IMPORTANCE OF DEFICIENCY RESPONSE IN PHARMACEUTICAL ENVIRONMENT FOR DRUG APPROVAL

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CASE STUDY

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ABSTRACT

This illustrates examples of series deficiencies, that's how really company faces problem due to deficiency. It's to convey the message if drug product manufacturer can visualize earlier all aspect of risks and manifest proactively, then there is always least chance to have the said deficiency received. However, even then if company also gets deficiency, company could have equipped with earlier data. So, what they need to do is to focus properly for addressing agency's query by utilizing proper scientific and technical writing skills. How lack of visualization creates problem, how review cycle prolonged and how by dint of this issue approval got delayed has been clearly discussed in this case study. The reason of so many rounds of questions and review cycles become longer and finally approval got delayed is from the beginning itself agency was not satisfied or convinced with the justification given by said Company.

Keywords: Impurity content, TGA, deficiency, Approval, Review process.

INTRODUCTION

Case background

A real time case is of a well-established Pharma Company named as Navaratna. Navaratna filed an application for drug approval of XX tablets, but due to deficiencies in quality profile (impurity content) of drug product the review process gets delayed. There are series of comments received from Therapeutic Goods Administration (TGA)(1) and Navaratna tried its level best to provide its responses. Through the real time dialogue between Therapeutic Goods Administration (TGA) and Navaratna, an attempt has been made to understand the flow of deficiency and its importance. It also helps to understand how by proper drafting of response, can eliminate further queries. Because, by dint of avoiding of deficiencies, review cycle can be compressed; this ultimately can be profitable for company and society too as early approval of drug will be helpful for needy people who are suffering with the concerned disease on which the innovator company is working while in case of generic drugs, people will get the benefits of same drug with cheaper price.

Note: Due to confidential and IP issue, special care has been taken to change the company name and for certain information we have manifested in terms of ---, xx etc.

Therapeutic Goods Administration (TGA) Comment with respect to drug product specification (1-5):

The following known impurities are specified in the United States Pharmacopoeia (USP) monograph of XX tablets but not in the proposed finished product specification:

- 2-{3-1-Methylplperidin-4-yl}-5-2-methyl sulfamoyl-ethly-indol-1-yl) ethanesulfonic acid methylamide (NMT 0.2%); and

- 4-[1, 5-Bis-(2-methylsulfamoly-ethyl)-1H-indol-3-yl]-1-methylpyridinium chloride (NMT 0.2%)

Since a USP standard is claimed, it was requested that the finished specifications be amended to specify these impurities which can be adequately controlled under the limit of not more than (NMT) 0.20% for individual unspecified impurities. The response should

include analytical results, methodology and validation.

Response:

As per the drug substance manufacturer's route of synthesis for XX DS, it has a low likelihood for the formation of four impurities specified in the USP monograph for chromatographic purity of the drug product (Table 5.1).

Navaratna currently monitors 3-(-1-Methylpiperidin-4-yl)-1H-indole (ZZZ (DP Related company) I/RCA) and 2-[3-1(1-Methyl-1, 2, 3, 6- tetrahydropyridin-4-yl)-1H-Indol-5-yl] ethanesulfonic acid methyalmide (AAA (DP Related company)-I/ RCB). Navaratna propose to control these USP impurities in the drug product as unidentified impurities, each at a limit of NMT 0.20%, which is tighter than the USP limits.

It is required to refer section 3.2.P.5.6 (Justification of specification of impurities of drug product) for the justification report of using in-house High Performance Liquid Chromatography (HPLC) method (degradation products) to corresponding USP method and section 3.3.P.5.3 for method validation.

Table 5.1: Comparison of USP HPLC method limit to Navaratna's limit

Compound name	USP Limit (NMT%)	Navaratna's Limit (NMT%)
3-(-1-Methylpiperdin-4-yl)-1H-indole	N/A	0.20
2-[3-1(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-Indol-5-yl]ethanesulfonic acid methylamide	0.1	0.20
Unidentified Impurity	0.2	0.20
Total Impurities	1.5	1.5

TGA Comment: With respect to analytical methods and validation:

The method equivalency of in-house HPLC ----IMTB-20-IN (degradation products), ----IMTB-40-IN (assay and content uniformity) to the corresponding USP methods must be demonstrated.

Response: The method equivalency of Navaratan in-house HPLC methods—IMTB-20-IN (degradation products), IMTB-40-IN (assay and content uniformity) to the corresponding USP methods is provided in section 3.2.P.5.6 of the response.

