAPIs), Occupational Exposure Limit (OEL)

I. INTRODUCTION

HAPIs are the compounds in medications that provide therapeutic effects. What differentiates HAPIs from APIs is their potency. They are the active ingredients that make a drug product effective and provide the pharmacological activity of any drug product or dosage form.

MARKET POSITION OF HAPIs:

The high potency market has seen steady growth in recent times and according to market researcher RNCOS¹, (HAPIs) represent the fastest growing segment in the global API industry. RNCOS estimates this market will reach US\$15.3bn by 2017. Such potent active ingredients typically include particular hormones, peptides and cytostatic² agents, as well as many new chemical entities (NCEs), i.e., chemicals that have not yet been fully characterised.

APPLICATIONS:

The selective targeting property of HAPIs is widely deployed in the treatment of cancer. HAPIs are also increasingly being used in the form of Antibody Drug Conjugates (ADCs)³ which is

an important and effective breakthrough in cancer treatment. ADCs are a combination of monoclonal antibodies and biologically active drugs. They combine the unique targeting ability of monoclonal antibodies and the cancer-killing ability of cytotoxic drugs. Highly potent anti-cancer drugs are efficient as they target cancers while minimizing the drug's exposure to the healthy tissues.

II. HAPI MANUFACTURING- CONVENTIONAL PROCESS

The process begins with un-milled HAPI powder being brought at the Production Plant.

➤ MILLING:

Milling is the process of mechanically reducing the size of solids. It is also referred to as comminution, grinding, disintegration and pulverizing. It is an important step in the process of turning the raw materials into viable drug products. It increases the rate of in-vivo⁵ dissolution and/or increases its bioavailability. It also results in narrower particle size distribution which makes products more uniform and effective. Particle size distributions impact powder mechanical properties, compression characteristics and dissolution performance. Milling can take place either in gas (dry milling) or in liquid (wet milling).

➤ BLENDING:

Subsequent to milling, the HAPI powder is blended. The purpose of blending is to homogenize the batch. Batch homogenization serves two related purposes. First, it means fewer samples have to be taken to obtain a representative sample of the powder population. Second, it helps ensure final product consistency.

