Validation of cleaning in a multipurpose facility for non-sterile products

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OBJECTIVES
Preparation in Hospital Pharmacies aim at meeting special patient needs. In general facilities and equipment are intended for multi-purpose preparation of different products containing a diversity of Active Pharmaceutical Ingredients (API). Cleaning validation has to be performed according to EU GMP.

GMP guidelines state: 9.6 Where a worst case product approach is used as a cleaning validation model, the rationale for selection of the worst case product should be justified and the impact of new products to the site assessed. When there is no single worst case product when using multi-purpose equipment, the choice of worst cases should consider toxicity and PDE value as well as solubility. Worst case cleaning validation should be performed for each cleaning method used. (Draft Eudralex, vol 4., annex 15. Expected adoption by EC)

The aim of this project was to develop a general model for establishment of limits for MAC and selection of worst case API. The results were used to set limits for cleaning validation of equipment used for preparation of suppositories.

METHOD
The worst case equipment train for production of suppositories consists of a vessel heated with recirculating steam, a mixer and a suppository molding apparatus. The surface area of the equipment train was calculated to 13,571 cm².

By examination of the equipment train and the method of cleaning, hot spots were identified. Hot spots are difficult-to-clean locations. Cleaning of these is of particular importance, as improper cleaning may lead to build-up of impurities from batch to batch. This may lead to an unpredictable contamination e.g. when a lump breaks loose.

During the cleaning validation samples must be taken from all hotspots, and for this validation rinse samples was chosen. The acceptance criteria for the cleaning validation were established as:

- No quantities of residue should be visible on the equipment after cleaning procedures are performed
- The API residue on the equipment must after cleaning be reduced to a concentration below the quantity of compound permitted to carry-over in subsequent product without any adverse effects to the product or consumer (MAC).

Worst case API and MAC
The model for establishment of MAC was developed in close cooperation with acknowledged toxicologists with experiences from Food science.

All API were scored in relation to Lowest Therapeutic Dose (LTD), possible adverse effects and solubility. On the basis of these scores the APIs were ranked to determine the worst case API.

As prednisolone was assessed to be the worst case API, MAC was calculated for prednisolone:

\[
MAC = \frac{LT D}{(0.001 \times LSA \times DD_{\text{max}})}
\]

Where LTD = Lowest Therapeutic Dose of worst case API

The model for establishment of limits for MAC and selection of worst case product could easily be transferred to other formulations such as liquids and semi-solids.

RESULTS
Equipment used for production of suppositories was successfully cleaning validated up to the determined MAC utilizing a validated Riboflavin UV analytical method.

DISCUSSION
The general model for establishment of limits for MAC and selection of worst case product could easily be transferred to other formulations such as liquids and semi-solids.

Riboflavin as a marker for other API than prednisolone could with great probability be a good alternative considered that the validated analytical method has a short time of analysis and a very low LOD. Other markers could be used taking the matrix and the solubility in consideration e.g. TOC for aqueous products.

CONCLUSION
A general method was developed to establish worst case API and MAC and it was proved, that it can be used in relation to cleaning validation of equipment used for preparation of suppositories.

<table>
<thead>
<tr>
<th>API</th>
<th>LTD mg/kg</th>
<th>Adverse effects</th>
<th>Solubility water</th>
<th>Solubility Ethanol</th>
<th>Score</th>
<th>Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>0.06</td>
<td>e.g. Edema, leukopenia, lymphopenia, thrombocytopenia, leucocytosis, adrenal insufficiency, hypokalemia</td>
<td>Very slightly soluble</td>
<td>Soluble</td>
<td>1/1/2</td>
<td>1</td>
</tr>
<tr>
<td>Mornphine</td>
<td>0.25</td>
<td>e.g. Nausea, obstipation, loss of appetite, loss of muscle strength, dry mouth, abdominal pain, pouting, headache, dizziness, confusion</td>
<td>Slightly soluble</td>
<td>Slightly soluble</td>
<td>2/1/2</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 1 Toxicological assessment of prednisolone and morphine

A suitable method of analysis would therefore need to have a LOD below 2.4 µg/ml.

In this case riboflavin (base) was chosen as a marker primarily because of the work hazards with prednisolone. Therefore a validated UV analytical method for riboflavin with LOD = 0.005 µg/ml was used.

The volume of rinse water was set to 5500 ml, and the rinse water acceptance limit was calculated as:

\[
\text{Safety factor} = \frac{0.0024 \text{ mg/ml}}{0.00097 \text{ mg/cm}^2} = 0.00097 \text{ mg/cm}^2
\]

A suitable method of analysis would therefore need to have a LOD below 2.4 µg/ml.

The acceptance criteria for the cleaning validation were established as:

- No quantities of residue should be visible on the equipment after cleaning procedures are performed
- The API residue on the equipment must after cleaning be reduced to a concentration below the quantity of compound permitted to carry-over in subsequent product without any adverse effects to the product or consumer (MAC).

The results were used to set limits for cleaning validation of equipment used for preparation of suppositories.