Drug Development and Industrial Pharmacy, 22(6), 541-554 (1996)

Problems Involved in the Manufacture of Penicillin Products

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ABSTRACT

We present an examination of the problems and requirements of the various international standards relating to the production (manufacture and control) of noninjectable, solid penicillin products. We describe a system developed in the setting up of a production department in a penicillin plant, and its treatment for subsequent validation.

PENICILLIN CONTAMINATION IN THE MANUFACTURE OF NONINJECTABLE MEDICINES: EFFECTIVE BARRIERS

Cross contamination is understood to be the accidental mixing of one product with another of a different type. If the contaminant is highly toxic, very potent in small doses, or a sensitizing agent (e.g., antibiotics such as cephalosperines and penicillins; antineoplastics; alkaloids; steroids or vaccines with living microorganisms), the consequences can be particularly dangerous. The standards of Good Manufacturing Practice (GMP) refer to cross contamination between products in several of their points, making special mention of those contaminations considered most dangerous, of which penicillin contamination stands out. However, these references are neither extensive nor conclusive, and the person responsible for the setting-up or maintenance of a plant or department of penicillin product manufacture may encounter numerous technical or even logistical problems. The view of the British inspector Hutton (1) is very orientative in this respect, extending the idea to products such as digoxin, cephalosporines, etc.

This work is not intended as a guide, but rather is presented as a summary of the work carried out in the setting-up of one particular penicillin area. If it is in any way valid, or serves to help other professionals, our aim will have been achieved.

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A Question of Professional Ethics: Anaphylactic Shock. Anaphylactic shock is an extremely serious complication of penicillin therapy. It occurs rarely but due to its sudden presentation and the seriousness of its symptomology (alarming fall in blood pressure, rapid heartbeat, and paleness) is considered a medical emergency which requires effective treatment to save the life of the patient. Some symptoms usually precede the shock, such as urticaria, sweating, breathing difficulties, dizziness, or chest pains. It should be pointed out that this reaction can come about following both intravenous and oral administration.

Nonpenicillin products contaminated with penicillin particles can cause serious problems if they are ingested by a person who is sensitive to them, and may even result in death. It is often stated (above all in staff training courses) that, from an ethical point of view, laboratories are not mere businesses, in the commercial sense of maximizing profits, but also carry out a task of public service to society. Patients can have no faith whatsoever in products whose therapeutic activity is erratic or which lack a total guarantee of quality, especially if the products offered to society are ineffective or unsafe. Laboratories involved in the manufacture of medications build a reputation based on the quality and reliability of their products, which must not be undermined in any way by mistakes or lack of control over the products.

REVIEW OF CURRENT GUIDELINES RELATING TO CROSS CONTAMINATION BY PENICILLIN PRODUCTS

With regard to guidelines, the standards of good manufacturing consider, in a rather generalized way, the subject of cross contamination. Most of them suggest barrier and control mechanisms against the propagation of any type of contamination, and the same, but with greater detail, against highly dangerous products (those which sensitize in low doses). The indications are identical in most of the guides; thus the following is a specification of the most extensive indications regarding cross contamination: first, those provided by the European Union (EU) guide in its Spanish, Health edition (2), followed by the British "Orange Guide" (3), and then by those specific indications which relate to penicillin contamination, compiled from the other international guides (4).

European Union Standards Relating to Medications: Guide to the Standards of Correct Manufacturing Practice of Medications

EU Standards (in their last Spanish edition, Ref. 2) dedicate several points to the subject of contamination of pharmaceutical products by others. In general,the following points stand out from among the guidelines which are proposed to avoid contamination (be it by sensitization or not):

- Minimize the risks of contamination on the premises and facilitate cleanliness (*3.01).
- Separate facilities for different product (*3.06); physical separation (for the most dangerous products), temporary separation or separation during each period of production (when the former is not feasible), or the establishment of systems of enclosed manufacture.
- Precisely delimited work flows (*5.44), applied to both manufacture (*3.7) and conditioning (*3.15).
- Avoid the simultaneous manufacture or conditioning, in either space or time, of different products (*5.9).
- Avoid the production of dust in manufacturing operations (*3.14) and its diffusion (*5.11), installing adequate systems of extraction (*5.19b).
- Provide protection for the products against possible contamination (*5.10) in every phase of manufacture.
- Avoid the *recirculation* towards production areas of insufficiently treated air (*5.19.c).
- Establish procedures for cleaning and decontamination which are adequate for each product, piece of equipment, or facility used (*5.19.e), observing the maximum permitted level of residues in same (*5.19.g).
- Use protective clothing (*5.19.d) or materials, which should not be reused in the production of other, different products.
- Monitor levels of contaminants, with previously established sampling plans and permitted levels (*5.20).

It should be borne in mind that the previous points, and other, similar criteria, reflected throughout the Standards, should be adapted and applied according to the philosophy of each production department, as it is extremely difficult to generalize. Without a shadow of doubt, each person in charge will have to evaluate which procedures minimize or increase the risk of cross

contamination, as well as those factors which will help in the reduction of such risk.