III. MANUFACTURING PROCESS

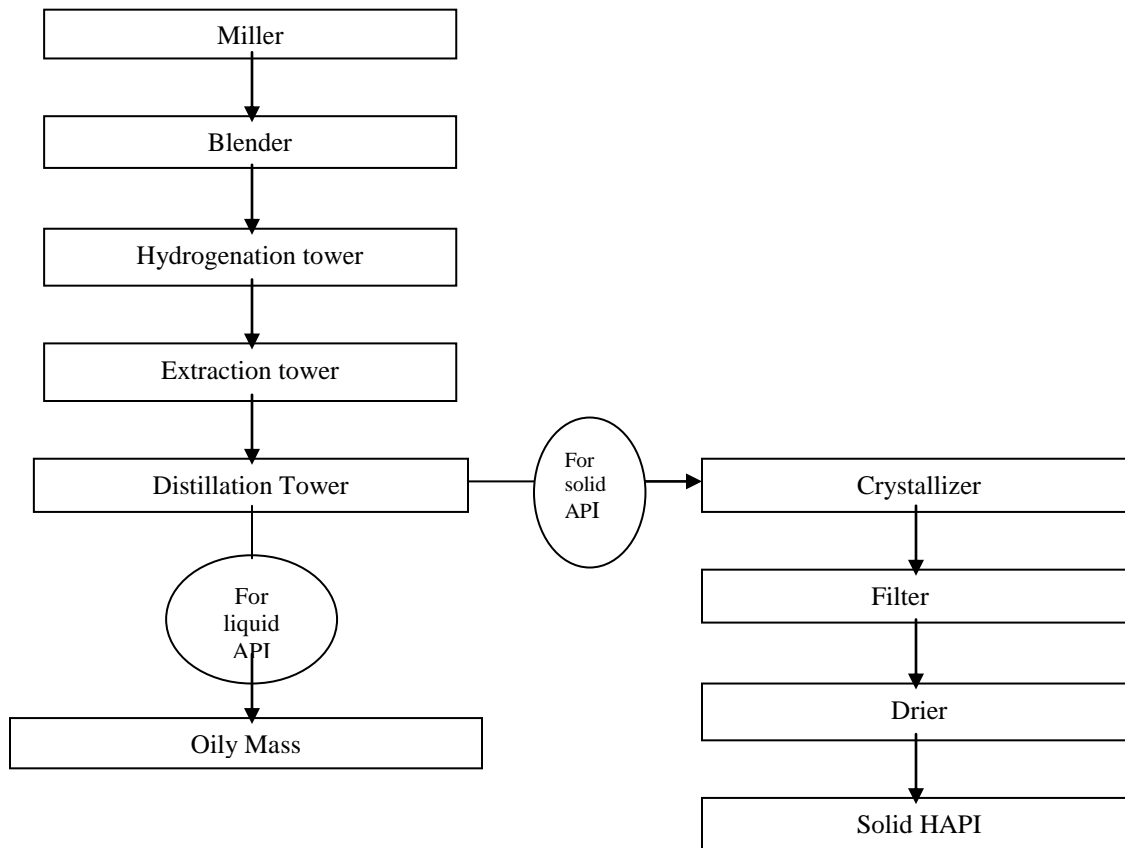


Figure 1: Block diagram for HAPI manufacturing

IV. DRAWBACKS OF THE CURRENT PROCESSES

The conventional process of HAPI manufacture has quite a few drawbacks when considering the environmental sustainability of the process.

- Milling generates fine dust particles. Hence milling units need to be deeply analysed and investigated to ensure proper levels of containment, ergonom⁴ and process accuracy.
- A cleaning step takes place between successive batches. If the next batch utilizes the same HAPI, the operator might perform a cursory cleaning step since he will not have to worry about cross contamination. If the next batch utilizes a different HAPI, then the operator performs a thorough, verifiable cleanse of the processing equipment to prevent cross-contamination. This process is quite time-consuming and we estimate that in the current process setup it can take seven to ten days for cleaning and verification.
- HAPIs have the potential to cause serious health effects in workers at very low airborne concentrations. They are known to exhibit carcinogenic, mutagenic, teratogenic⁵ or cytotoxic⁶ effects. The current process is such that it runs huge risk of environment and worker exposure.

- Powder flow-ability might be an issue if the flow path of material from one unit of production plant to the other is not well taken care of. This may lead to production constraints.

V. PROPOSALS

We propose that manufacturers utilise safe handling systems to protect workforce and the environment against the adverse effects of HAPI materials. We suggest the following remedies:

➤ USE OF CONE MILLS:

Cone milling is one of the most common methods of milling in the pharmaceutical and allied industries. Cone mills produce less dust than alternative forms of milling, thereby reducing environmental contamination.

➤ USE OF CONTAINMENTS:

‘Containment’ focuses on methods and equipments that prevent environment and operator exposure to HAPI powder by using engineered equipment solutions, administrative controls and Personal Protective Equipment (PPE).

Containment device selection: The principles of selecting containment equipment and verifying its effectiveness are: (i) A step by step analysis of the process to produce a detailed list of

all tasks that pose a threat to the environment and human workforce. (ii) Setting a containment performance target (CPT) (iii) Specifying and selecting containment equipment based on the task list and the CPT (iv) Verifying containment performance at the factory acceptance test (FAT)⁷ and the site acceptance test (SAT)⁸ (v) Assessing occupational exposure to workers during actual operations involving the HAPI.

Containment devices:

