Philosophy and Validation Approach to Cleaning and Decontamination in Antibiotics Facilities

Wael Allan and Trevor Deeks*
Raytheon Engineers & Constructors Ltd and Boehringer Ingelheim UK Ltd (*while at Raytheon Engineers & Constructors Ltd)

This paper describes a cleaning philosophy for different types of antibiotic facilities. The objective was to remove all traces of antibiotic from the internal and external surfaces of equipment and the surrounding areas, in order to prevent the contamination of any future product by the antibiotic in that facility. Because of the nature of the antibiotics involved (penicillin and cephalosporin), no detectable traces must remain. The paper considers both change of use and campaign manufacture.

The cleaning philosophy was based on grouping equipment, utilities and facilities into types of product contact surfaces. Part of the strategy was to determine a sequence for executing cleaning activities, to provide an orderly movement of cleaning personnel and mobile equipment.

The HPLC methods for residue-limit determination were specific for products and related compounds, and in each case the sensitivity was quantified for each compound detected. The acceptance criteria were that no residues should be detectable. This philosophy was adopted only where it was possible to demonstrate that the detection limits provided a reasonable safety margin of potential contamination when compared to the quantifiable toxicological parameters of the antibiotic, and where it was possible to show good recovery from surfaces.

US Food and Drug Administration (FDA) guidelines for the manufacture of penicillin and cephalosporin antibiotics require such manufacture to be undertaken in dedicated facilities, or on a campaign basis in a multi-product facility. Campaign manufacture should only be undertaken after a thorough, fully-validated decontamination and cleaning operation between products.1,2

The FDA, if pressed, will also say that campaign manufacture is not encouraged and that it should not be considered as a long-term policy, but may be practical as a short-term expediency using closed systems, with a view to providing dedicated facilities in the longer term.1,2 In our experience, international regulatory authorities, including those of the European Union member states, have a similar policy for such operations3,4 and there is a considerable level of agreement on this issue.

Penicillins and cephalosporins are, therefore, normally manufactured in separate dedicated facilities. It is unacceptable to manufacture both in the same facility for a further reason; since hypersensitivity reactions to penicillins are not necessarily seen in the same patient population as for cephalosporins, it is quite common for people who are hypersensitive to penicillins to be prescribed cephalosporins. Consequently, trace contamination of one product type by the other is highly undesirable.

A dedicated facility can be very costly, representing a significant investment even for a large company. When the demand for the antibiotic falls, the facility may be needed by the company for another purpose. At this stage, it is necessary to clean and decontaminate the facility prior to taking it into an alternative usage.

The work presented in this paper looks at the various approaches that can be taken to decontaminate a facility, either for changing to alternative usage or for decontamination between campaigns. It presents a philosophy for the decontamination process and discusses the validation approach for such an operation. The approach is based on various examples where such a decontamination process has been undertaken. However, as none of the projects referred to in this paper involved the manufacture of sterile products, microbiological sampling was not undertaken.
Figure: Cumulative recovery of target compounds from different surfaces.

Notes:
(a) The different 'related subs' (substances) are intermediates and breakdown products in a bulk manufacturing process.
(b) Swabbing times indicate repeat swabbing of the same area.
- Related substances
- Cephalosporin
- Related substances
- Related substances.
Defining the scope of the decontamination programme

In order to determine the scope of the decontamination programme, it is necessary to define the ‘facility’ to assess the potential for contamination of utilities shared with other facilities, such as steam and water, to determine the movement of people, equipment and materials to and from this facility, and the controls that are in place for this traffic. Cleaning is an activity carried out within the decontamination programme which may also include replacement and painting of certain non-product contact surfaces such as electrical wiring.

A consideration of these factors will provide information on the physical area or areas which require decontamination and the need for removal and replacement of utilities. It will also provide information for determining the sequence in which the decontamination procedure should be carried out.

The ‘facility’ may be a discrete building on a multi-product site or it may be the entire site. Alternatively, it may be a segregated portion of a building in which other processes are run. The facility should, for example, have its own dedicated HVAC system (air-handling units, extract and duct work) and the rooms should be separated in such a way that there is no potential for contaminated air to blow from the defined ‘facility’ into other facilities in the same building.