The "Orange Guide" (Good Pharmaceutical Manufacturing Practice 1983)

The Orange Guide (3) contains detailed information on cross contamination, dedicating an appendix (No. 2) to the subject. In addition to those general points—which are, by and large, the same as those of the EU (*4.4, *4.35, *5.42)—the following are notable for the specific detail they contain:

- The recommendation that *compressed air* or *brushes* should be used with care in cleaning processes (*4.21), wet cleaning and vacuum methods being preferable. Compressed air contributes to the dissemination of dust in the atmosphere and brushes always retain particles, in their bristles, which are easily disseminated if the brushes are reused. In the case of vacuum cleaners, the use of those that incorporate a filter system in the extractor which ends in a HEPA filter would be advisable.
- The need to study the location of air intakes, outlets, and ducts, with the aim of avoiding as far as possible their contamination by the recycling of extracted air (*4.16).
- The cleanliness of containers in the course of manufacture or awaiting report, and the closure of same in the case of noncontinuous work flow processes (*5.6).
- Reliable sampling operations, avoiding deterioration of the sampled material (*8.21).
- Safe storage of products, avoiding risks of mixing or contamination with others (*18.4).

In Appendix 2 of the guide, the points given in the EU Standards are examined in more detail. For example, point 2 indicates that the precautions to be taken should be directly related to the type of potential contamination, and clearly states that the necessary *quantities and flows of air* should be established to minimize the risk of cross contamination, though it gives no specific norms. In point 3 it emphasizes that the materials and personnel that enter these segregated areas should do so through pressurized antechambers (SAS adequate), using changes of clothing, and that there should be *decontamination procedures*. In point 4 there is a reminder that defective *cleaning* is a common source of cross contamination which must be avoided. It emphasizes that, due to its complexity, care must be taken in the cleaning of piping, valves, joints, and bearings; and of drying, grinding, sifting, or mixing equipment. Point 5 returns to the subject of special *clothing*, which must not leave the segregated area and must be adequately washed and decontaminated. Point 6 mentions equipment which, due to its size, has the capacity to operate on more than one product at a time (such as stoves), a practice which should be avoided. Finally, point 7 emphasizes the necessity of *monitoring the contamination* of products which are highly potent in small doses or are sensitizing agents.

Standards of Good Manufacturing Practice of the FDA (Current Good Manufacturing Practice for Finished Pharmaceuticals)

These are the strictest standards insofar as concerns penicillin contamination and the only ones which set a limit to observe. There are only three points but they are extremely demanding:

1. In general, if there is a possibility that a nonpenicillin product has been exposed to contamination from penicillin products, it must be analyzed immediately and must not be commercialized if detectable levels are found, in accordance with the official procedures, "Procedures for detecting and measuring penicillin contamination in drugs"(*211.176). All of these products use microbiological methods.
2. With regard to buildings and facilities, the formulation, processing, and conditioning of penicillin products must be carried out in facilities which are separated from those used for other ends or pharmaceutical products (*211.42).
3. Furthermore, the treatment of the air dedicated to the area of penicillin products must be independent of the rest of the pharmaceutical plant (*3211.46).

Australian Standards of Good Manufacturing Practice (Code of Good Manufacturing Practice for Therapeutic Goods, 1993)

The Australian guide has been included here because it includes some guidelines which are very practical regarding cross contamination and because of the novelties it offers with regard to the other subjects.

Cross contamination is considered in various sections of the guide and general guidelines are offered for those

potent products (*629) which produce physiological effects in small quantities (living microorganisms, steroids, or antineoplastics). The production of penicillin products should be carried out in separate buildings, with systems that are totally segregated from the rest of the plant, although the possibility exists that it could be done in a department of the general plant, accepted by the inspecting authority as an internal, segregated unit, with an adequate program for the control of waste materials. The guide also insists on validated cleaning procedures when the conditioning of the penicillin products is carried out in manufacturing campaigns.

In the case of cephalosporines, it indicates that they must be manufactured in segregated areas, using exclusive equipment, including the conditioning line; or the manufacture may be carried out in campaigns, complemented by validated cleaning procedures. As a differentiating factor, it states that there should not exist contamination between cephalosporines and penicillins.

As far as other potent products are concerned, measures such as the following should be applied: manufacture in buildings which are separated, or completely isolated in the case of manufacture in campaigns, and produce successive batches in the equipment, which must be exhaustively cleaned and fumigated in an appropriate manner.

In the control of environmental contamination (for these zones), the following will be applied:

- Appropriate pressure differentials in the process area, adequate filter systems, and control of air circulation.
- A reserve of equipment for each product (when possible).
- The use of airlocks (SAS with two or more doors between the segregated zone and the exterior, and with doors which cannot remain open at the same time).
- Decontamination of containers and materials that leave the segregated zone.
- Changes of clothing for personnel, with clear separation of clean and contaminated clothing.
- Validation of the cleaning and decontamination procedures.

Japanese Standard of Good Manufacturing Practice (Provisions of the Pharmaceutical Affairs Law Concerning GMP Regulations for Manufacturing Control and Quality Control Drugs)

Regarding the regulations for facilities, in the Japanese Standards (section 3, Regulations for Building and Facilities, point 2), it should be pointed out that when a drug is capable of producing anaphylactic reactions and is, in addition, easily dispersed, special operations must be carried out to control contamination. They consist of special procedures of prevention and the performance of residue determination tests, following the cleaning of the equipment or, alternatively, the availability of exclusive machinery and facilities for each product. Another interesting point is that if two different products that may cause anaphylaxis are being manufactured, they must be kept separate from each other, in order to prevent their cross contamination.

There is also a special mention for physiologically active medications (such as the adrenocorticoid hormone, point 3): when these are manufactured along with other products in the same facilities, measures must be taken to avoid contamination, and exhaustive controls must be carried out following the cleaning of the equipment used in the manufacturing process. There may be residues left which cannot be removed, and which would require that the equipment be reserved exclusively for that product.

With respect to penicillin contamination, question number 56 of the self-inspection questionnaire draws attention to certain points: there must be no recycling of the outlet air from the penicillin area circuit, and processing of the air must be inspected regularly. It also mentions, however, that these standards need not be applied if it is only secondary conditioning of a decontaminated material that is being carried out (question 57 of the self-inspection questionnaire).

