

Impurity Profiling in Pharmaceuticals

Industry Perspectives and Challenges

What is Impurity Profiling ?

- All the related substances that are likely to be present in the desired drug – either drug product or drug substance
- Impurities are unwanted chemicals present in the API or FDF arising from normal manufacture. They are not chemicals accidentally or maliciously introduced
- Impurities have no therapeutic value and are potentially harmful. Therefore they need to be controlled.
- Starting materials, intermediates, reagents, catalysts, solvents, water, by-products, degradation compounds of the drug substance, acids, alkali/bases, filtration aids, clarifying carbon particles, etc
- Reagents could be organic or inorganic chemicals
- Absolute absence of the impurities is not likely and is not expected also.
- Excipients are not part of impurity profile. They are additives for improving the product performance.

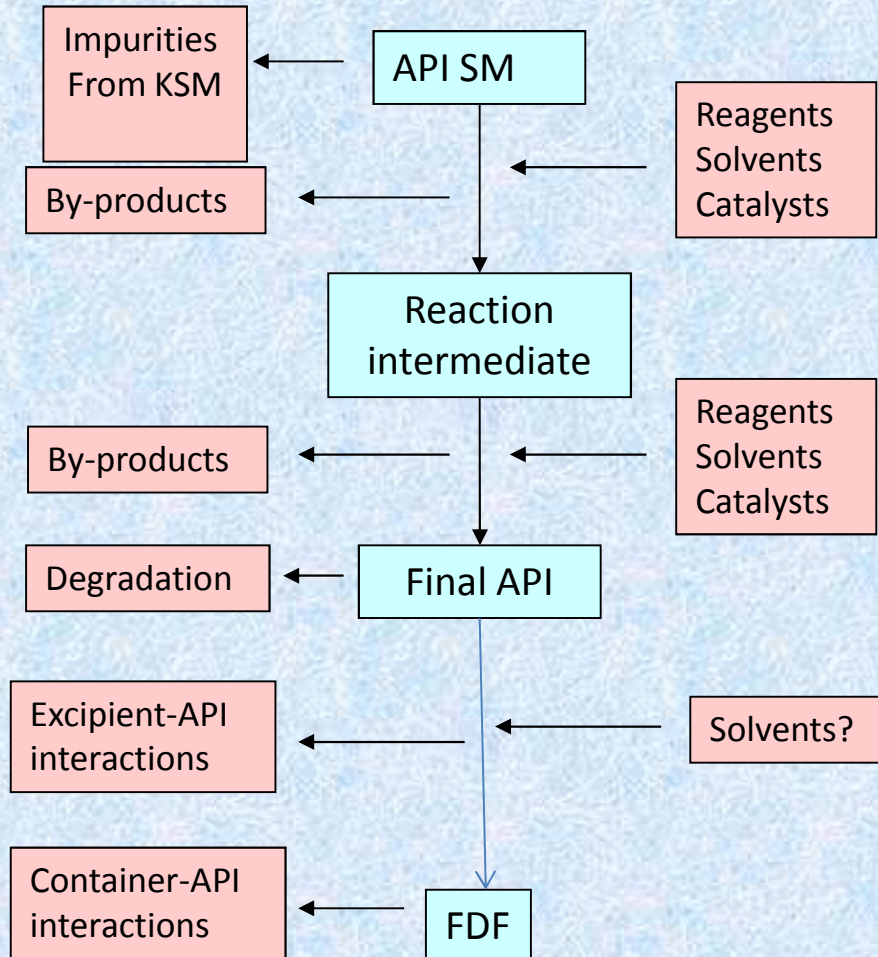
Impurities

- Most of the organic impurities are either process related or degradation resultants.
- Organic impurities are either present as an additional substance or produced during the storage of the drug substance or drug product
- Inorganic impurities are carryover of the reagents used in the synthetic processes and are not removed completely by the purification process of the API.
- Sometimes, inorganic impurities are due to the traces of likely by-products from the reagents used
- Certain genotoxic impurities need to be detected and controlled at a very low levels – like 1.5ppm – which is 0.00015% level.

What are the potential impurities?

- The first step in setting up impurity specifications is to consider what potential impurities might be present, based upon all available information.
- This step is often poorly performed by some of the applicants.
- There is a tendency to skip this step in discussions and just adopt pharmacopoeia specifications, when an official monograph exists.
- It is essential to have a detailed knowledge of the preparation of the API and the controls placed upon the API starting materials, reaction intermediates, reagents and solvents.
- It is essential to know how the API degrades and the likely degradation impurities generated.

What are the potential impurities?



Potential Impurities

- Residue of the SM
- Residue of the intermediate
- Impurities in the SM
- Reagents
- Solvents
- Catalysts
- Reaction by-products
- Degradation products
- Excipient-API interactions
- Container closure interactions

Industry Position

- Pharma industry is poised for very high growth rate in India.
- The pharmaceutical active ingredients are being produced and sold for the regulated markets, like US, EU, Canada, Australia, UK, Brazil, etc
- The manufacturing organizations have wide variety of talent, financial back-ground, analytical capability etc.
- Synthesis and characterisation of the impurities is a cumbersome job for a portion of the manufacturing companies

Sources of Impurity Standards

- LGC is the main source for many of the impurities listed by EP, USP, etc
- There are good number of other organisations engaged in synthesis and supply of the impurity standards to the industry.
- The cost and lead time of sourcing these impurities are major hurdles for many manufacturing companies to complete the method validation, using all the listed impurities.