The ‘facility’ should have dedicated equipment and controls should exist to prevent the spread of contamination via shared utilities, such as water systems. Additionally, personnel movement should be restricted and controlled between ‘facilities’, ideally by having dedicated operations. Where it is necessary for other personnel (engineers, quality assurance staff, and so on) to move between facilities, this must be done with great attention to control of gowning and washing procedures.

This paper will not provide details of control mechanisms and personnel flow, but it is necessary to raise these issues in order to arrive at our definition for the ‘facility’ and determine the scope for the decontamination programme. Having done this, it is then necessary to consider the philosophy and approach for conducting the decontamination effort.

Philosophy and validation approach to cleaning and decontamination

The cornerstone of any philosophy for cleaning and decontamination of a penicillin or cephalosporin facility must be to assess the ability to clean equipment and room finishes. If there is any concern over being able to do so, a decision must be made to replace. This option may seem drastic, but if cleaning proves difficult, the ensuing repeat cleaning and repeat validation could prove to be as costly and time-consuming as opting for replacement.

The other prime consideration is whether the equipment lends itself to cleaning validation. In some cases, the recovery of the product from certain porous absorbent surfaces may be so low as to make residue detection meaningless (there is far more residue left on the sampled surface than on the sampling swab, for instance).

It might be argued that if the residue is so strongly adhered to the surface, then the possibility of it presenting a contamination risk to the new product(s) is negligible. However, even a very small risk of contamination of beta-lactams on product contact surfaces is very difficult to defend. Absorption to such surfaces is a dynamic event. An equilibrium always exists between that which is absorbed and that which can be removed by other product contact and this could result in trace contamination of future product for many batches to come.

The Figure demonstrates the differences in recovery that occur between different surfaces and between different molecules on a given surface. In this instance, cephalosporin is more than 50 per cent recovered from epoxy resin and steel plate, but on both of these surfaces there is a wide spread of recovery rates for related substances. In both cases, there is a slight increase in the amount recovered after the second swabbing, which illustrates the dynamic nature of the recovery. Recovery from plaster board and silicate, although not normally used as product contact surfaces, was investigated. Neither of these surfaces could be considered as cleanable or validateable and were either replaced or coated with an impervious coating.

The objective of the cleaning and decontamination effort must be to reduce all residues on all surfaces to below detectable levels. This is the only permissible acceptable criterion. This approach, therefore, places much importance on the sensitivity of the detection method. Facility design and the material, personnel and process flows of the antibiotic manufacturing process must be evaluated to determine potential contamination of equipment, facility finishes, utilities and support areas.

Cleaning procedures must be developed for all aspects of cleaning and decontamination. These procedures must be sufficiently detailed and well defined to be consistently reproducible. If the cleaning process is not consistent, then it is impossible to ‘demonstrate that it consistently achieves the desired quality specification’ as required by the FDA. All procedures must be written, reviewed and approved before decontamination begins and it is advisable in such cases to prepare a master plan documenting the approach, procedures, responsibilities, scope and acceptance criteria.

Sampling and analytical procedures must be developed, written, reviewed, approved and validated at the outset. This work should demonstrate the sensitivity, specificity and recovery of the antibiotic, potential related compounds, degradates and cleaning agents from the complete range of surfaces to be decontaminated. It is at this point that the decision to clean, or remove and replace, will be made.
For each item of equipment, and for each room, a sampling plan for surface swabs and rinse solvents must be determined and the solvents used for sampling must be appropriate for the solubility of the residues which might be expected. This may vary in different parts of the facility. In some instances it may also be necessary to carry out active air-sampling using an air-impingement device which sucks air into a suitable solvent. This is particularly important in areas where large quantities of bulk drug or starting material are handled and dust contamination is a major consideration.

The philosophy of defining cleaning procedures carefully, before decontamination, is clearly desirable for a facility where campaign manufacture is undertaken. However, for a one-off decontamination exercise, the concept of ‘cleaning until clean’ is one which should not be totally discounted, since the important feature in such instances is not the consistency and reproducibility of the procedures, but the ultimate level of cleanliness of the new facility before being taken into new use. This is one instance where the development of the process may need to be overlooked in favour of getting the job done.

In either case, it is important, not only to validate the decontamination process, but also to monitor for the absence of the antibiotic in a number of batches of the next product. Although the FDA recommends monitoring three batches, our experience suggests that it may be necessary to carry out more monitoring than this. The number of batches required to be monitored should be decided on a case-by-case basis depending on the scale of the operation, the length of time before change of use and the solubility of the product.