"DESIGN" OF A NONINJECTABLE PENICILLIN PRODUCTION PLANT

In principle, a laboratory which has penicillin products on the market should evaluate the income which these products generate, against the investment required to set up a plant or department dedicated exclusively to their production. It may, on occasions, be more economical to contract the manufacturing to a third party, a manufacturer of recognized prestige, rather than make a heavy investment which will take years to recoup.

Should one want to set up a penicillin plant, the ideal would be to design a new building, physically separated from the current one and equipped with the most modern logistical characteristics available, with the aim of achieving a White Zone, as recommended in the GMPs. In this case we recommend reading the article on the general conception of a pharmaceutical manufacturing facility (5), bearing in mind the inclusion of characteristics peculiar to the penicillin area, such as barriers,

decontamination, etc. This option has, of course, a negative side, which is the heavy financial investment involved. Close study of the projects should also take into account that they require additional personnel, more machinery and increased maintenance, etc.

Should the previously mentioned high investment not be of interest, another option will have to be taken, one which is more "dangerous" from the GMP point of view. This would be the adaptation of a department in the plant, physically isolating it, and would require strict but easily adopted prevention and control procedures.

Standards of good manufacturing allow another option, the least desirable of those mentioned, which is that of working in campaigns, thus avoiding investment in machinery or the contracting of personnel. The manufacturing process is programmed for a time when no other products are being produced and, following the manufacture of a batch, exhaustive cleaning or fumigation is carried out to ensure the extraction of any residue. This option is feasible for production in small quantities or for conditioning of products, *though the functional character and reliability of the last two options must always be supported by validated cleaning and working procedures.*

As with any manufacturing operation, the conception and development of a pharmaceutical facility requires a number of basic regulatory norms or texts. These are well known by professionals in engineering but not by technicians in the pharmaceutical industry. In general, the classic phases of the project are:

- Reliability study
- Preproject summary
- Detailed preproject
- Detailed technical specifications
- Works execution plans
- Company consultation dossier
- General control of work
- Reception and discounting of work
- Dossier of the work carried out and validation of the facilities

EFFECTIVE BARRIERS FOR THE PREVENTION OF PENICILLIN CONTAMINATION

Various basic points from the consulted bibliography and the abstract of international GMP standards are worthy of note and should be respected, as they will be helpful in isolating penicillin production and avoiding the spread of contamination:

1. Work flows (materials) precisely established, supported by written documents, and known by all the personnel.
2. Air-conditioning of the area independent from the rest, with reliable, controlled filtration systems. A zone in atmospheric depression with respect to its surroundings and the study of air flows, and the air extraction system of the area.
3. Personnel: adequate training.
4. Exclusive materials and equipment for penicillin products.
5. Treatment of penicillin residues.
6. Issue of documents.
7. Quality control operations.
8. Validations to be carried out: confirmation of the effectiveness of the preceding measures.

No other general practices or characteristics which avoid cross contamination are considered, such as fixed windows, smooth surfaces without nooks, nonporous floors and sanitary skirtings, absence of corners, lighting which is protected by continuous glass or plastic, and not by grills (which are difficult to clean), etc.

See the example diagram (Fig. 1) of a penicillin area with two conditioning lines: blistering and packeting.

Work Flow

Good work flow indicates that the operations for each stage of manufacture and for all of the products being manufactured are well defined. In the case of penicillin products, this may be structured in various operations:

1. Special reception for penicillin materials.
2. Admission to the White Area.
3. Sampling and quarantine inside the area.
4. Control and preparation of raw materials for the manufacturing process.
5. Preparation of the batch for manufacture.
6. Admission, into the area, of nonpenicillin products for the manufacturing process (excipients, and other active constituents).
7. Reweighing of raw materials and preparation of the batch.
8. Manufacture: sifting, grinding, granulation, etc.
9. Dosification; tablets, capsules, etc.
10. Final conditioning.

Quality controls will be established at the different stages of the process, though the best procedure, and that proposed, is to carry out the maximum number of controls within the area (e.g., humidity, granulometry, etc., and that only the samples for analysis, suitably

