

## **1 Purpose**

The purpose of this guideline is to describe the process for generation, approval and management within R&D of specifications for release of materials used in clinical trials during drug development. It also gives guidance on the contents of such specifications for drug substance, several common types of investigational medicinal products and excipients.

## **2 Scope and Applicability**

The guideline covers Specifications for non-complex bulk drug substances (APIs) and investigational medicinal products for clinical trials and is also intended for specifications for excipients during the development phase. Specifications for primary packaging material and container closure system are covered in another manual.

## **3 Definitions**

### **3.1 Active Pharmaceutical Ingredient (API)**

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product that when used in the production of a drug becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

### **3.2 Analytical Procedures**

The method of analysis that is unequivocally related to a certain specification document is called "the analytical procedure" in this guideline. It may be the analytical procedure for each individual specification requirement or it may be one document containing all procedures needed to demonstrate compliance to the specification. It may be the regulatory version or a more detailed internal (local) version of the procedure depending on phase of development.

### **3.3 Internal Specification/Specification**

For the purpose of this guideline the word specification means the specifications used for formal release within R&D. Thus, for sites using internal specifications or provisional specifications those are the specifications covered.

If internal specifications are not used the regulatory specification and the release specification will be the same.

An internal specification may be used to cover all requirements included in the different regulatory specifications submitted to different authorities, without having to update all different regulatory specifications when new requirements need to be included for a certain region or country. For the purpose of compliance and formal release of materials in clinical studies (covering all relevant countries)

R&D Analytical Chemistry (AC), R&D Early Development (ED) or Analytical Development (AD), and by R&D QA.

Specifications for Drug product and Drug product intermediate as well as excipients shall be approved by R&D Early Development (ED) or Analytical Development (AD) line management and R&D QA. Packaging material specifications are approved by Product Development (PD) and R&D QA.

#### 4.1 Author

The author for the release specification is responsible:

- for writing the specification document in a timely manner so that it is ready (and valid) before release of material for clinical studies. Generic specifications following the requirements for phase 1 (outlined in Appendix 1) may be used at early stages of development. At early development stages analysis may have been performed prior to the existence of a valid release specification, e.g. Campaign 2 drug substance.
- for consulting with the relevant people within project teams or sub-teams as appropriate (e.g. ED, AD, PD, R&D, CMC Documentation, QA) and/or line functions according to local routines.
- for the detailed contents of the specification. Standard requirements for an API/IMP or excipient are given in Appendices 1 and 2.
- that, if the specification does not follow the standard requirements, e.g. those given in the Appendices, this should be justified/documentated, e.g. in formally approved meeting minutes, a formal internal document "justification of specification" or an appropriate history log.

A specific "function"/person (which could be the author) at the R&D site should be responsible for initiating, indexing and finalizing the specification document and distributing it according to local procedures.

#### 4.2 Line management

The line managers within R&D Analytical Chemistry and R&D Early Development or Analytical Development (depending on the stage of development) (function or team managers or appointed person with special delegation), are jointly responsible for approving the API specification together with R&D QA.

The line manager within R&D Early Development or Analytical Development (function or team manager or appointed person with special delegation), is responsible for approving the specification for either the Drug product and Drug product intermediate as well as excipients together with R&D QA.

In both cases the approval shall ensure,

## 6 Appendices

### 6.1 Appendix 1

#### 6.1.1 Contents of Specifications for the release of Non-Complex Active Pharmaceutical Ingredients and Drug products for clinical studies

In this Appendix the word specification is used for the specification used for release of materials for clinical trials. Also included are standard quality requirements of material intended for toxicological studies (GLP-studies). The analytical testing of a new drug substance or drug product should normally not be restricted to that formally required by the specification.

Collection of additional data to support the ultimate NDA/MAA/JNDA specifications (and the analytical methods supporting those) can/should be made in parallel to the formal release testing. Such items may be included as "For information" in the specification. If a "for information" clause is included in a regulatory specification it should be accompanied by an explanatory footnote eg. "a review will be made for the need of this specification clause and if required acceptance criteria will be established at a later phase of development"

- Specifications during development must be subject to change control
- The name of the API or Dosage Form should be clearly stated in the heading of the specification. Specifications used during development should follow the general format of NDA/MAA specifications.
- The following Specifications/Tests should be included in all specifications for Drug Substance and Drug Product:
  1. Description (may be omitted as requirement for drug substance for Phase I and II if Appearance of solution is included)
  2. Identification: typically by IR or NMR for the API and minimally by a chromatographic retention measure for the drug product; include a chiral identity and a counter-ion identity as appropriate
  3. Assay (non-chiral is acceptable); normally 90-110% at release and end of shelf life for stable oral and parenteral dosage forms. If significant degradation takes place in a drug product during shelf life a tighter specification limit at release should be considered.

#### 6.1.2 Bulk Drug Substance (API)

In addition to Description, Identification and Assay the following specification tests marked x should be included or their absence justified.

Specification tests marked (x) should be considered (inclusion or not depending on drug substance properties and intended dosage form).

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 <sup>a</sup> Or 0.5% <sup>c</sup> Whichever is lower	40 <sup>a</sup> Or 0.5% <sup>c</sup> Whichever is lower	20 <sup>a</sup> Or 0.5% <sup>c</sup> Whichever is lower	10 <sup>a</sup> Or 0.5% <sup>c</sup> Whichever is lower	1.5 <sup>b</sup>   c

<sup>a</sup>Probability of not exceeding a 10<sup>-6</sup> risk is 93%;

<sup>b</sup>Probability of not exceeding a 10<sup>-5</sup> risk is 93%, which considers a 70-year exposure;

<sup>c</sup>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.

**6.1.3 Tablets and Capsules (immediate release (IR) and extended release (ER)), Oral powders and granules, Oral solutions and suspensions (unit dose)**

In addition to Description, Identity and Assay the following specification tests should be included (examples of wording given below):

Uniformity of dosage units	Meets appropriate Pharmacopoeial requirements (Ph Eur and/or USP)
Dissolution (for IR)	In "medium", "volume ml", 37°C Apparatus 2 (paddle), 50 rpm. After xx minutes (normally 30 or 60 minutes) not less than 80 (Q) per cent of stated amount. Evaluation according to USP. No requirement needed for "oral solutions".
Dissolution (for ER)	In "medium", "volume ml", 37°C, Apparatus 2 (paddle) 50 rpm. After x hours $y \pm 10\%$ of stated amount. (At least three time points) After xx hours not less than 80% of stated amount. Evaluation according to USP.
Degradation products	<p>A test for degradation products, e.g. "for information" may be included in the specification since some authorities may insist on specifications for degradation products being included in the regulatory specification already at Phase I/II. Limits (in the specification) for degradation products may not be needed before Phase III or even later for stable products (Data on degradation product should be collected and available). Organic impurities should normally be expressed as per cent of the active moiety, not of the salt form.</p> <p>In line with synthetic impurities, any degradants present in the API should be reviewed in terms of their potential genotoxicity. This assessment should be conducted in accordance with the AZ Internal Guideline – AstraZeneca Guideline for the risk assessment of potential 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 e.g. AMES appropriate control must be exercised.</p> <p>The limits and approach are analogous to that taken for organic impurities (see Table 1 in section 9.1.1.2) If significant degradation is expected during shelf-life limits for total and relevant specified degradation</p>

## 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 10<sup>2</sup>CFU/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.