Justified Approaches

- Manufacturing company need to review the listed impurities in a given monograph and classify them into different categories like potential process impurities from the RoS, not likely impurities by the ROS, degradation products, impurities that are controlled well before the final API stage, etc
- These classifications help decide on the likely impurities to be detected in the final API and consider them for the purpose of method validations
- Scientific rationale for such selection is very important
- Degradation potential of the API due to the finished dosage form is also necessary to be considered.
- Forced degradation studies as per the ICH Q2B is an important step in determining the likely impurities that could be formed upon storage and/or process steps adopted further to the release of the API.

Control of impurities

- Not all the possible impurities could be tested for their levels on routine batch release.
- It is the concepts of cGMP that prevails in the manufacturing of the drugs that could lead to testing only a limited number of impurities for the purposes of batch release.
- All the possible impurities should be listed and a risk assessment and potential carryover chances should be verified to take a call on including/excluding of specific impurities in the routine release specifications

Control of impurities

- All significant changes done in the manufacturing processes should involve scientific rationale to justify the impact/change in impurity profile, as triggered by the changes done to the manufacturing processes
- Similarly, all significant deviations occurred in the batch processes should be investigated to verify the likelihood of impact on the impurity profile.
- Similarly, changes in the sources of the KSM and the other chemicals/reagents should be reviewed to conclude the possible impact on the impurity profile and the necessary re-evaluation of the level of those impurities that are not part of the routine batch release procedures.

Setting up limits for impurities

Organic Impurities

An organic impurity above the applicable ICH qualification threshold needs to be qualified.

	Maximum daily dose	Qualification Threshold - The lower of:	
		% of API	TDI
API	< 2g	0.15%	1.0 mg
	> 2g	0.05%	-
FPP	< 10 mg	1.0%	50 ug
	10 mg - 100 mg	0.5%	200 ug
	> 100 mg - 2 g	0.2%	3 mg
	> 2 g	0.15%	-

Setting up limits for impurities

When the impurity level is greater than the ICH qualification threshold then it should be qualified:

- Through toxicological trials.
- By comparison to a limit specified in the Ph.Int., Ph.Eur., or USP for a **specific** impurity. It could even be in a monograph for another substance. A statement in a monograph of "any other impurity NMT 0.5%" cannot be used as justification for an impurity limit, as it is not specific.
- By comparison to levels found in an innovator or prequalified FDF.
- By comparison to a limit previously approved in a prequalified FDF.
This is a last resort.

Setting up limits for impurities

- The limit for any unspecified impurity should be at the ICH identification threshold.
- The limit for total impurity content should reflect batch data.
- These concepts are applicable to synthetic APIs, but could be used on a case by case basis for semi-synthetic APIs.

Impurity profile vs reported impurities on CoA

- CoA is always issued for the tests intended to be performed on the batches by the validated manufacturing process
- CoA is NOT the complete list of the impurities present in the batch samples
- When the manufacturing process is maintained at the state of validation, the CoA issued based on the committed tests will stand as the assurance of the quality attributes.
- Whenever there are changes and deviations, the specifications and CoA does not give assurance of the impurity profile and the quality attributes of the batches need to be ascertained by some additional means of testing.
- Under these circumstances, a comparison of the impurity profile and the risk assessment of the adequacy of the same specification committed are very important.

Unknown impurities vs unreported impurities

- Unknown impurity is rather an impurity eluting at the specified RRT and is monitored always and is controlled as unidentified impurity.
- Unreported impurity is something that is expected to be controlled by the manufacturing process and is not controlled by the specification limits. These are not necessarily eluting in the MoA for the batch release.
- Process capability factor drives the level of those impurities, which are controlled by the specifications as well as those impurities controlled by the manufacturing process.
- When the process capability factor is measured as part of one of the parameters, it mostly reflects the likelihood of the level of other parameters, as well.
- Scientific rationale is adopted to avoid the testing of the impurities that are controlled by the manufacturing process. When there are some changes/deviations from the routine manufacturing process, the impact on those impurities, not being tested routinely, needs to be reviewed and justified.