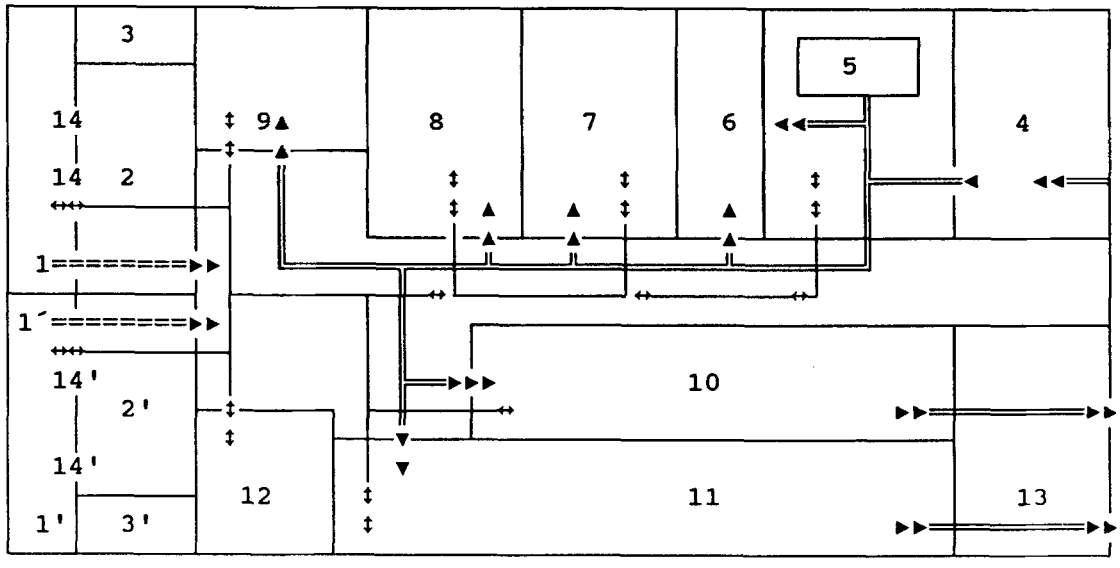

Figure 1. One type of penicillin area (with two conditioning lines) (10,11). 1, 1′: SAS of personnel entrance: change of laboratory clothing (♂ and ♀); 2, 2′: SAS of the penicillin area: penicillin area boiler-suit; 3, 3′: toilets; 4: SAS of the materials entrance; 5: laminar flow cabin: sampling of penicillin raw materials and preparation of the batches for manufacture (weighing); 6: storage zone for raw materials; 7, 8, 9: manufacturing areas; 10, 11: conditioning lines (blistering and so forth); 12: quality control and in-process control laboratory; 13: SAS of finished products exit (and penicillin descontamination); 14: showers.

diluted, leave the area). This laboratory should be equipped with sufficient material (apparatus) and be run by a person with adequate experience in quality control, under the direct supervision of the technician in charge.

The layout which may be used in an area of penicillin production is set out below:

a. Reception—Penicillin Raw Materials: The most practical approach to this problem is for the penicillin materials to be stored in the penicillin area. This requires the establishment of a special reception procedure, eliminating the usual quarantine. The drums are labeled (with a different label from that usually used), and the products are admitted directly into the penicillin area. The quantities should be previously established and agreed upon with the supplier, and should, in any case, be the minimum possible, to avoid unnecessary accumulation of stock in the penicillin area. In the case of large consignments, the sampling plan (if a 100% sampling is not effected) could be applied on reception of material, and only those drums to be sampled would be admitted to the area. Should the consignment be approved, the remaining drums may be admitted, or labeled and left outside, awaiting admission. As a security measure, analytical identification of each drum could be carried out prior to its use.
b. Admission to the SAS of Material: The procedure must be in writing and available on both sides of the SAS. In this point, the steps and precautions to be taken are listed: do not leave doors open at the same time if there is no automatic blocking device, use air showers (of some minutes duration, to remove dust from the exterior of the recipient), change pallets, etc.
c. Removal to the Area of "Pending Sampling": Labeling of the drums, date of admission if the drums are a fraction of a determined number in a consignment, etc.
d. Sampling of penicillin products in a laminar flow cabin.
e. Chaotic admission to the store—quarantine and approved materials: The materials in quarantine and those that have been approved may be distinguished by using yellow cellophane indicators for those that are in quarantine, or by referring to the labels. The quantities to be admitted will be minimal and in proportion to the size of the batch to be manufactured, whenever possible.

f. Fractioning of the raw materials per batch: The organization of the area should be based on the fewest possible movements of the product between the area and the exterior. All nonpenicillin raw materials (gelatine capsules, starch, sugar, etc.) will be admitted to the area, already fractioned for the batch to be manufactured, through the SAS for materials. The same will occur with materials for conditioning; the quantities will be adjusted to the size of the batch to be manufactured, including possible wastage.
g. Manufacture:
   1. Mixing, . . . precompression.
   2. Compression, capsuling, packeting, or bottling (in the case of manufacture of suspensions).
h. Quality control: Quality control must have a laboratory at its disposal in the area and capable of carrying out the preliminary tests for humidity, identification, pharmotechnical experiments (depending on the equipment available), etc. The analyst will carry out all tasks of quality control in the area: sampling, preparation of samples for analysis (such as the preparation of the flasks for HPLC, controls in process, etc.
i. Conditioning: The final conditioning (sometimes simultaneous with manufacture)—blister packaging, etc.
j. Removal of products from the area and decontamination: The removal of penicillin products stands out as one of the most serious problems of the penicillin area, as it is the factor which most influences the dissemination of penicillin contamination, if the final decontamination has not been effective. Among the different methods of decontamination are:
   1. Washing with sodium hypochlorite solutions (1.22% v/v), which is effective, noncorrosive, and inexpensive (6). The disadvantage of this method is the personnel required, who must be reserved for the decontamination of material or equipment that has to leave the area. This concentration of sodium hypochlorite is orientative, the most advisable being to carry out a microbiological study of different concentrations of the commercial brand of bleach to be used, with the aim of finding the most diluted, effective concentration. By way of orientation, it has been found that concentrations of 1% are usually ineffective.
   2. Laminar air showers have proven to be highly practical and do not need additional personnel, as the air is extracted by fans, which are situated under panels in the floor.
   3. Manual suction cleaning is also feasible, although it may require a person working full time, depending on the volume of production.

Machines should not leave the area unless they have undergone exhaustive cleaning and a control of the effectiveness of their decontamination. See the example layout (Fig. 2) for the operations of a penicillin area (7).

Environment of the Penicillin Area: Depression Conditioning

One of the most important features of a penicillin area is that it should be in atmospheric *depression* with respect to its surroundings. Contaminating particles will then always tend to be drawn inside, rather than out into the surrounding areas. For this depression to exist, the air-conditioning system must extract a greater quantity of air than it introduces.