Application of the decontamination philosophy

The above philosophy has been used successfully for the decontamination of facilities for bulk pharmaceutical chemical production for intermediate processing such as milling and packaging operations, and for secondary pharmaceutical production. Because of the confidential nature of this work, we are not at liberty to disclose either the facilities or the clients. However, it is an approach that has been used repeatedly and successfully.

<table>
<thead>
<tr>
<th>Table: Susceptibility of cephalosporin to sodium hydroxide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment with 0.5% NaOH aq</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Treatment with 0.5% NaOH aq</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Cephalosporin content (mg/ml)</td>
</tr>
<tr>
<td>Analogue II (%)</td>
</tr>
<tr>
<td>Analogue II did not contain beta lactam ring, but had very low water solubility.</td>
</tr>
</tbody>
</table>
Where bulk synthesis is being undertaken, chemical intermediates and degrade products may be produced. In cases where these compounds were not isolated, solubilities were assumed on the basis of the similarities of molecular structure with other known related compounds.

Where the water-solubility of the residues was low, a suitable solvent, usually alcohol, was used for sampling. However, in these instances, cleaning procedures were not modified because the hydrolysis of the beta-lactam ring normally renders compounds more water-soluble, and water rinsing is necessary to remove sodium hydroxide more effectively. Furthermore, the use of large volumes of flammable solvents, such as alcohol, represents a significant fire hazard.

Use of sodium hydroxide solution alone has been found to be more appropriate for external inaccessible non-product contact surfaces such as electrical wiring, the outsides of small pipes and tubing and inaccessible areas on secondary processing equipment. Dismantling of such equipment and washing in a suitable solvent was adopted wherever possible. The changeover from one campaign to another warrants thorough dismantling of equipment into its component parts. In all cases within our experience, there were no clean-in-place systems installed.

In some situations, cleaning was considered inappropriate, either because the cost of replacing items such as seals and gaskets is far cheaper than cleaning and validating them, or because they were virtually impossible to clean. In these instances, all seals, gaskets, ‘O’ rings and flexible hoses were removed and replaced, as were some change parts for secondary processing and packaging. The milling process involved screens, socks and filters and during the campaign manufacture these were either replaced or were dedicated to the processing of the individual antibiotic.

**Sampling regimes**

Having identified all cleaning procedures, certain items of equipment were demonstrably critical, representing worst-case examples for residues. Additional attention was given to sampling regimes for these items.

Sampling locations represented worst-case situations wherever possible. However, in some instances, such as the sampling of duct work and electrical conduits, a practical and reasonable sampling regime must be adopted and a ‘risk assessment’ is advocated to determine the most appropriate sampling regime.

The more samples that are taken, the more information will be known about the cleanliness of the equipment. On the other hand, there is also a greater likelihood of obtaining a result which does not meet the acceptance criteria. However, our experiences have indicated that such failures are attributable to variability and lack of definition in the cleaning process rather than to the size of the area to be cleaned compared with the number of samples.

The cleaning procedures for the internal product contact surfaces of equipment are generally far more reproducible than the procedures used to clean non-product contact surfaces such as the external surfaces of equipment and the walls, floors and ceilings of the facilities. Any ‘risk assessment’ must take such issues into consideration.

Far more important than the numbers of samples are the sample type and location. Selection of sample locations must consider material flow, process flow, process sequences and personnel flow.

The preferred sampling method is swab sampling for all accessible surfaces. There are two reasons for this. First, swab sampling with a suitable solvent ensures that any residue present is picked up by the swab (whereas rinse samples may not actually dissolve the residue because of binding of the residue to the surface being sampled).

Secondly, our experience has shown that when incomplete cleaning has occurred, it is normally shown by swab samples, not by rinse samples. In addition to swabs and rinse solutions, we would also advocate active air sampling using air-impingement devices to look for residues of dust within the environment as a result of inadequate HVAC circulation or as a result of residues being dislodged from HEPA filters and duct work.

**Residue detection limits**

The sensitivity of the detection method dictates the acceptance criteria, since the only acceptance criterion for residue limit is ‘no detectable residues’. A careful choice of detection method is required and the most commonly used method for penicillins and cephalosporins is HPLC with UV detection. This method is very specific and very sensitive, if expensive. The sensitivity is of the order of 0.01 μg per ml for rinse solutions, and 0.01 μg per swab sample.

