Ardena Insight

Defining acceptable impurity levels for drug substances in GLP toxicology studies

Toxicology studies conducted under Good Laboratory Practice (GLP) are a crucial element of preclinical development, as the resulting safety profile drives the selection of the dosing range of subsequent first-in-human studies. While specific regulatory guidelines exist on the quality criteria of drug substance (DS) batches intended for clinical use, there are no such guidelines for preclinical DS. This document aims to provide a conceptual framework to achieve appropriate quality for DS batches used in GLP toxicology studies.

It is a common misconception that DS batches used for GLP toxicology studies should be as pure as technically possible to minimise impurity-related toxicity. In our view, however, the focus of DS development in the preclinical stage should not be on achieving maximum purity but rather on obtaining a DS with an impurity profile that is likely to be consistent with that of the later (GMP grade) clinical DS. This enables toxicological qualification of the impurities and ensures translatability of the GLP toxicology results to the clinical situation. Achieving a similar impurity profile between GLP toxicology and clinical DS batches almost invariably implies that these materials be produced via the same synthetic route and using the same purification techniques, and that the scale of manufacturing of the GLP toxicology batch be representative for that of the clinical batches.

The general development strategy at Ardena is to conduct GLP toxicology studies with a so-called demonstration batch, i.e. a non-GMP batch produced via the same chemical process as the later GMP grade material. The primary purpose of this batch is to demonstrate that the production process indeed delivers material of acceptable quality, and to qualify impurities in the toxicology study. In addition to demonstrating the utility of the manufacturing process, this demonstration campaign also delivers material that is ideally suited to support GLP toxicology studies.

The table below summarises the quality attributes, acceptance criteria and test procedures used at Ardena to release DS batches for GLP toxicology study use. Release analyses are conducted with the same analytical methods that will be used to release the later GMP grade material.

Quality attribute	Acceptance criteria	Analytical procedure
Appearance	Conforms	Visual inspection
Identity	In agreement with structure	Nuclear magnetic resonance spectroscopy (NMR)
Assay	>97%	Quantitative NMR
Related impurities	<3%	High-performance liquid chromatography (HPLC)
Elemental impurities	Cfr. ICH Q3D	Inductively coupled plasma mass spectrometry (ICP-MS)
Residual solvents	Cfr. ICH Q3C	Head-space gas chromatography (GC)
Water content	For information purposes	Karl Fisher titration
Solid form	For information purposes	X-ray powder diffraction (XRPD)
Particle size	For information purposes	Laser diffraction

Typical quality attributes, acceptance criteria and analytical procedures utilised at Ardena to release

At Ardena, the demonstration batch used to support GLP toxicology studies is an important benchmark for future DS batches. The impurity profile of every newly produced DS batch is cross-compared to this demonstration batch to ensure consistency in the toxicological profile. This comparison is typically enabled by parallel chromatographic analysis of an aliquot of the demonstration batch and the newly manufactured batch.

In addition to use in GLP toxicology studies, a demonstration batch that meets the above quality criteria is also ideally suited to serve other development purposes such as the preparation of reference standard, the generation of DS stability data (to determine the shelf life of the later GMP grade DS) and the conduct of solid form screening, preformulation and early formulation studies.