The depression should be progressive (greater in workrooms than in the corridors), or in "showers," according to the operations carried out. On some occasions it may even be of interest to have the interior overpressurized, such as in the area of quality control (to avoid particles entering the analysis laboratory), or in the air flow cabin (to prevent foreign particles from passing to its clean environment).

No specification of degrees of depression has been found in the bibliography consulted (with the exception of the orientative 2–3 mm of water column, in Ref. 8); however, most standards coincide in considering that the depression should be adequate. If we extrapolate the overpressurization (or relative pressure), standardized by GPM for sterile areas, of +1.25 mm of water column (WC) by the FDA and +1.5 mm WC by the French BPF or by the Orange Guide '83, it is logical to consider that a depression of this order would produce acceptable protection against penicillin escaping to the exterior. The British standard, BS 5295 (9) referring to clean areas, establishes a pressure differential between a class M zone and another, unclassified zone, of 10 a.p., or 1 mm of WC, as a minimum (zone M is considered to be a clean zone in which a greater number of particles is permitted than in a White Zone).

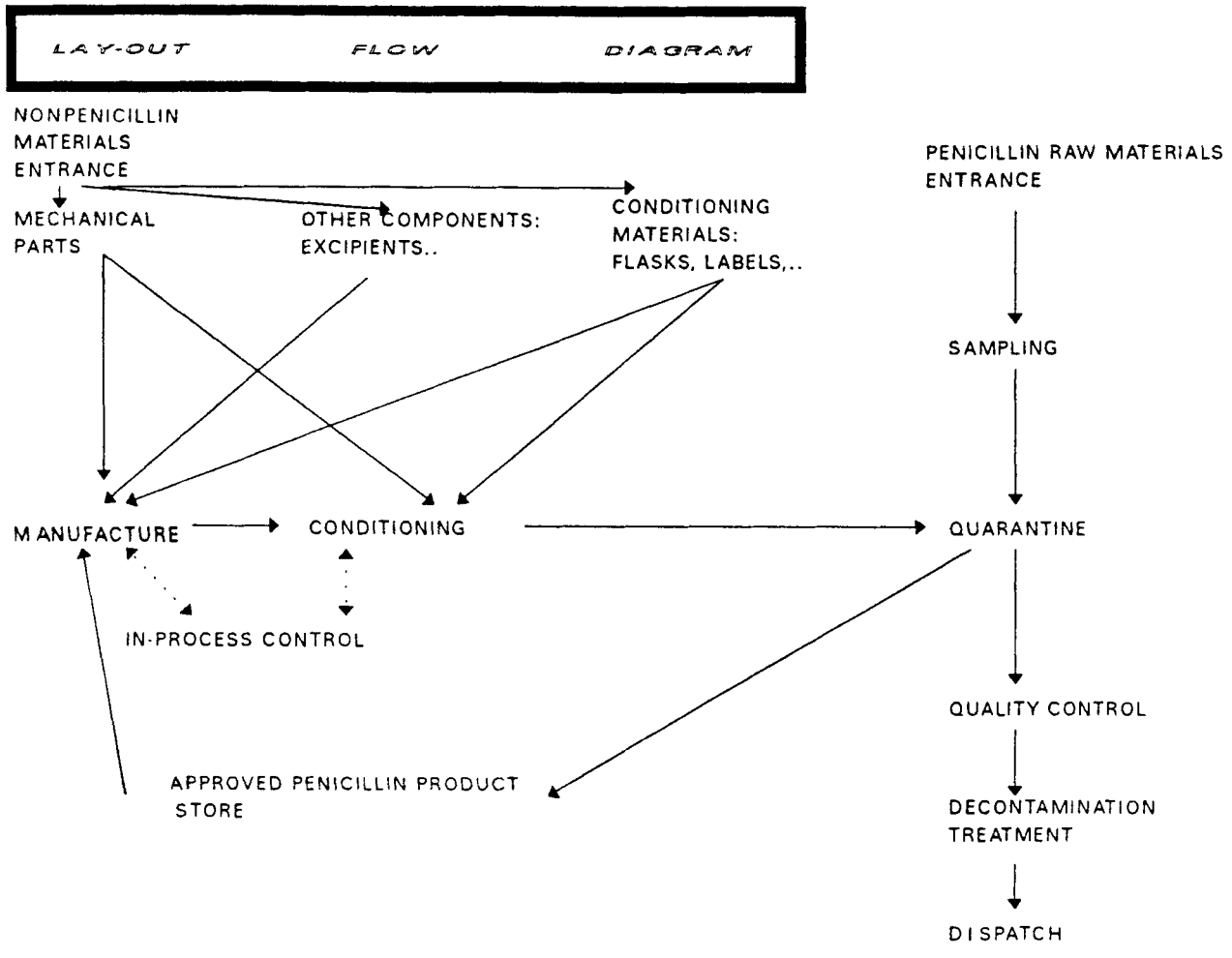

Figure 2. Layout flow diagram.

Daily control, or the register of the depression in the area, is recommended, and pressure gauges should be available at the following places:

1. SAS personnel/exterior, which should be greater than 1.5 mm WC.
2. SAS material/exterior, which should be greater than 1.5 mm WC.
3. Between the rooms which produce large quantities of dust and the corridors, etc., a difference of 1 mm WC would be acceptable.

In general, all those areas or rooms in which any quantity of dust is produced should be monitored. As a precaution, controls should be carried out with the doors closed, and with the machines in operation (in the case of the air flow cabin, in the sampling area). In this way it is possible to ensure that any adjustment made will be totally functional in the working conditions envisaged.

