Manual 031

6.1.2 Bulk Drug Substance (API)

	Tox (GLP-studies)	Phase I & II	Phase III
Chiral identification as appropriate (e.g. Optical rotation)	-	X	X
Appearance of solution	-	(X)	X
pH of solution	-	(X)	(X)
Sulphated ash/ROI	-	(X)	X
Water/LOD	(X)	(X)	X
Residual solvents	(X)	X	X
Organic impurities	X	X	X
Chiral purity	X	X	X
Catalyst residues	(X)	X	X
Polymorphism	-	(X)	(X)
Particle size	-	(X)	(X)
Microbiological limits	(X)	(X)	(X)

6.1.2.2 Organic Impurities: Figure1

Phase	Requirement (normal)
Tox (GLP-studies)	Total impurities ≤ 3% Single impurity ≤ 1% Unknown impurity ≤ 0.5%*
Phase I & II	Total impurities ≤ 2% Single impurity ≤ 0.5 (1)%**** Unknown impurity ≤ 0.2%**
Phase III	Total impurities ≤ 2.0% Single impurity ≤ 0.5 (1.0)%**** Unknown impurity ≤ 0.1*** (0.2)%

6.1.2.2 Organic Impurities: Figure 2

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.

6.1.2.6 Assay

Phase	**Limits (for chromatographic (e.g. LC) and spectrometric (e.g. NMR) methods)**
Tox studies	Not less than 95%
Phase I & II	(96) 97* – 102%
Phase III	(97) 98* – 102%

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

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± 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	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. 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 – AstraZenenca 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. 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

products may need to be included in the specification (but need not necessarily be tested for at release). Such limits should be worded similarly to " Organic impurities" for the API. Process impurities should not be included unless they are also degradation products.

For IR dosage forms Disintegration may replace Dissolution, if appropriate. Data for Water (KF), Hardness and Disintegration should be collected, if relevant, but should normally be kept out of the specification at least till the start of the stability studies for MAA/NDA or included "for information".

For suspensions/solutions a specification requirement for pH should be considered.

For capsules a description of both the capsule and the contents should be included.

For dosage forms intended for the oral route a limit of not more than 10^3 micro-organisms(CFU)/g may be appropriate, if included in the specification.

6.1.4 Placebo (for tablets etc)

Description, that corresponds to that of the active formulation
Absence of the API (e.g. < 1% of the active by a suitable chromatographic assay. Note - this is a test for negative identity – not a purity test.).
Disintegration and Mass variation/weight variation should be considered optional for tablets and capsules
The use of generic specifications for placebo should be considered.

6.1.5 Parenteral solution (Single Dose Containers)

In addition to Description, Identification and Assay the following specification tests should be included:

- Particulate Matter — Ph Eur or USP
- PH — Lower limit to upper limit
- Degradation products — Same as for tablets etc (see above)
- Sterility — Ph Eur or USP
- Endotoxins — Ph Eur or USP

6.1.6 Placebo (for parenteral solution)

Description	As for 9.1.3
Absence of Active	As for 9.1.3
Particulate Matter	As for 9.1.4
pH	Suitable limits
Sterility	As for 9.1.4
Endotoxins	As for 9.1.4