- *Barrier isolator*: The rigid or fixed walled isolator provides a contained environment within which a wide range of tasks can be performed. Thus whatever be the process taking place inside the containment, its effect on the outside atmosphere is nil. Typically, an isolator will operate at a slight negative pressure, though in some cases (to ensure product sterility) isolators can operate at a slightly positive pressure. The contained environment inside the isolator is ventilated with air entering and leaving the isolator. Operator access to the isolator chamber is usually via glove ports, which allow materials and equipment to be handled and to facilitate transfers in and out of the isolator.
- *Transfer chambers (passive)*: The transfer chamber is an enclosed chamber attached to the isolator with one sealable opening with a door into the isolator and the other sealable opening with another door to the outer environment. The chamber is not under negative pressure. This arrangement can be used to pass materials into a clean isolator, opening only one door at a time. It improves product flow-ability and facilitates safe transfer of material.
- *Airlock (active)*: The airlock is similar to the transfer chamber except that in this case the airlock is ventilated and is under negative pressure. This reduces the potential for airborne transfer from the contaminated isolator. If in addition, decontamination of materials leaving the isolator is possible, then this arrangement can be suitable for safe transfers out of the isolator whilst maintaining very high containment performance.
- *Bagging device*: The bagging transfer device (or bag-in/bag-out port) uses a specially constructed tube of flexible film material such as polythene (or continuous liner), attached to a port and fitted with double-seal rings. This arrangement enables continuous closed bags to be produced which can be used to enclose items transferred in or out of the isolator in a sealed bag. This solution to transferring materials and equipment is capable of high levels of containment.
- *Flexible charging bags*: A relatively recent innovation in containment equipment is the flexible charge bag. This device can deliver contained charges of small quantities of HAPI with good containment performance. One advantage of this device is its cost, allowing potent and highly potent APIs to be pre-packaged in a disposable contained transfer device.
- *Intermediate bulk containers*: These are large sacks or bags capable of holding one tonne or more of powdered or granular materials. Such containers are generally manufactured from woven fabric, generally

polypropylene. In order to make these bags waterproof, an impervious inner liner is added within the outer envelope. The product being transported is actually contained within the inner line. Liners previously used have generally been in the form of a cylindrical length of polyethylene or other impermeable plastics material. In the filling region of the container one end of the liner may be brought through a filling opening in the outer envelope and may be tied off after the container has been filled. At the discharge end of the container the liner is closed off and may be either laid loosely within the outer envelope or disposed in a predetermined relationship to an outlet spout from the outer envelope. The liner constructions are loosely fitted within the outer envelope and are prone to distortion within the envelope. This invention seeks to provide a container that avoids the disadvantages previously experienced with liners, yet can still be completely waterproof.

Split butterfly valves: The split butterfly valve (SBV) is widely used for transfers of potent and highly potent APIs. It is particularly useful where large quantities of material are being transferred. The details and principle of operation of the valve are well established and allow for good containment performance during contained transfers.



Figure 2: Intermediate Bulk Containers



Figure 3: Split Butterfly Valve

Containment performance: This analysis will provide the information required to specify the design of the containment system and the containment performance target (CPT) for the containment device will usually be based on the OEL of the material being handled. The aim of containment performance verification should be to demonstrate that the airborne concentration will not normally be exceeded. The containment performance is broadly defined as the airborne particulate concentration measured around the containment device and in the operator's breathing zone during simulated or actual operations.

Containment performance verification: Overall containment performance of an isolator system or a device may not be predictable. It is therefore usually necessary to verify containment performance prior to handling the HAPIs in the containment device. Containment performance verification assesses performance of the contained device or system either as built at the factory (FAT), when newly installed in a production facility (SAT) or when in routine use (ongoing occupational hygiene testing). Where several ancillary devices are present, such as with transfer devices fitted to an isolator, the use of all devices must be included in the containment performance evaluation.

➤ **SEGREGATION OF PRODUCTS BASED ON TOXICITY**

An occupational exposure limit is an upper limit on the acceptable concentration of a hazardous substance in workplace air for a particular material or class of materials. It is typically set by competent national authorities and enforced by legislation to protect occupational health and environment safety. It is an important tool in risk assessment and in the management of activities involving handling of highly active substances such as HAPIs. Hazard banding or control banding strategies can be used to ensure safe handling. Occupational Exposure Banding method shows 5 bands of products based on their Occupational Exposure Limit (OEL). HAPIs fall under the bands 4 and 5, i.e. OEL ranging from 100- 5000 $\mu\text{g}/\text{m}^3$. Each control band is associated with a safe handling guideline which describes in detail how a material of that potency should be handled in the different environments encountered in the workplace.