The air-conditioning of the area is also of vital importance. The basic principle of an air-conditioner is to take air from the exterior by means of air intakes, condense the humidity out of the incoming air with a cold-water or cold-air system, and systematically heat the volume of air which has been dried, by other batteries of hot air or water, or through steam coils. As a final step, the air must pass through a series of filters (Fig. 3, Refs. 10 & 11) which range from large pore size to the final, HEPA filter (capable of retaining 99.97% of particles bigger than 0.3 μm). This air is driven into the zone through diffusers, most of which are located in the ceiling. Should laminar air be required, HEPA filters may also be placed at the outlet. The return is driven by

1. Large-pore prefiltration, with 80% efficiency.
2. Fine filtration, with 90% efficiency.
3. HEPA filtration, with efficiency between 99.97% and 99.99%.

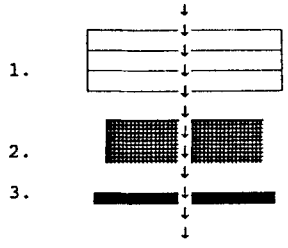

Figure 3. Three-stage filtration plan.

a fan, adequately situated in the return circuit to produce a vacuum and thus draw out the air. The expelled air must also go through an exhaustive system of filtration, with prefilters (of the covered, dry-pack variety), and another, final filter (HEPA, with 99.95% efficiency, BS 3928). In principle, all of the filtered air should be expelled and its return should be avoided, even though it has been filtered. This is not compulsory (95% of 5 μm, BS 3928) if the procedure has been validated and adequate monitoring of the system is carried out. The filter batteries should be fitted with saturation indicators, either by means of control of load loss through adequate pressure gauges (in the HEPAs) or by establishing periodical renewal of the prefilters (depending on the volume of production). In general, it should be recalled that HEPA filters need specific controls (DOP or dioctylphthalate test) to verify their integrity, and thus the efficiency of the filter.

Air injection outlets may be of different types, the most useful being those which are fitted with an air-volume regulating device, with which the degree of depression may easily be controlled. They also distribute the air uniformly throughout the area, without causing outlet turbulence. The air extraction grills are usually situated in the walls, at a level slightly lower than working height, thus facilitating a more effective flow. Regulation of the depression should be done with the doors closed, the equipment in operation, and without external equipment such as vacuum cleaners being in use. The vacuum process equipment should, however, be functioning when the system is regulated.

On occasion, due to lack of space, the intakes and outlets of the air-conditioning system may be too near to each other or to other systems. This creates the danger of recirculation of expelled air and should be avoided at all costs. Cifuentes (11) states that even with the best HEPA filter after a dust collector, 0.3 g of dust is recirculated to the production zone. Precautions must, therefore, be taken against the recirculation of contaminated air, by distancing the intakes and outlets of the system.

The recirculation of air necessary for a clean area should be of 20 replacements per hour, even for class D (EU), and thus a penicillin area should be designed to conform to this level. As far as temperature and %RH conditions are concerned, the standards indicate that they should be comfortable for the personnel and not affect the products that are being manipulated. Only the French standards give any orientation on this and set a norm for temperature of 21 ± 2°C and a %RH between 40% and 60%.

Maintenance operations must also be considered an important source of contamination, above all during the change of filters (the chassis is usually outside), because, if an exact procedure is not established, a serious dissemination of contamination may be caused. A very practical system is indicated in Fig. 4 (7). The personnel should wear disposable clothing (similar to that used in the penicillin area) which, after the operation, should be incinerated along with the used filters. It should be established that showering is compulsory following this task.

The system of vacuum cleaning in the area of the manufacturing process must also be independent of the other systems in the plant. It consists, basically, of a central vacuum pump, with intake filters and several points of use, all of which may be controlled by means of an automatic control station. The procedure for the collection of vacuumed dust should be carried out in a way to avoid its dissemination, with protective covers and desechable bags.

Although this is not often taken into account, consideration should be given to whether the system will continue operating at minimum output during periods when the penicillin area is not functioning, or alternatively, if it should be completely stopped. Given the energy costs that continuous operation would entail, the zone should be closed and locked during rest periods (nights and weekends), and, half an hour after closing, the systems should be shut down. At the beginning of the following workday, the procedure is reversed, the systems being started up some 30–45 min before work and the opening of the facilities (12).

Personnel

The personnel that work in the penicillin area represent another significant source of dissemination of contamination. In order to avoid this problem as far as possible, personnel who are going to work in the penicillin area should be carefully selected. This process may involve a specific course, intensive or otherwise, which makes them understand the environment in which they will be moving and the problems surrounding penicillin. They should also be made to learn and find out about the barriers which they have at their disposal to fight against these problems. Filming the new area or new procedures that the personnel must adopt, such as the use of special clothing, is a very efficient training method. Movement of personnel from the penicillin area to the nonpenicillin area in the same day should be avoided. There should be a preliminary selection of candidates from the persons interested or recruited, who should undergo a sensitizing test to detect those who may develop allergies. Neither these nor persons suffering from skin afflictions should be considered.

The subject of protecting the personnel from the product, and the product from the personnel, often causes the manufacturer of medications many conflicts, as the personnel do not always know or understand why such trying precautions need to be taken.

Standards of Hygiene to Be Respected on Entering

The following instructions should be known by all personnel (including personnel of other areas, for cases of substitutions, visits, etc.) and be written in SOP format, and the principle norms should be summarized on posters in the dressingroom.