Check-point alerts in execution

- Establishment of the LoD/LoQ should be based on the relative concentration of the test sample, not on the absolute concentration of the solution preparation.
- Standard runs for test of residual solvents and other impurities should be equal to the specification limits of those solvents/impurities. When there is revision in the specification limit, the MoA also should be revised to ensure that the relevance of standard runs are maintained.
- Method of analysis should be reviewed – subsequent to the completion of the method validation, including the forced degradation.
- Indication of the LoD/LoQ, solution stability data, other factors affecting the analytical results, due to the method should be highlighted and described, as part of the MoA – based on the results of the method validation.
- Any new impurity, away from the routinely detected impurities, should be picked up as an alert, irrespective of their levels within the specification limits.
- Unknown peaks in residual solvent testing is a common issue discovered and discussed in many API's. Scientific rationale with the clear investigation methodology is important to confirm the impurity profile of the API's.
- Some solvents that are not reported routinely on CoA of API's creates some questions from finished dosage manufacturer. To avoid such confusions, the MoA should capture the RRT of those solvents also that are not routinely reported, along with their LoD/LoQ.
- Verification of the sample solution stability as part of the method validation and capturing the acceptable storage time for the sample preparation/solution as part of the MoA is critical to avoid OOS results, due to absence such information in MoA.
- Cleaning and validation of the cleaning procedures of glassware is extremely important to avoid contamination of the sample preparations and generating OOS results, due to QC practices/procedures.

Purge and Fate of impurities

- The specifications for a KSM is generally accepted as is– when any other/unknown impurity is to be justified, based on the design of the further steps and the limits of impurities further.
- The process capability factor is very important in considering and concluding this limit for any other/unknown impurity.
- Purge-off of the related impurities that are not reactive to the chemical reactions from KSM to API is an acceptable approach. KSM should be injected in the method of analysis for the API and the co-relation of the presence/absence of the impurities of KSM in the final API method should be verified and justified.
- Reactive impurities of KSM to the chemical reactions should be studied for the appropriate derivatives of the API and the method suitability of detection and quantification should be verified and reported.
- Fate of those reactive impurities in the manufacturing process and the purification process are very important to establish the impurity profile of the final API.
- Residual solvents used up to the KSM stage can be proved for the purge off levels below the 10% of ICH limits to avoid listing them as part of the API specifications. However, method validation should cover all the solvents for the RT/RRT, specificity, LoD and LoQ of all the solvents used for the manufacture of the KSM and further to the API.

Chemistry is Mathematics

- All materials added should be removed or reported for their levels during the process
- Mass balance is applicable and is required – all by-products should be part of the reaction scheme, to show the full chemistry, this will help to understand the impurity profiling
- Dilutions and calculations for all tests are purely mathematics and no chemistry knowledge is mandatory, but should be accurate
- The consistency of operations will yield the correct results always.

Chemistry is NOT Mathematics

- $1+2$ and $2+1$ would give the product/result as 3 in Mathematics. But, adding water to sulphuric acid and adding sulphuric acid to water are not going to result in the same reaction/result.
- Sequence of the operations have a critical bearing for the chemistry.
- The kinetics and the reaction rate in laboratory scale are not comparable/proportionate to that in the manufacturing scale, using reactors etc.
- Response ratio of different impurities and the active ingredients can vary from small to large differences and that depends on the chemistry of the measurement method/instrument.
- A batch as per the process validation cycle shows an unknown impurity @ RRT 0.6 to the level of 0.07%, while the routine production batch shows an unknown impurity @ RRT 1.4 to the level of 0.07%. Both are not equivalent.

Forward and reverse process integration

- Setting up specifications based on the ROS adopted by the R&D and knowledge gathered from the development of the process and methods is forward way of process integration
- Reviewing the specification for compliance w.r.t. the official monographs and including/adding controls on listed impurities in the monographs is reverse process integration.
- Revising the MoA based on the total knowledge from the process/method development, review wrt to the official monographs and adding specific controls from the forced degradation studies performed will make a robust control strategy for the manufacturing companies.

Current Challenges for the Industry

- ICH – M7 – for the mutagenic impurities and the assessment and control of the same
 1. The level of control required for these impurities are very low level and hence the method development and validation etc involve high cost impact and lead time for the establishment.
 2. CAD – Charged Aerosol Detectors are handy for the detection and control of these low level impurities that are mostly not possible to be controlled with UV detection.
 3. The guideline clearly defines the categorisation and verification procedures.
 4. There are few third party analytical services laboratories who support the manufacturing industries for compliance for this requirements and involve very high cost and time.
 5. Control of these impurities at the intermediate stage of manufacturing is best possible option for manufacturing industries.

Current Challenges for the Industry

- ICH – Q3D – Elemental impurities
 1. The risk assessment with the complete knowledge on every material used is required.
 2. Testing at such a low levels using ICP-MS or equivalent is not affordable for small and medium size industries
 3. External laboratory testing is cumbersome for trials, changes, validations, etc
 4. Approach to the risk assessment is given in the guidelines and involves evaluation of data from the sources of each and every vendor for ALL the materials – include their complete RoS. Most of the times, vendors do not disclose the usage of some catalysts in their RoS, due to the proprietary nature of the same.
 5. Selection of the worst case manufacturing process, using the same set of equipment and testing the worst case product for those class 1 and 2A elements is a possible approach.
 6. The testing sample concentrations and the specification limits require very high level of precision in instrumentation and also the homogeneity of the test samples to that degree of precision.
 7. Buying and maintaining instruments like ICP-MS is very costly.

Questions? Clarification?

