100 TIPS FOR DESIGNING, MANUFACTURING, PACKAGING AND MONITORING BETA LACTAM FACILITIES

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This article is based self experience of 25 years of the author

INTRODUCTION

Beta lactam antibiotics are one of the largest group of antibacterial products used clinically to combat the most resistant pathogens. It basically includes the following drugs:

1.Penicillin's (e.g., Benzyl penicillin , Methicillin , Nafcillin , Cloxacillin , Dicloxacillin, Ampicillin,Amoxicillin, Bacampicillin, ,Pivampicillin , Carbenicillin , Ticarcillin , Azlocillin Mezlocillin, Piperacillin)

2. Cephalosporin (e.g., cephalexin, cefaclor)

3. Penems (e.g., imipenem, meropenem)
4. Carbacephems (e.g., loracarbef)
5. Monobactams (e.g., aztreonam)

The penicillin's, cephalosporins, Penems, and Carbacephems are a characteristic bicyclical core structure, which is believed to initiate allergic reactions. The Monobactams aztreonam has a unique monocyclic beta-lactam nucleus and rarely cross-reacts with penicillin and cephalosporin's. Aztreonam and ceftazidime have a common side chain, and cross-reactivity between aztreonam and ceftazidime has been reported

Unfortunately, most of the Beta lactam are associated with hypersensitive reactions. As per information available in medical journals about 7% to 8 % of individuals in world are allergic to penicillin's and the allergy may be a life threatening for an individual

The Code of Federal Regulations 21 CFR § 211.42(c) lays down that the storage, sampling, manufacture; processing and packing of penicillin shall be performed in separate facilities. This is commonly misunderstood that "the separate facilities "means separate site and /or separate building. However, it is not so. Further, the FDA expects from manufacturers to treat non-

penicillin beta lactam-based products (e.g. Cephalosporin) in regard to separation exactly like penicillin.

The major challenges in designing, manufacturing and packaging Beta Lactam Facilities are as per follows:

1. How to physically and functionally isolate Beta lactam Facility from adjacent facilities
2. How to design Man and material Flow for handling and processing the Non Beta lactam products?
3. How to design the HVAC, spillage control and decontamination systems?
4. How to detect, measure and avoid the cross contamination?
5. How to control process wastes and how to dispose off the same safely?

TIPS FOR DESIGNING, MANUFACTURING, PACKAGING AND MONITORING BETA LACTAM FACILITIES

1	Do use dedicated facility and AHU system for manufacturing each class of Beta lactam Products. FDA has recommended dedicated facility for each of the following group of Beta lactam: 1.Penicillin's(e.g., ampicillin, oxacillin) 2.Cephalosporin (e.g., cephalexin, cefaclor) 3.Penems (e.g., imipenem, meropenem) 4.Carbacephems (e.g., loracarbef) 5.Monobactams (e.g., aztreonam)
2	If Beta lactam and non Beta lactam production occurs in the same building the penicillin area must be structurally and functionally isolated. Nothing shall be common between the two facilities.
3	Do Fulfill all regulatory and related requirements to comply with environmental and occupational health safety from Beta lactam Antibiotics
4	Do have proper procedures to restrict misuse, spillage, dusting and occupational health hazardous from Beta lactam products.
5	Do train employees, suppliers and contractors on environmental, occupational health and safety from the use of Beta lactam products.
6	Do Closely monitor gowning, sampling, weighing, mixing, filling and packing of Beta lactam products for likely cross contamination of other products.
7	Do validate LAF hoods and filter systems used for handling Beta lactam Products
8	Do ensuring that the vessels, equipments, machines, used for processing Beta Lactam products are adequately and efficiently decontaminated prior to repeat use.
9	Do ensure that airlocks, change rooms, pass boxes are robust in construction to avoid cross contamination of Beta lactam products.
10	Do ensure that entry and exit doors, for materials and personnel, have an interlock mechanism to prevent the opening of more than one door at a time
11	Do ensure that the man/material entry and exit facilities are independent. The exit

