TYPICAL FDA COMMENTS ON IMPURITY PROFILING IN CTD/CEP/DMF SUBMISSIONS

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This article is solely written by him to guide, educate and train young Regulatory, QC and QA personnel at large. The article is based on self experience of 25 years of the author

1. INTRODUCTION

Impurity profiling is a highly intelligent, tedious and expensive task in standardizing the drug products for marketing Authorization. This task usually more complex when the proper impurity standards are not available and synthesis of the same require extra ordinary high cost and time. It has been observed that many a time application for ANDA/DMF/CEP is delayed due to extra ordinary delay in compiling impurity profiling. Further, the approval of many of drug product is denied for inadequate impurity profiling.

This article provides typical FDA comments on data on impurity profiling included in Regulatory submissions for marketing Authorization. The purpose of the article is to assist the regulatory professionals to understand the FDA perspective on Impurity Profiling and to avoid queries on the same.
Many of the queries are referenced from FDA 483 Notes and Scientific Discussions available on the internet.

2. DEFINITIONS

Impurity Profile:	**It** is a description of the impurities present in a typical lot of a drug substance produced by a given manufacturing process. The description includes the followings: Identification by any instrumental method, Absolute Characterization and Quantitation by spectral means or Relative Characterization / Quantitation using a typical reference standard, Comment on acceptability of the products based on the results
Identified Impurity	**An** impurity for which structural characterization has been achieved
Unidentified Impurity	An impurity for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (for example: relative retention time)
Specified Impurity	An impurity that is individually listed and limited with a specific acceptance criterion in a monograph. A specified impurity can be either identified or unidentified
Unspecified Impurity	**An** impurity that is limited by a general acceptance criterion and not individually listed with its own specific acceptance criterion
Process Contaminants	**Process** contaminants are identified or unidentified substances which get included in the drug product during synthesis.
Related Substances	**The** impurities which are structurally related with the drug products
Potential Impurity	**An** impurity that theoretically can arise during manufacture or storage of the drug product
Ordinary impurities	Ordinary are those species in bulk pharmaceutical chemicals that are innocuous by virtue of having no significant, undesirable biological activity in the amounts present. These impurities may arise out of the synthesis, preparation, or degradation of compendia articles. The value of 2.0% was selected as the general limit on ordinary impurities in monographs. Unless otherwise specified in an individual monograph, estimation of the amount and number of ordinary impurities is made by relative methods rather than by strict comparison to individual Reference Standards.
Qualification Threshold	A limit above which an impurity is to be qualified.
Impurity Qualification	The process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified
Nominal Concentration	Concentration calculated on the basis of the concentration of the prescribed reference and taking account of the prescribed correction factor
Identification Threshold	A limit above which an impurity is to be identified
Disregard Limit	The nominal content at or below which peaks/signals are not taken into account for calculating a sum of impurities

3. TYPICAL COMMENTS

1	You have not provided adequately data on inorganic, organic and solvent impurities which may be present in your drug product.
2	The manufacturing and purification process adopted by you is inadequate to remove potential impurities and solvent impurities
3	There is no documentary evidence on control of residual amounts of metal catalysts used in the synthesis of API produced by you.
4	The Impurities in the drug substance exceeds the Limits for Total Impurities permissible by ICH Guidelines
5	There is no historical data on impurity profiling
6	The process validation is inadequate to control impurities present in drug product
7	Only historical data has been provided for impurities in drug substances. The study has not been repeated over last two years to detect possible changes in impurity profiling
8	"It is difficult to identify and estimate impurities" is insufficient rationale for not studying the impurities present in the drug
9	The impurities in the drug product manufactured by you are not adequately identified and qualified.
10	The impurity profile of current batches do not match with the historical data on impurity profiling provided in DMF
11	The API is sourced from two different vendors. However, the specific impurity profile for each source is not provided.
12	The unidentified impurities preset in your product are alarmingly high l
13	API involves use of Toluene in the synthesis. However, the same has not been analyzed for possible impurity of benzene.
14	The drug substance is "L isomer ". The specific method for detecting corresponding "D isomer "as impurity is not defined.
15	The drug substance is known to exist in different polymorphic forms. The type of polymorph and polymorphic impurities are not described.
16	Forced degradation studies have not been performed to indicate the possible degradants which can contribute to the impurities in the drug substance.
17	The method used for impurity profiling is not stability indicating
18	The impurity profiling has been performed without using standard impurities as reference
19	The reference standard used for impurity profiling is in-house. However, the structure and purity of the same has not been established.
20	The impurity profiling provided by you, does not match with the route of synthesis adopted.
21	The drug is manufactured by two different routs. However, the specific impurity profiling for each route is not provided.
22	Potential impurities arising from the starting materials, bye products and reagents are ignored.
23	The impurities for the solvents used in the initial stages of the synthesis are ignored.
24	The sum of all individual impurities exceed to that described in recently amended compendia monograph

