

EGA POSITION STATEMENT (FINAL)

SUBJECT: EDQM (CERTIFICATION OF SUBSTANCES DIVISION) GENERAL MONOGRAPH ON PRODUCTS OF FERMENTATION

DATE: 13 March 2008

EGA member companies highly appreciate the EDQM's call for the industry's position regarding the application of the "removal of residues" as required by the monograph on Products of Fermentation.

The experience accumulated by companies with both the EDQM and the various National Health Authorities in the EU over recent years demonstrates a certain degree of ambiguity with respect to this issue:

- Requests referred to DMF submissions, but also to clinical trial applications;
- Not only true products of fermentation (ie, when fermentation yields the molecule constituting the active substance), but also very early intermediates from fermentation (eg, cephalosporin used for semi-synthetic cephalosporin active substances) were subject to the request;
- In some cases science-based assessment was accepted, but we have also seen cases where analytical data were requested.

1. Recommendation in Favour of a Science & Risk Based Approach

The EGA favours the application of a science and risk-based approach to ensure the proper application of the requirements as defined in the general monograph on Products of Fermentation (1468), particularly in consideration of the following requirement:

"It must be demonstrated that the process or processes chosen reduce to a minimum or remove:

- *residues from the producer micro-organism, culture media, substrates and precursors. ... If necessary, suitable tests are performed either as in-process controls or on the isolated product of fermentation."*

The action(s) required to meet that particular requirement is(are) determined after the assessment of three relevant criteria: the stage of the substance in the life-cycle, the route of administration, and the manufacturing process.

1.1. Stage of the substance in the life-cycle

A substance may represent a new chemical entity, which is still in the phase of clinical trials or is ready for submission. On the other hand, substances may have been on the European market with proven history of safe use.

For new chemical entities with no history of use on the market, the assessment needs to address both the route of administration and the manufacturing process in order to come to an appropriate decision. In case of substances with a proven history of safe use on the market, no further action is required.

1.2. Route of administration

The oral and the parenteral routes of administration must be clearly differentiated:

- Oral administration results in the destruction of proteins in the gastro-intestinal tract. This in turn eliminates the risk of protein residues based on the generally accepted definition of risk: HAZARD X EXPOSURE = RISK.

The hazard, which could be the residual protein, is eliminated due to the denaturation of the protein. The exposure is reduced to a minimum, because there is no systemic uptake of the hazard.

- Parenteral administration, however, involves a potential for immunogenicity due to systemic incorporation of the residual protein and should therefore be adequately controlled. This is assessed by means of the third proposed criterion.

1.3. Manufacturing process

Typically, the purification processes of classical fermentation products involve operations which remove residual proteins, eg, solvent extraction, activated charcoal treatment, ultrafiltration or crystallisation steps.

More specifically, extraction steps with organic solvent are highly capable of removing proteins: first, due to solubility and second, due to the denaturation of proteins in the organic solvent phase. In the case of organic solvent extraction, the protein remains in the fermentation broth as this represents the aqueous phase where proteins are readily soluble. The proteins will not dissolve into the organic solvent phase. Any small fraction of the protein pool that possibly dissolves into the organic phase would end up as denatured particles. These are removed during such further process steps as polishing, solvent changes, and charcoal treatments.

In case a purification process does not include organic solvent steps or an equivalent operation (eg, charcoal treatment), removal of protein residues is regarded as a critical operation, which is subject to process validation (please refer to the decision tree below). The testing data must meet the scientifically based acceptance criteria as defined in the process validation.

Thorough manufacturing process validation therefore ensures consistent and adequate minimisation (or removal) of protein residues during the production process. Routine batch-to-batch testing is, in this particular context, not deemed necessary.

Accordingly, science and risk-based assessment review will occur on the occasion of process modifications and will incur, if applicable, revalidation.

In addition, this approach allows—and even favours—continuous improvement of the process, including the use of new technologies or methodologies (eg, improved sensitivity) as they appear.

In conclusion, it is regarded suitable to choose the science and risk-based approach for defining such cases which actually make testing for residual proteins necessary. The assessment, as proposed and discussed above, is depicted in the attached flowchart entitled “Decision tree for determining a requirement for testing for residual proteins”.

2. Additional Considerations

The applicability of the general monograph on Products of Fermentation should be clarified with regard to the active substances for which a CEP was granted. The EGA would very much welcome the EDQM perspective on this point.

3. Attachment

Decision tree for determining a requirement for testing for residual proteins