	side must incorporate air showers to take off Beta lactam residues from the operator's body.
12	Do ensure that facility is maintained at a negative air pressure to the environment. This will restrict environmental contamination with beta lactam drug residues
13	Do ensure that the premises (and equipment) are appropriately designed and installed to facilitate batch to batch cleaning and decontamination
14	Do ensure that the man and material flow is properly designed to avoid undue exposure and spreading of the Beta lactam residues
15	Do ensure that the activities carried out in the vicinity of the site are closely monitored for likely contamination
16	Do ensure that the HVAC outlets of Beta lactam section does not cross match with HVAC inlet of No Beta lactam facility.
17	Do ensure that that Beta lactam facility is a well-sealed structure with no air leakage through ceilings, service penetrations, door, windows and ventilators.
18	Do ensure that HVAC system is appropriately designed, installed and maintained to ensure protection of product, personnel and the environment with Beta lactam residues. The direct venting of the air to the atmosphere is strictly prohibited.
19	Do ensure that the principals of airflow direction, air filtration standards, temperature, humidity and related parameters are designed to protect the operators from direct touch, deposition or inhalation of beta lactam products.
20	Do ensure that appropriate air pressure and alarm systems have been provided to warn of any pressure cascade reversal or loss of designed pressure status. The appropriate design, alert and action limits should be in place.
21	Do ensure that starting and stopping of the supply and exhaust air fan should be synchronized such that the premises remain at the required negative pressure during start-up and shut-down.
22	Do ensure that air pressure cascade within the facility, although negative pressure to environment, should comply with normal pharmaceutical pressure cascade requirements with regards to product protection, dust containment and personnel protection.
23	Do ensure that there is adequate light in the facility to indicate deposition of Beta lactam residues on walls, roof and machines is in place.
24	Do ensure that the air is exhausted to the outside only through HEPA filters and not recirculated except to the same area, and provided that further HEPA filtration is used
25	Do ensure that where possible, single-pass air-handling systems with no recirculation are provided.
26	Do ensure that the exhaust air or return air should be filtered through a safe-change or bag-in-bag-out filter housing containing pre-filters and HEPA filters, both of which should be removable with the safe bagging system.
27	Do ensure that Changing rooms are supplied with air filtered to the same standard as that for the work area they serve.
28	Do ensure that airlocks and pass-through hatches are effectively covered by AHU to provide necessary air pressure cascade and containment. The final air lock or pass-through hatch bordering on non-GMP area should be at a positive pressure to prevent the ingress of contaminants into the facility.

29	Do ensure that operators leaving the containment area pass through air showers, to remove dust particles from their garments.
30	Do ensure that all contaminated garments are safely bagged before leaving the facility for laundering
31	Do ensure that Appropriate measures are taken to prevent airflow from the primary packing area (through the conveyor "mouse hole") to the secondary packing area.
32	Do ensure that HEPA filters in the supply air system should be terminally mounted to avoid cross-contamination from backflow in the event of a supply airflow failure.
33	Do ensure that biosafety cabinets or glove boxes are used to handle highly potent Beta lactam products
34	Do ensure that there is a system description including schematic drawings of the filters and their specifications, the number of air changes per hour, pressure gradients, clean room classes and related specifications.
35	Do ensure that pressure indicators are designed to monitor the pressure gradients effectively.
36	Do ensure that suitable energy backup systems such as diesel based electricity generators are employed to maintain the system from reversing and resulting into undue contamination
37	Ensure that air supplied in the facility confirm to international standards and is consistent with the zone concepts and the product specific protection required.
38	Do conduct risk analysis for potential cross-contamination of the non beta lactam products from beta lactam or contamination of one Betalactam with other Betalactam Product.
39	Do ensure that if return air is adequately processed to exclude possible Beta lactam residues. Further , ensure that when recirculated air is used, fresh air should be introduced into the system at a rate of 15% of the supply air
40	Do ensure that HVAC and exhaust fans are started and stopped in the correct sequence to ensure that a negative pressure is maintained during power-up and power-down.
41	Do ensure that to meet an emergency shut-down an automatic shut-off damper has been located in the supply air stream to ensure the rate of decline of the supply air quantity exceeds the rate of decline of the exhaust air quantity
42	Do ensure that Safe change or bag-in-bag-out filter housings should be suitably designed to inhibit dust from the filters entering the atmosphere
43	Do ensure that that the exhaust systems are protected from two banks of HEPA filters in series.
44	Do ensure that all filter banks are provided with pressure differential indication gauges to indicate the filter dust loadings and life span of the filters.
45	Ensure that plastic and rubber tubing's are not used for connecting pressure gauzes as the same can perish resulting in environmental dusting
46	Do ensure that Monitoring of filters is done at regular intervals in order to prevent excessive filter loading that could force dust particles through the filter media, or can cause the filters to burst, resulting in significant contamination.
47	Do ensure that Computer-based data monitoring systems is installed, to monitor filter condition.
48	Do ensure that Filter pressure gauges are marked with sign to indicate recalibration

	and change of filter assembly.
49	Do ensure that Installed filter leakage tests should be performed in accordance with ISO 14644-3.
50	Do ensure that exhaust air fan on a safe change filter system should be located after the filters so that the filter housing is maintained at a negative pressure.
51	Do ensure that filter housings are installed at exhaust points on FBD, Coating Pan, and Compression Machines. Further these housing shall be designed for quick replacement.
52	Do assure that all air exhaust points are located as far as possible from air entry points in the facility. Further the exit points should be at higher level to air inlet points so as to minimize the possibility of re-entrainment of exhaust air. The dominant and seasonal wind directions should also be taken into account when positioning exhaust and supply points.
53	Do ensure that the maintenance staff is provided personal protection equipment (PPE) and breathing air systems for attending the maintenance of damaged ducts and machines laden with Beta lactam residues
54	Do Ensure that dedicated airlocks are provided for cleaning and sanitizing HEPA Filters. Further ensure that all cleaning operations are performed by specially trained persons well equipped with Personal Protective Equipments
55	Do Ensure that all contaminated filters are suitably disposed off and records are maintained.
56	Do Ensure that all Portable Vacuum Cleaners, Portable Dust Collector are fitted with HEPA Filters
57	Do Ensure that the operators are fully decontaminated during entry and exist through over head and lateral air showers operating at high speed
58	Do Ensure that sufficiently large air extract grilles at low level are provided to draw the contaminated air away and return it to the filtration system.
59	Do ensure that the sufficient number of vertical unidirectional airflow system is provided at various places to flush the contaminants from the operators and machines.
60	Do Ensure that Air filtration on the supply air and return/exhaust air comply with the same filtration standards as used in the manufacturing facility
61	Do ensure that the air showers are activated as soon as the door is opened for entry.
62	Do ensure that there is timing device on the exit door of interlocks to allow sufficient time for the decontamination process to be effective.
63	Do provided Flushing devices similar to air showers for material exits to assist flushing off the contaminants.
64	Do use wet mist/fog system for decontaminating the entire system including the operators and their garments for floating residues
65	Do ensure that Air Showers are subjected to appropriate qualification
66	Do ensure that Liquid and solid waste are suitably disposed to avoid environmental contamination.
67	Do use special scrappers in mixing devices to scrap almost 100% of the Beta lactam Products.
68	Do design Beta lactam and No Beta lactam Facilities separately. Further, avoid common entrance, stores, and packaging and dispatch areas. Don't appoint common