25	The method used for qualifying the individual impurity is not validated.
26	Although the Manufacturing Process have been modified but the corresponding effect on Impurity profiling has not been provided
27	Class I solvents are used in the synthesis of the drug substances. However, the drug product is not analyzed for the residual amount of the same on regular basis.
28	There are gross deficiencies in detection, identification/structure elucidation and quantitative determination of organic/inorganic impurities and residual solvents in bulk drugs produced by your company
29	The experimental data on LC-NMR, MS, GC-MS, and LC-MS techniques used in identification and Qualification of impurities is inadequate.
30	Impurities arising from the use of Reagents, Metal catalysts , Filter aids and charcoal are not adequately addressed under impurity profiling
31	There are no comments on the impurities carried forward from intermediates sourced from two different manufacturerers
32	The impurity limits provided for impurity A and B are very high. The same may be tightened to the level …….
33	The starting material specifications do not include potential impurities which can be carried over in the drug substances.
34	The drug intermediate used by you are known genotoxic. However, you have not paid any attention on detecting and quantifying the same in the final product.
35	The limits for enantiomeric purity should be tightened
36	The structural formula, stereochemistry, molecular formula is not provided for identified impurities.
37	The starting material used for the drug product synthesis show a chemical group which is known to be carcinogen. However, no limits on the same are proposed in impurity profiling.
38	Specific impurity profiling on batched produced using different purification processes is not provided.
39	There is no discussion on impurities which can be contributed by the starting materials.
40	Issues on potential genotoxic impurities based on confirmed “alerting structures” present in the staring materials and intermediates of drug substances are not discussed.
41	Detection, identification, structure elucidation, assay of impurities and residual solvents is not provided.
42	The limits for total impurities should be tightened in line with batch analysis data and stability results submitted in the application;
43	Inorganic impurities should by reduced in accordance with the requirements of CPMP/SWP/QWP/4446/00 (15);
44	Confirm that the proposed related substances methods used for the analysis of production batches are the same as those used for the samples used for clinical studies.
45	Analytical results should be presented for at least three batches with the level of impurities discovered
46	Reference standards of all identified related substances and other specified impurities should be characterized suitably and data provided in the dossier.
47	List of Specified Impurities and Unspecified Impurities is not provided.
48	Explain how the potential impurities were identified and characterized.

49	The method of manufacturing adopted by your company may produce a new impurity which is not adequately controlled by EP Monograph. Please discuss on the same.
50	Provide revised impurity profile .Report each individual impurity above 0.05 %. Identify all the impurity above 0.1 %. Qualify each impurity above 0.15 %
51	USP monograph for the product manufactured by you does not provide any test for impurities. However, you can not ignore impurity profiling of your drug substance. Please details the studies conducted to detect potential impurities based on your typical process.
52	Your HPLC method for impurity profiling is unacceptable as it lacks description on Composition and pH of Mobile Phase ,Type width and length of HPLC Column ,Flow Rate of mobile Phase ,Column Temperature ,Type and description of Detector ,Injection Volume ,Run Time ,Retention Time, Sample Preparation System Suitability etc..
53	You have shown that Genotoxic impurity is well within the control (Less than 15 ppm). However, you have not included this observation in COA
54	You have adopted a new route of synthesis which may lead to new impurities in your product. However, your submission does not reflect any change under impurity profiling.
55	You have used Benzene in the synthesis of final stage. Your COA does not reflect residual benzene in the final product.
56	You have not analyzed Toluene used in the synthesis for its benzene content. You must know that Benzene is limited to 0.05% as impurity in toluene
57	Your compound contains structural elements such as NN hydroxyaryls, N-acetylated amino aryls, aza-aryl N-oxides, alkylated amino aryls, N Nitrosamines, nitro compounds, epoxies, aziridines, hydrazine, alkyl esters of phosphonates, mesylates, primary halides which are well identified structural alert for Genotoxicity. However you have not provided any specific discussion on the same
58	You have maintained residual solvents just at safety limits described in ICH Guidelines. However, you must improve the process to eliminate the residual solvent to the highest extent possible
59	You have not provided summary of each non-USP method for impurity profiling. Further, presentation of impurity data is confusing. The impurities are neither tabulated distinctly nor described adequately in text form.
60	Impurity profile is not in accordance with ICH Q3B(R2)4 and ANDA Guidance
61	The evidence on the validation and suitability of analytical procedures used for the detection and assay of impurities is inadequate
62	Your drug substance passes the test for related substances as per current USP Monograph. However, you have ignored other impurities which may be present in your drug substance from the proprietary synthetic route adopted by you.
63	Grignard reaction is involved in the synthesis of your product. Have you checked the possibility of formation of dime compound as possible impurity?
64	Residual catalysts levels are not determined

