the appropriately updated internal specification is used.

The internal specification is a release specification and limits may not necessarily cover end of shelf-life requirements. Those are covered in the regulatory specification and may also be included for information in the internal specification.

An internal specification may also include tests for the purpose of collecting additional data for the possible inclusion/exclusion in a later version of a regulatory specification. In such cases the specification limit(s) may be substituted by "for information".

Specifications/Internal specifications must be subject to change and version Control.

3.4 Investigational Medicinal Product (IMP)

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization when used or manipulated (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

3.5 Genotoxic Impurity

An impurity for which there is experimental evidence for genotoxic activity from a relevant validated test.

3.6 Potential Genotoxic Impurity

Any impurity where there is believed to be cause to believe it likely to be genotoxic. This is most likely to result from either comparison with FDA structural alerts or through a SAR evaluation process.

3.7 Product Specification File (PSF)

A PSF is a reference file containing, or referring to files containing all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.

3.8 Regulatory Specification

A regulatory specification (file specification) is the specification included in the submission to regulatory authorities (IND, CTA, MAA/NDA) and that subsequently will be/has been approved by a health authority and includes the tests, acceptance criteria and analytical methodology.

4 Responsibilities

Specifications for API shall be jointly approved by line management within

genotoxic impurities in development compounds (in draft when this guideline was issued).

For those impurities for which there are structural alerts and/or safety data indicate genotoxicity (e.g. positive AMES test) appropriate control must be exercised, either by specification limits or by other procedures, e.g. documented in a genotoxic strategy document.

Limits will depend upon several factors including, among others, the clinical phase (duration of treatment) and the therapy area. Limits should be set in line with the guidance provided in the internal guideline and due to the complex nature of how such limits are derived should be agreed jointly between relevant functions within the GPT. An example of permissible limits is given in Table 1.

Table 1: Adopted Allowable Daily Intakes (µg/day) for PGIs during clinical development, a staged TTC approach depending on duration of exposure.

	Duration of Exposure				
	≤1 mo.	>1-3 mo.	>3-6 mo.	>6-12 mo.	> 12 mo.
Allowable Daily Intake (µg/day) for different duration of exposure (as normally used in clinical development)	120[a] Or 0.5%[c] Whichever is lower	40[a] Or 0.5%[c] Whichever is lower	20[a] Or 0.5%[c] Whichever is lower	10[a] Or 0.5%[c] Whichever is lower	1.5[b] [c]

[a]Probability of not exceeding a 10^{-6} risk is 93%;
[b]Probability of not exceeding a 10^{-5} risk is 93%, which considers a 70-year exposure;
[c]Other limits (higher or lower) may be appropriate and the approaches used to identify, qualify and control ordinary impurities during developed should be applied.

In order to determine the permissible level in concentration terms in the API the likely daily dose needs to be established.

Tests for PGI impurities must be clearly identified within the specification and the results from these analyses must be part of the formal release process.

For PGIs results should normally be expressed in terms of parts per million.

6.2 Appendix 2

Contents of Specifications for Excipients during development

6.2.1 Pharmacopoeial excipients

In regulatory files reference is given to that the excipient fulfils pharmacopoeial requirements (Ph Eur, USP/NF or JP/JPE). No regulatory specification is included in the file.

A specification is needed for release purpose only. Alternatively, the excipient may be released against the relevant pharmacopoeial monograph.
For phase 1 and 2, requirements of only one pharmacopoeia has to be fulfilled.
For phase 3, it is recommended that the release specification fulfil the requirements of that pharmacopoeia, which is legal in the region where the clinical studies are performed (USP/NF in US; Ph Eur in Europe; JP/JPE in Japan), although this is not an absolute requirement.

6.2.1.1 Content of specification

Provided

- the manufacturer is an established excipient manufacturer or otherwise well known, e.g. currently supplying other excipients.

- good knowledge about the excipient/(class of excipient), e.g. similar excipients have previously been approved and used.

- the excipient will be used in early phase studies (phase I/II).
  the analytical results can be taken from the manufacturer's CoA without prior assessment and approval of the manufacturer for the specific excipient.. This decision should be documented appropriately.

The specification should clearly show, which results that are to be taken from the manufacturer' s CoA and the requirements for those test points. Alternatively, the requirement in the in-house specification can be that a CoA from the manufacturer is available that shows compliance to the relevant pharmacopoeia, e.g. Ph Eur.

As a minimum, identification should always be performed by the receiving company. Also description is recommended, as well as microbiological testing (not more than 102CFU/g is a mandatory requirement in some countries).

6.2.2 Non-pharmacopoeial excipients

A specification for a novel non-pharmacopoeial excipient should normally include the same requirements as those for an API. For a non-novel excipient an existing pharmacopoeial monograph for the same class of excipient should be used as a " template", if possible.

Any new excipients must be assessed in terms of their potential genotoxicity.