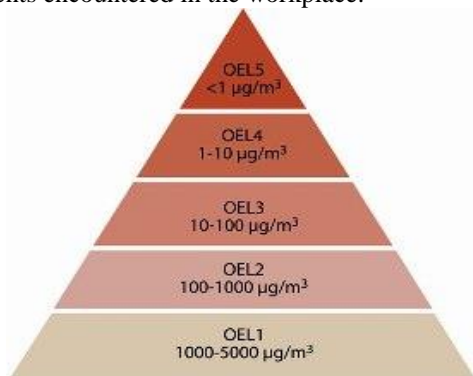


Figure 3: Occupational Exposure Banding

➤ **USE OF GOOD MANUFACTURING PRACTICES (GMPs):**

Maintaining the quality of HAPIs:

The quality of HAPIs is defined as meeting the appropriate specifications for the APIs and being produced in an appropriate

facility. Good Manufacturing Practices (GMPs) govern pharmaceutical product quality. Within the US, the Food and Drug Administration (FDA) enforces product quality standards using its version of GMPs termed current Good Manufacturing Practices (cGMPs).

Cleaning in Place (CIP):

It is used in hygiene critical industries such as Food, Beverage and Pharmaceutical, to clean a wide range of plant. CIP refers to the use of a mix of chemicals, heat and water to clean machinery, vessels or pipe work without dismantling the plant. It is performed to remove or obliterate previous Cell Culture batch components. It is used to remove in-process residues, control bio-burden, and reduce endotoxin⁹ levels within processing equipment and systems. Repeatable, reliable, and effective cleaning is of the utmost importance in a manufacturing facility. Cleaning procedures are validated to demonstrate that they are effective, reproducible, and under control. In order to adequately clean processing equipment, it must be designed with smooth stainless steel surfaces and interconnecting piping that has cleanable joints. The chemical properties of the cleaning agents must properly interact with the chemical and physical properties of the residues being removed. A typical CIP cycle consists of many steps which often include (in order):

- Pre-rinse with WFI (water for injection) or PW (purified water) which is performed to wet the interior surface of the tank and remove residue. It also provides a non-chemical pressure test of the CIP flow path
- Caustic solution single pass flush through the vessel to drain. Caustic is the main cleaning solution
- Caustic solution re-circulation through the vessel
- Intermediate WFI or PW rinse
- Acid solution wash – used to remove mineral precipitates and protein residues
- Final rinse with WFI or PW – rinses to flush out residual cleaning agents
- Final air blow – used to remove moisture remaining after CIP cycle

Critical parameters must be met and remain within the specification for the duration of the cycle. If the specification is not reached or maintained, cleaning will not be ensured and will have to be repeated. Critical parameters include temperature, flow rate, supply pressure and chemical concentration. Similar to CIP, there is Washing In Place (WIP). It is fully integrated with process controls and works by directing sufficient flow and pressure of water to remove residues inside the reactor. Cleaning cycles vary depending on the complexity of cleaning. After cleaning, the water re-circulates back into the system. Benefits include standardization of the cleaning process and reduced cleaning time.

VI. CONCLUSION

HAPIs play an important role in the drug product industry. They make a drug product effective. Owing to their curing abilities, their manufacturing amount cannot be reduced drastically. Having stated that, the harmful effects of the

manufacturing process cannot be ignored as well. Environmental degradation is a matter of global concern, and no such process should be allowed that adds to it. The best way to protect the environment and humans from their harmful effects of exposure is to take the necessary precautions at the root level itself. These include elimination or minimisation of the any and every possibility of environmental exposure. The methods in which the same can be accomplished have been stated above. Practicing these will make the HAPI manufacturing process an environmentally sustainable one.

APPENDIX

1. RNCOS- industry research and consultancy firm
2. Cytostatic agent- a drug that blocks cell division
3. Antibody Drug Conjugates (ADCs) - drugs designed as a targeted therapy for the treatment cancer
4. ergonomy- science of equipment design, to maximize productivity by reducing operator fatigue and discomfort
5. teratogenic- causing malformations of an embryo or a foetus
6. Cytotoxic- producing a toxic effect on cells.
7. Factory Acceptance Test- test conducted to determine if the requirements of factory are met
8. Site Acceptance Test- test conducted to determine if the requirements of the site are met
9. Endotoxin - heat-stable toxin present in the intact bacterial cell but not in cell-free filtrates of cultures of intact bacteria

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