65	The finished products are not tested for the likely residual impurities carried by starting materials.
66	You have used class I solvent in the synthesis. But you have not demonstrated that the residual quantities of the same are below 30% of their ICH limit. You are required to provide Supporting data for the analysis of residual solvent on 6 consecutive pilot scale batches or 3 consecutive industrial scale batches
67	You have documented Impurity profiles for the drug substance used in clinical studies. However, the process used for manufacturing the product is different from that used for manufacturing clinical samples. You must demonstrate that impurities in productions batches are within control.
68	You have not applied "heavy metals limit "test to control General Inorganic Contaminants in your product.
69	You have not included specific control test for iron and copper which are used in the synthesis of the drug product
70	You have applied traditional limit test for heavy metals as given in USP. However, you have not applied any quantitative test for specific metal contaminants that are used in manufacturing.
71	Please justify the limits for genotoxic impurities presented in your dossier.
72	COA of toluene shows benzene content more than 20 ppm which is not acceptable. Further each and every batch of toluene is not analyzed for benzene content.
73	"It is manifestly impossible to include in each Pharmacopeial monograph a test for each impurity that might be present. The new impurities may arise from a change in the processing, or may be introduced from extraneous sources. Tests suitable for detecting such occurrences should be employed in addition to the tests provided in the individual monograph. "
74	Kindly justify setting of the limits for impurities in light of the followings: the parenteral application of the product , the daily dose of drug being very high, the senior citizens being as target population and the duration of therapy over 15 days
75	Your impurity test methods are incapable of capturing side reaction products, degradation impurities, metal catalysts, and residual solvents used in the synthetic process.
76	Residual solvent limits are not within the ICH safety limits
77	You are using a new solvent which is not listed ICH Q3 Guidelines. However, you have not qualified its residual levels.
78	You have not qualified the impurities using impurity standards. Even you have ignored the Relative Response Factors for impurities.
79	You have ignored reference to Compendia Guidelines as well ICH Q3B (R2) for Impurity profiling of your product
80	You have not summarized and discussed the results of stress testing of the drug product and analytical methods used.
81	You have used in-house reference standard for API product manufactured by you. However the same has not been characterized completely.
82	You have not provided any details on how the potential impurities were identified and characterized.

83	You have failed to provide even RRT/HPLC for unidentified impurities present in significantly high levels in your product.
84	Justify scientifically higher reporting thresholds for an unusually highly toxic impurities A present in you product
85	The Reporting Threshold (RT), Identification Threshold (IT), and Qualification Threshold (QT) of impurities do not match with the Maximum Daily Dose indicated on the label of your product.
86	The forced degradation studies provided by you show degradation less than 5%. The study may be repeated to targeted degradation at least between 10 to 15%.
87	You are manufacturing the drug as per USP wherein no related substances are listed in the monograph. However, you have not referred other Pharmacopoeias such as EP and JP for likely impurities and related substances which may be present in your product.

4. PLEASE NOTE

This guidance is not applicable to biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation and semi synthetic products derived there from, herbal Products, or crude products of animal or plant origin. The recommendations in this guidance are effective on publication and should be followed in preparing new applications and supplements for changes in drug substance synthesis or process.

Any query on this article or any personal query may be addressed to the author at guptarmg1952@gmail.com

5. REFERENCES

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MY NOTES