Impurity Qualification at JRF

Impurity profiling or qualification is the process of evaluating data for the biological safety of an individual impurity.

When we consider benefits of pharmaceuticals, it always comes with certain risk factors and products in the market available are amalgamated, balancing both aspects.

Whenever we speak of impurities, cautionary thoughts about their qualification, start crowding our mind. Various guidelines have been in place which describes the process of evaluation and describing control measures to limit impurities in drug products and drug substances.

However, certain issues are not addressed in these guidelines, for example, control of relevant or genotoxic impurities, acceptable limits of impurities in drugs during the development process. CQR approach, i.e. Categorization, Qualification, and Risk assessment, is an important tool to understand the requirements of the regulator. In general, impurities in the pharmaceutical products are categorized into five classes i.e., class 1 to class 5.

CLASS 1

Genotoxic carcinogens fall in class 1, which are capable of producing cancer directly by changing the genetic material of target cells and it is always recommended to eliminate these impurities via purification step or perform a quantitative risk assessment to determine acceptable daily intake (ADI). If no safe exposure is identified, it is advisable to follow staged Threshold of Toxicological Concern (TTC) approach established by FDA initially for chemicals migrating from packaging into foods.

CLASS 2

Consists of impurities with known mutagenic properties with unknown carcinogenic potential, which can be qualified based on a threshold mechanism or staged TTC if no safe threshold is identified. However, it is better to follow permitted daily exposure (PDE) approach of Q3, if the safe threshold is calculated.

CLASS 3

Impurities have structural alert, but it is unrelated to the parent structure. These impurities are of unknown genotoxic potential and need to pass *in vitro* AMES test in neat form or spiked into API at $\geqslant$ 250 µg/plate to be considered as a safe impurity. If these impurities are found genotoxic, threshold approach is required.

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CLASS 4

Impurities with structural alert related to the parent API comes under class 4 for which API has to undergo potential genotoxic test using point mutation or AMES test, and if results are positive, a risk-benefit analysis is required. If found nongenotoxic, it can be considered as a safe impurity.

CLASS 5

Impurities are with no structural alerts or indication of genotoxic potential, and it can be controlled like an ordinary impurity.

As per Q3A(R2), it is mandatory to summarize all potential impurities of synthesis origin, generated during work-up or purification process and emerged on storage of new drug substance. Q3B(R2) covers drug products of active substance including reaction products with excipient or packaging material or container system.

At JRF, we have strong and proven capabilities of handling animal studies with state-of-the-art animal facility and ample historical control database.

The battery includes an assay for the gene mutation, chromosomal aberration, and micronucleus test, repeated dose toxicity in rodents as well as non-rodents for 14 days, 28 days, 90 days or up to Carcinogenicity depending on the class of impurity. JRF's strong chemistry expertise is available to support isolation, purification, characterization using spectrometry and quantitation using various chromatographic techniques.