	QA personnel for collecting samples
69	Do check that SOP for decontamination of operator's gowns, plastic bags, corrugated cardboard boxes is robust.
70	Do check all materials, documents, and sample containers are decontaminated prior to removal from manufacturing blocks
71	Do restrict movement of personnel from Beta Lactam area to Non Beta lactam areas.
72	Do ensure that suitable SOP is in place for wiping operator gowns, plastic bags and corrugated cardboard boxes before their disposal
73	Do check that floor, walls ,roofs and machine surfaces are regularly monitored for residual amounts of Beta lactam Products
74	Do ensure that surface testing procedures are capable of reflecting true levels of contamination.
75	Do ensure that the surfaces alerts system is available to warn possible failures in Cross Contamination Control System
76	Do ensure that the surface recovery studies for Beta lactam residues are suitably validated
77	Do ensure that the analytical methods employed for analyzing beta-lactam contamination on porous surface materials such as operator gowns, corrugated cardboard boxes are fully validated.
78	Do ensure that if swab surface sampling method is used to detect residual levels of Beta Lactam in any equipment : (a)The recovery studies are adequately performed (b)All hard to clean surfaces are including in the sampling program. (c)The swabs of appropriately large sizes are used for extraction of impurities
79	Do ensure that the cross contamination inspection points include worst case areas
80	Do address the Contamination Control and Risk Analysis plans for preventing cross contamination.
81	Do conduct the root cause investigations/OOS in case of cross contamination. Do identify assignable cause for unintentional contamination of normal products with beta lactam
82	Do ensure that the organizational structure, procedures, processes, resources, and activities are adequate to maintain integrity of Beta lactam products
83	Do provide dedicated space for eye wash/hand wash/feet wash/bathing in case of heavy contamination with Beta lactam
84	Do provided dedicated storage area for Beta lactam Actives and Finished products
85	Do provide emergency exits in case of accidental contamination
86	Do conduct Cross Contamination audits and Annual Cross Contamination Review
87	Do impart Regular training on cross contamination and dust control to all production employees
88	Do practice Mock drills to check vigilance to accidental cross contamination, system failures
89	Do maintain MSDS for all Beta Lactam Materials/Products
90	Do ensure Proper signage and safety symbols to handle Beta lactam products safely
91	Do provide tight fitting dust covers to all machines
92	Do use easily cleanable Teflon, PVDF, hastelloy, stainless steel for lining the utility

	pipers for handling Beta lactam Products
93	Do Use Contamination Control ,Management and Monitoring System ,Supervisory Control and Data Acquisition systems for contamination control
94	Do use Zero hold systems for mixing, separation , size reduction, drying and filling of beta lactam products
95	Do use automated systems for inspecting, counting and packaging of beta lactam products.
96	Do use Vacuum transfer system for handling granular and liquid Beta lactam products
97	Do use wherever possible disposable clean garments for all manufacturing, inspection and handling of Beta lactam products.
98	Do provide 24 Hours First Aid and Medical facility to treat any untoward side effects resulting from sensitization from Beta lactam.
99	Do use Monolithic Epoxy Coated Floorings in core production areas to discourage deposition of Beta lactam Dust on floor.
100	Do use CCTV system for continuous monitoring of operations which can result in cross contamination
101	Do insulate all door, windows, hatches for possible leakage of beta lactam residues

SUMMARY

This article provides numerous tips for designing the facility for storage, manufacturing and packaging of Beta lactam Products along with other products side by side in the same premises or at different premises situated at the same site. The guidelines are also effective in controlling accidental inhalation and sensitization to Beta lactam Products in a dedicated facility

The author recommends that all possible precautions shall be taken to restrict cross contamination or mixing of Beta lactam products with non Beta lactam.

The articles provides specific procedures for designing man and material flow, material handling, cleaning of equipments to ensure that there is no cross contamination .The major contribution of the article is that it provides solutions to many deficiencies raised by FDA during inspection of Beta lactam facilities.

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