Whatever the detection method used, it is of great importance to determine the significance of the detection limit in comparison to known data on toxicology. The minimum allergic dose, or minimum amount for anaphylaxis manifestation (MAAM) should be available, and a calculation can be made to determine the amount of antibiotic which would be carried over from one batch to the next if the detection limit were reached.

This is the reverse of the normal calculation and it involves assuming a 100 per cent carry-over of residue (worst case), multiplying residue concentration by the product contact surface area and making the assumption that the quantity of residue is distributed evenly throughout the next batch. This latter assumption is reasonable, since any residue will be spread over the total product contact area and the likelihood of de-mixing and concentration of the antibiotic residue into a small number of dosage units is infinitesimally small.
Thus, for a total surface area of 10 m², an MAAM of 0.01 µg, a typical swab area of 100 cm², and a maximum daily dose of 1 g, if MAAM is carried over into the maximum daily dose this represents 0.1 µg x 100,000 in a 100 kg batch (100,000 doses). Distributed over 10 m², this equals:

\[
\frac{0.01 \times 100,000 \, \mu g/cm^2}{10 \times 100 \times 10} = \frac{0.01 \times 100,000 \times 100 \, \mu g}{swab} = 1 \mu g/\text{swab.}
\]

If the limits of detection are 0.01 µg per swab, this represents one-hundredth of the sensitivity required to detect carry-over of the MAAM. These figures are typical of the values we have seen for bulk product, and the surface areas for secondary production are often lower. It can therefore be seen that the HPLC detection methods used are sufficiently sensitive to ensure a suitable detection limit. Similar figures can be applied to rinse solutions.

**Sequence of decontamination**

In all cases, a sequence for cleaning or decontamination has been developed as part of the master plan, or as part of a validated cleaning procedure between campaigns. Sequencing has required a consideration of process, materials and personnel flow and also of HVAC design. Equipment which must be removed or disassembled is normally taken to an equipment cleaning area and is not replaced or reassembled until satisfactory cleaning has been demonstrated.

Failure to do this may result in the need to repeat the entire cleaning process. Care must also be taken not to put cleaning equipment in areas which have not been demonstrated to be clean. It is, therefore, important to continually review the status of all equipment, utilities and areas during cleaning and decontamination.

Sequencing and the extent of cleaning have presented complications in two distinct situations. In the first, penicillins and cephalosporins were being processed in separate facilities within one building with shared utilities, support areas and personnel. In this instance, the decontamination programme necessitated taking into consideration the impact of each process on the other, the need to isolate utility connections, and the movement of people during cleaning operations.

In the second situation, there was insufficient information about the movement of people and materials. Clearly, the solution here was to establish a good control over process, materials and personnel flow and over the movement of materials, people and analytical samples through support areas. Campaign processing should not be undertaken without such controls in place.

One other major consideration in the determination of the decontamination sequence is the HVAC design. This topic probably warrants a paper of its own, but good HVAC design can reduce decontamination problems significantly. The key features are no recycling of air, exhaust air outlets being positioned well away from air inlets, HEPA filtration of both supply and extract air, and a ductwork design which facilitates the changing of filters, particularly exhaust filters in areas remote from the processing rooms. Procedures for disposal of filters must also be carefully considered.

**Summary**

Following the philosophies and procedures discussed in this paper, we have been able to achieve cleaning and decontamination of penicillin and cephalosporin processing facilities. In one case, a penicillin facility producing medicine for human use has been approved by all the major regulatory authorities and permission given for other production in the same building.

In other instances, the validation data have shown no detectable residues following intensive sampling. We have also been able to assess the sensitivity of the sampling methods and to determine their suitability by comparison to quantifiable toxicological parameters of the antibiotic.

Decontamination and change of use of a penicillin or cephalosporin facility is a feasible option without replacement or rebuilding, but implementation must be carefully planned and executed. Campaign manufacture as a short-term strategy is feasible; however, particular attention must be given to surface finishes, equipment cleaning procedures, replacement of non-cleanable parts and control of materials, people and sample flows.

Campaign manufacture as a long-term policy is discouraged and is an expensive option because of all the cleaning and change controls required between campaigns, which are the same as those required for a change of use. The monitoring of batches of the new product following an antibiotics campaign would also prove costly. Furthermore, where manual cleaning is required, the definition and validation of such procedures can prove difficult.

**References**

2. Personal communication from FDA dated 29 September 1995.