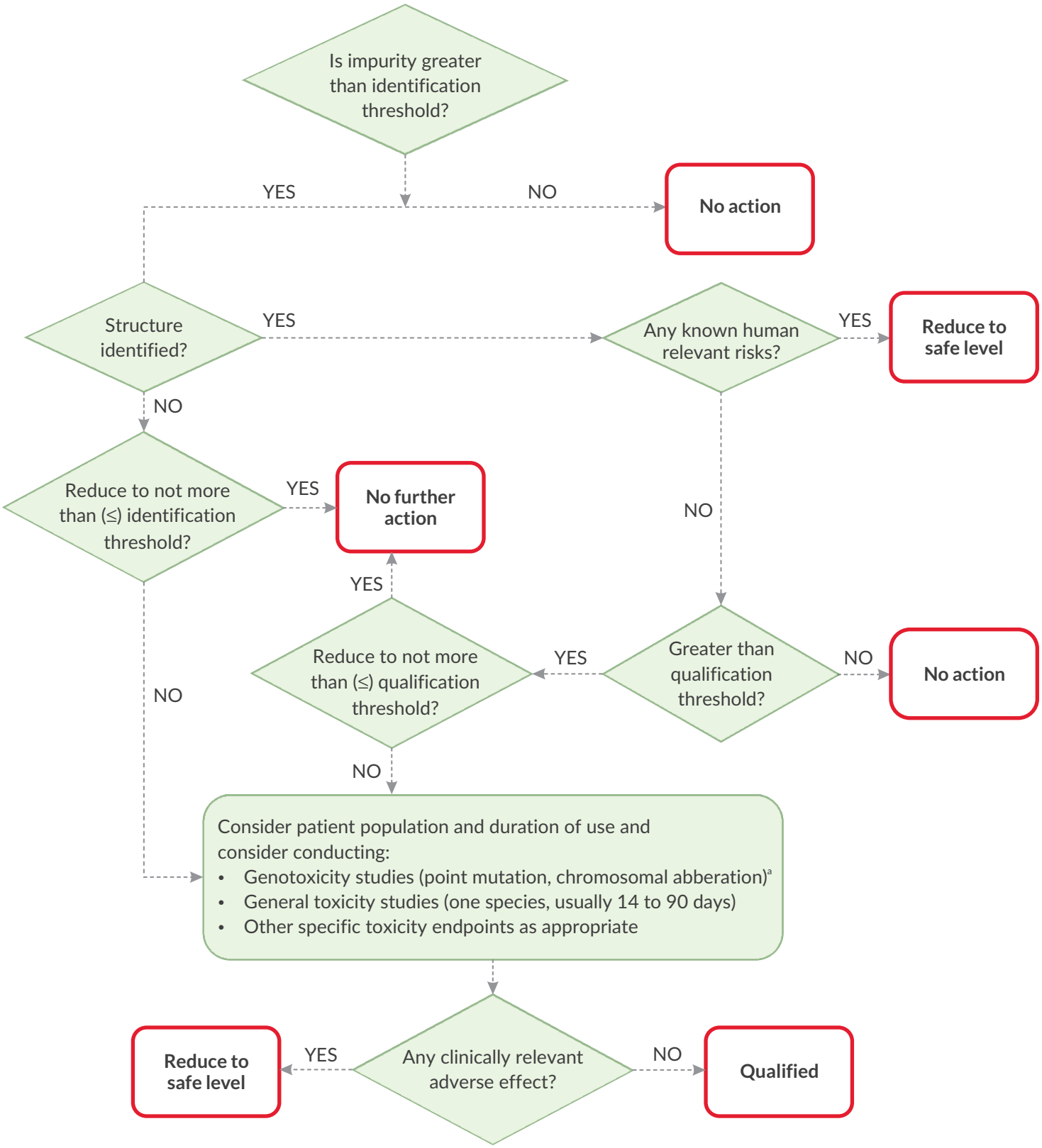
The chemistry support could be extended to undertake toxicokinetic studies as well, if and when needed.

Guideline provision to carry out these studies on API containing the impurity seems to be quite insensitive, even for powerful mutagens.

At JRF, with enormous experience, we assist our sponsors in deciding whether to perform these studies on impurity alone or on API containing an impurity. For impurities with known toxicological data, we refer EP or USP, and if pharmacopoeial data is not available, we set the limit based on available literature. For toxicology, we recommend our sponsors to use batches containing impurities which help in setting specifications based on administered doses and NOAEL and LOAEL values observed. In the early developmental stage, we do comparisons in mg/Kg and mg/m2 for assessment at the NDA stage. In case, a batch of drug used in phase 1 containing impurities is not tested in toxicology qualification, we follow a conservative approach and apply qualification threshold (0.2%), but specific qualification or bridging *in vivo* studies is last resort considering the risk of generating new findings.

In general, the concept is to identify and classify structural alerts in parent compound and impurities and to establish a qualification strategy with acceptable limits.

DECISION TREE FOR IDENTIFICATION AND QUALIFICATION



Reference: Guidance for Industry Q3B (R2) Impurities in New Drug Products, U. S. Department of Health and Human Services Food and Drug Administration, July 2006 ICH Revision 2

STUDIES REQUIRED FOR IMPURITY QUALIFICATIONS AS PER ICH Q3B (R2):

GENOTOX	1) Ames Test – OECD 471	To detect point mutations
	2) HLCA – OECD 473 or *in vitro* MNT – OECD 487	To detect chromosomal aberration
REPEAT DOSE TOXICITY	14-90 days toxicity study in rats	Generally in a single species is acceptable) at the level higher than the threshold limit.

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