1. On arrival at the first dressingroom you are wearing the laboratory uniform. You should leave your clothes here, putting on the disposable underwear and the cap, and pass to the second dressingroom through the one-way door (it is recommended that this door be automatic).
2. Put on your work clothes, which may be disposable (of the "Tyveck" type) or made of special fabrics which do not shed particles. The clothing is a kind of boiler-suit with feet, similar to those used in the sterile area. It should be of a color distinctive from other areas, so that it is rapidly noticed when it leaves the penicillin area.
3. Cover the first cap with a second and, when necessary, use a beard or moustache cover.
4. Carefully wash your hands.
5. The uniform should be checked (there should be a mirror just before the dressingroom door) before leaving the SAS and finally entering the area.

Standards of Hygiene to Be Observed on Leaving

These should also be in writing and be summarized on posters that highlight the basic norms of leaving the area. "Leaving" will be considered as any visit to the first dressingroom.

1. Take off the used uniform and deposit it in the disposable materials bag (a black bag, destined for incineration).
2. Nondisposable material (shoes, etc.) must be deposited in the bag for material to be decontaminated (of a different color, blue, for example).
3. Open the exit door. This is a glass panel, protecting a water shower device. Showering is compulsory before leaving the area. Should it be possible to have an air shower instead of the water shower, then it should have a security system to keep the doors closed during the descontamination shower.
4. There is a towel dispenser on one side. Take one and dry yourself.
5. Deposit the used towel in the collection device in the shower cabinet.
6. Open the second door of the panel which communicates with the first SAS. Once in this SAS, put on your usual laboratory uniform.

Special Cases

Visits, Maintenance Personnel, Calibration

The problem occasionally arises of the entry of personnel "passing through," but this should be avoided, as far as possible (in modern plants there are usually glass panels which allow visitors to see inside the area, without entering). When entry is unavoidable, all the previous standards should be observed, although using, in this case, disposable uniforms.

In the case of maintenance personnel, it is advisable that there should be a delegate or person responsible for knowing the lines and equipment in the department. These persons should also use disposable uniforms.

Cleaning Personnel

It is recommended that the department personnel themselves should take charge of the cleaning of the area (on a rotational basis; they should also be paid a bonus). When external personnel are necessary, they should be instructed on how to carry out the cleaning without direct technical supervision. There are some important points on which to insist: the need to prevent contamination from leaving the area (although the area is not operating, there is dust "floating" in the air, and thus contamination); the need to explain the reason for keeping the doors closed—open doors are the greatest danger of contamination in an area where discipline is lapse (it is easier for contamination to spread); the need for well-organized waste collection; the bags which leave through the materials SAS and the bags with materials for decontamination (of a different color); indication of the place where cleaning materials and products should enter the area (if necessary); materials must not be removed from the area without prior decontamination.

Materials, Equipment, and Premises

In principle, any material which enters the area should not leave it again, unless it has undergone an exhaustive process of decontamination and cleaning. Inside the area, all surfaces should be smooth and free from "nooks and crannies," to facilitate their cleaning.

Equipment should be in line with the usual standards in a manufacturing area: the utensils should preferably be made of stainless steel or plastic (of the polypropylene, neutral or inert type), avoiding wood, even if it is painted. There should be easily cleanable cupboards in which to keep the utensils, and an adequate number of portable vacuum cleaners (with internal HEPA filters). Brushes should not be used but should be replaced with vacuum cleaners or with cloths which do not shed particles.

Wherever possible, conditioning should be separate from packing, in order to prevent the exterior of the conditioning materials from becoming impregnated with particles.

The decontamination or cleaning plan (6) should be commenced at ceiling level (lighting installations, air intakes or outlets, cable ducts, etc.), then proceeding to the walls and floors. It is recommended that machinery be disassembled, cleaned and disinfected, and then reassembled, this being the most effective measure against contamination.

Residues

Residues from the penicillin area go directly to incineration, above all in the case of the filters, raw material containers, waste paper, cardboard used in conditioning, and used disposable clothing, etc. There is a process known as "inerting" for the residues from products (dust deposits in the machine vacuum cleaners, surplus dust from defective units, etc.), which consists of mixing the active products with "earth or powders" which dilute them to the point where they may be considered inactive. The resulting material is usually disposed of by outside contractors. Incineration in adequate installations is, without doubt, the cheapest option and the one which avoids excessive manipulation of contaminating residues.

In addition to solid residues, liquid residues (from the cleaning of machines, utensils, floors, etc.) must also be seriously considered. They must not be allowed to enter the drainage system without first undergoing neutralization or degradation treatment. Most industries now have access to treatment plans which cleanse the residues to the point where they hardly contaminate at all.

As well as visible residues, there are also those that are not visible. They are found in washable clothing, towels, nondisposable cleaning cloths, and so on. All this material is accumulated during the day, in special bags which are taken at the end of the day to the laundry service. This should be different from the general service to the rest of the plant or, if this process is carried out in the plant, it must be done separately from the other clothing etc., and in accordance with a written procedure. In this case it will be necessary to validate the procedure to ensure that contamination is not disseminated.

Documentation

Documents are among the most serious problems of the penicillin area, as the papers which are handled in the area become impregnated with penicillin. Decontamination by vacuum cleaning each piece would be an extremely tedious job and, depending on the volume of production, may not be feasible.

The best solution in these cases is computerized management of the plant, in which computer terminals and monitors take the place of paper. The computer allows

each user access to his or her permitted level, where the parameters of the batch, phase by phase and signed with electronic signatures, appear. Printed documentation remains outside the area and thus does not need decontamination. Another feasible idea is the installation of a document transmission tunnel, in which the papers are cleaned by an air shower, one by one. This method depends on the results obtained in its validation process. The use of facsimile machines could also be a good idea, if there is not too much documentation.

