

POTENTIALLY GENOTOXIC IMPURITIES AND EUROPEAN PHARMACOPOEIA MONOGRAPHS ON SUBSTANCES FOR HUMAN USE

The European Pharmacopoeia Commission adopted the following text in March 2008. It defines the policy for dealing with potentially genotoxic impurities to be applied during elaboration and revision of monographs. This text is published for information. It will be taken on board in a future revision of the Technical Guide for the elaboration of monographs.

1. PROBLEM STATEMENT

Concern over the presence of potentially genotoxic impurities (PGIs) has been growing for some years and has stimulated the preparation of the CHMP *Guideline on the limits of genotoxic impurities* (CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006), which came into effect on 1 January 2007.

Many active substances described in Ph Eur monographs may contain PGIs and there is rarely adequate control via the test or tests for impurities (general related substances test or specific test for an individual impurity).

Potentially genotoxic impurities may be included in the transparency statement (Impurities section) of monographs, usually as 'Other detectable impurities'. This is analytical information concerning the capabilities of the method shown in the monograph. It does not necessarily mean that the occurrence of the PGIs at relevant levels has been demonstrated. For some routes of synthesis the impurities listed may be completely irrelevant, so that requesting regular testing would not be helpful. The Production section of monographs may also draw attention to the need for attention to PGIs.

Groups of Experts dealing with elaboration and revision of monographs on organic chemicals are confronted with the problem, which is also regularly raised in comments from National Pharmacopoeia Authorities on Pharmedropa drafts.

2. ACTION

The European Pharmacopoeia Commission needs to develop a policy for dealing with potentially genotoxic impurities that can be applied during elaboration and revision of monographs.

The policy must:

- take due account of the CHMP guideline, which limits retrospective application;
- define clearly the need for control of PGIs in substances described in new monographs;
- define clearly the application to PGIs in substances described in existing monographs.

The policy developed should be reflected in:

- the general monograph *Substances for Pharmaceutical Use (2034)*;
- general chapter 5.10. *Control of impurities in substances for pharmaceutical use*;
- the Technical Guide.

3. BACKGROUND

The present action by manufacturers and regulatory authorities has not been precipitated by concerns regarding existing products but is primarily aimed at adding an extra level of safety to medicinal products. This new level of safety can only be added gradually considering each individual situation, otherwise the consequences for availability of medicines would create more risk than that avoided by action on PGIs.

Potentially genotoxic compounds are identified initially by chemical structure, certain structural features being associated with genotoxic activity. In general, structural alerts are considered to be meaningful, although there is not complete agreement on the structural features that should give rise to alerts. Structural alert does not automatically imply genotoxicity, nor does genotoxicity necessarily imply undesirable effects such as tumorigenicity.

The usual way of following up a structural alert is to carry out a test for DNA damage, notably the Ames test. If the latter is positive then a compound is under suspicion of toxicity in man and as a precautionary measure in the absence of other, informative data the limit of 1.5 µg/day (acceptable threshold of toxicological concern) is recommended by the CHMP guideline. Under specific conditions as mentioned in the guideline, such as short-term exposure or use in life-threatening conditions, this 1.5 µg/day threshold of toxicological concern may be adapted.

According to ICH guidelines and Ph Eur general provisions, impurities in an API are investigated to chemical structure level where they are present above the identification threshold but not necessarily otherwise. The threshold of toxicological concern (TTC, 1.5 µg/day) is such that, depending on the maximum daily dose of the active substance, impurities far below the reporting threshold could be of concern. An API typically contains many impurities at very low levels of more or less unknown structure. Predictions can be made from knowledge of the chemical reactions involved in the synthesis and their typical by-products. There is general agreement that such predictions are a tool but not a guarantee that all PGIs have been identified.

Substances included in medicinal products authorised in recent years have been thoroughly evaluated for safety and in view of the experience with their use the need for retrospective application of a policy on genotoxic impurities is not considered necessary unless there is a specific reason for doing so, as indicated in the CHMP guideline. New synthetic routes for these substances could imply a need for further evaluation.

4. POLICY TO BE APPLIED

The European Pharmacopoeia needs to derive a pragmatic approach that takes account of the above when elaborating or revising monographs. This policy may also serve as a basis for assessments in the Certification Procedure.

Products that receive a marketing authorisation after the issuance of the CHMP guideline will have been evaluated for the presence of PGIs according to the principles of the guideline and this should be the basis for a new monograph. For active substances included in medicinal products authorised by the competent authorities before issuance of the CHMP guideline, the specifications as described in the dossier for marketing authorisation should be followed. Action is needed only where there is study data demonstrating genotoxicity of the impurity. The existence of structural alerts alone is considered insufficient to trigger follow-up measures. If a new

synthetic route is used that may give rise to different PGIs or to higher levels of previously recognised PGIs then the evaluation by a Competent Authority should be used as the basis for the PGI in question.

Where an issue concerning a potentially genotoxic impurity is raised by a Competent Authority (notably for revision of a monograph or in comments on a Pharmeuropa draft), this will be dealt with on the basis of data provided to the European Pharmacopoeia Commission by the Competent Authority.

The policy described applies to substances for human use. Where a substance is used in veterinary medicine, the Competent Authority will decide for each particular case the requirements to be applied for PGIs.

The table shown in the Appendix gives an outline of some common situations faced by groups of experts and suggested action.

Appendix

Decision table for use during elaboration or revision of monographs

Status	Action
Substance included in a medicinal product authorised after issuance of the CHMP guideline	Monograph should be based on marketing authorisation(s)
Substance included in a medicinal product authorised before issuance of the CHMP guideline: - no PGI expected from synthetic route	No action needed, monograph based on marketing authorisation
Substance included in a medicinal product authorised before issuance of the CHMP guideline: - PGI expected from synthetic route of first authorised product - subsequently authorised products (if any) have no expected PGI or same PGI as the first authorised product at same or lower level and - no data showing genotoxicity	No action needed during elaboration of monograph (based on marketing authorisation), no revision of existing monographs
Substance included in a medicinal product authorised before issuance of the CHMP guideline: - PGI expected from synthetic route of an authorised product and - data showing genotoxicity of an expected PGI	Monograph should be elaborated or revised based on evaluation by the Competent Authority
Substance included in a medicinal product authorised before issuance of the CHMP guideline: - PGI expected from synthetic route of first authorised product and - subsequently authorised products have a new expected PGI or same PGI as innovator product at a higher level and - data showing genotoxicity of an expected PGI	Monograph should be elaborated or revised based on evaluation of new PGI or higher level of previously known PGI by the Competent Authority
Substance included in a medicinal product authorised before issuance of the CHMP guideline: - PGI not expected from synthetic route of first authorised product and - subsequently authorised product(s) have a new expected PGI and - data showing genotoxicity of an expected PGI	Monograph should be elaborated or revised based on evaluation of new PGI by the Competent Authority