Quality Control Operations

The most important quality control operations related to the penicillin plant may be defined as follows:

1. Monitoring the environment for cross contamination.
2. Monitoring the cross contamination in finished products.
3. Control of finished products.
4. Validation of the procedures of decontamination and manufacture.

Quality control of the environment is a very important step when determining levels of contamination or the validity of a process of decontamination. Among the different types of analysis applicable to penicillin contamination—and as a contrast to the initial, microbiological methods indicated by the FDA (13) or those of thin-layer chromatography—the development of methods using high-performance liquid chromatography (HPLC), or even colorimetric assays, is notable. The HPLC method stands out for its speed, and, with the current increase in use of HPLC in routine analyses, it is now not difficult to develop and finally standardize methods.

The principal problem in the control of cross contamination is the lack of specifications. The techniques currently being applied are becoming more and more sensitive and the limits of quantification narrower, making it likely that a negative result obtained by the previous methods will now be shown positive using the current ones.

Of the limits currently available, none refer to environmental contamination. They are all concerned with the contamination of finished products, or food:

1. From the Spanish Ministry (8):
   Year 1973: 0.05 ppm
   Year 1976: 0.05 ppm
   Year ?: 0.06 ppm per dose in oral medications.
2. The works by Breslin and Knight (14) and the book *Modern Pharmaceutics* (16) mention limits of 0.05 IU for parenteral products and 0.05 IU for oral doses. [For orientation, 1 IU is equivalent to 0.6 μg of penicillin G (17)].
3. The document by the FDA (18) dedicated to food contamination gives: 0.05 ppm (which it qualifies as negligible) in raw, edible animal tissue; no trace at all in raw, edible chicken, pheasant, quail, pork, lamb, eggs, or milk or other product derived from milk; and 0.01 ppm in raw, edible turkey meat.

In principle, these standards could be considered out of proportion, though among the different methods considered, only the enzymatic system has a clearly lower limit of detection (14), with 12 ng for penicillin G. The problem is that the FDA, in point 211.176 of the latest edition, clearly indicates that beta-lactum contamination must not be found in finished products, applying the aforementioned microbiological techniques. The quantification of amoxycillin for example, by HPLC, is currently highly developed and optimized, and thus from the point of view of routine, it is preferable to carry out the test chemically. The problem may arise when samples which were negative according to the microbiological method are tested using the HPLC system and a perfectly quantifiable signal, above the detection level of the method, is obtained. In this case it would be proper to hesitate before assigning this level of contamination as a specification or, alternatively, deciding to demand the absence of signal against the standard.

With regard to the subject of sampling, it is important to distinguish the places where the samples are taken. If the samples are taken from the air, from the machines, or from the rest of the pharmaceutical products of the laboratory, the process will be very different.

Taking a Sample from the Environment

In this case it is advisable to analyze different areas outside the penicillin area. Above all, take samples in those areas that present greater danger of contamination (due to the movement of personnel and materials), or in zones of communication, such as:

- SAS, as much for personnel as for materials
- Corridor immediately in front of the SAS, on the way out
- Stairs and corridors used by all of the plant
- General store
- Reception
- General dressingrooms
- Quality control at strategic points: where the samples are left, awaiting analysis, etc.

A weekly control plan should be drawn up, including all the critical points of the plant. Risk diagrams should be made, showing the contamination found and serving to define the points to be decontaminated and checked.

The sample is taken by means of an air sampler, which passes a determined quantity of air (usually fixed at 1 m^3) through an adequate filter, which retains the different particles contained in the sampled air. These are then extracted from the filter, using an adequate solvent (water is usually a good solvent for amoxycillin), and these samples are analyzed by the appropriate method (HPLC, microbiological, TLC, or enzymatic). Whatever the method used, the result must be that contamination is not detected, against the standard.

Taking Samples from the Machinery and Installations

Samples must be taken from machinery and installations by rubbing clean swabs, which have been moistened with water, along with the walls and surfaces to be tested. Any penicillin that has been collected is then extracted, in the laboratory, using a suitable extraction method. The analysis should prove negative, against parallel standards.

The swab method should previously be validated and checked. As a minimum, its collection capacity should be standardized (as a rule, at least 75% of the quantity deposited on the surface to be tested should be collected).

Taking Samples from Other Pharmaceutical Products

This control should be established by all manufacturers who have a penicillin plant in their facilities, as a safety measure before the release of the batch.

The methods employed must be developed according to the pharmaceutical product to be tested but, in principle, the extraction should be made collecting only the contaminant (beta-lactum), and not the active agent. In the specific case of pills, consideration should be given as to whether only a superficial control is required (they should be washed with water and the water then centrifuged) or if it would be of greater interest to pulverize the pill (followed by centrifuging and filtration) and carry out the extraction of all of the penicillin. In this case, comparison with standards is also necessary.

In extreme cases it has been suggested that even products manufactured on the same trading estate (and, of course, in different plants) as penicillin products should be verified (as an absolute level of security; air/water).

Final Validation of the Area and Procedures

The final validation of the area means that, following sufficient time in operation and having ratified each and every step—such as sampling points, the analyses that have been carried out, and the consideration of extreme situations such as that of the area at night and the danger that an accidental, complete shutdown of the air-conditioning system would imply, residues, etc.—a validation certificate is issued. This is signed by the technical committee, made up of representatives from technical management, production management, and management of quality control or quality guarantee, should this department exist.

Any unforeseen situation should be evaluated immediately, to determine the risk of dissemination of the contamination and to decide on the action to be taken. Given such a case, the area, and the working and organization procedures should, once again, be submitted to revalidation.

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