2nd Round deficiency:

TGA Comment- The response to Question 9 of the Clarification Request dated November 25, 2006 is considered to be incomplete. It has been requested that data demonstrating the USP specified impurities (adequately controlled under the limit of NMT 0.20% for individual unspecified impurities) by in-house HPLC method must be submitted. However, the impurities are not irrelevant to the manufacture's route of synthesis.

Response:

Navaratna has revised the justification report for degradation products using in-house HPLC method ----IMTB-20-IN to corresponding USP method. Please refer to section 3.2.P.5.6 of this response for justification report (degradation products) for the data demonstrating that USP specified impurities can be adequately controlled under the limit of NMT 0.20% for individual unspecified impurities by Navaratna in-house HPLC method.

TGA Comment:

The response to question 9 of the clarification request dated November 25, 2006 is considered to be incomplete. It was requested to demonstrate equivalency of in-house HPLC methods (Degradation products), (assay and content uniformity) to the corresponding USP methods by submitting comparative analytical results obtained by these methods; in the case of impurity method, result should be provided for

samples containing or spiked with the USP specified impurities at or near the specification limits. Please note that no such data was included in section 3.2.P.5.6 of response.

Response:

Navaratna has revised the justification report using in-house HPLC method--- IMTB-20-IN (degradation products) and ---IMTB-40-IN (assay and content uniformity) to the corresponding USP method. A copy of the revised justification report for degradation products and assay and content uniformity is provided in section 3.2.P.5.6 of this response.

3rd Round deficiency:

TGA Comment- The response to question 9 of the clarification Request dated November 25, 2006 is considered to be incomplete. It was requested to submit data demonstrating that USP specified impurities can be adequately controlled under the limit of NMT 0.20% for individual unspecified impurities by in-house HPLC method. Please note that justification in Section 3.2.P.5.6 does not contain this data. Please also be reminded that these impurities are not relevant to the manufacture's route of synthesis for Drug substance (5).

Response:

Round deficiency: Navaratna has performed the analysis of XYZ Tablets USP, X and Y mg comparing the USP method with the in-house HPLC method ---IMTB-20-IN (degradation products).

Please note that the USP method does not require individual standards of specified impurities which are identified by relative retention time (RRT) and quantitated by using relative response factor (RRF).

Therefore, due to non-availability of USP listed impurities either from USP or the drug substance manufacture, Navaratna could not spike these USP impurities however Navaratna has spiked the impurities A and B (USP listed impurity) in system suitability preparation of related compound (RC) method (USP and in-house) and proved their separation.

The samples analyzed for degradation product (Condition 24 months, 25^0 C/60%RH) in USP RC method does not show any peak at USP specified RRT's for the specified impurities.

The USP and in-house methods, when applied for degradation products testing of XYZ Tablets was shown to be equivalent.

Please find in Table 5.2 the data of impurity comparison between the USP method and Navaratna's in-house method.

All listed USP specified impurities except related compound B (identified impurity) have been considered under unidentified impurities with a limit of not more than 0.20% each in the in-house method.

Please refer to section 3.2.P.5.6 of this response for full justification report (degradation products) for the data demonstrating that USP specified impurities can be adequately controlled under the limit of NMT 0.20% for individual unspecified by Navaratna's in-house HPLC method.

Table 5.2: Comparison data of USP chromatographic purity method to the Navaratna's degradation method (Condition months, 25^0 C/60%RH)

	USP 33 NF28			Navaratna in-house method (-----IMTB-20-IN)		
Compound name	USP LIMIT (NMT%)	1 mg (Batch No.---)	2.5 mg (Batch No.---)	Navaratna LIMIT (NMT%)	1 mg (Batch No.---)	2.5 mg (Batch No.---)
3-(-1_Methylpiperidin-4-yl)-!H-indole(NAR-I/RCA)	.	.	.	0.20	ND	ND
2-[3-1(1-Methyl-1,2,3,6-tetrahyddropyridin-4-yl)-1H-indol-5-yl]ethanesulfonic acid	0.2	ND	ND	0.20	ND	ND

methylamide (NAR-II/RCB)						
2,2-Bis-[3-(1methylpiperidin-4-yl)-1H-indol-5-yl]rthane sulfonic acid methylamide	0.2	ND	ND	..	..	..
Unidentified impurity	0.2	0.050	0.031	0.20 each	0.091	0.031
Total impurity	1.5	0.158	0.031	1.5	0.186	0.056

. Navaratna's specific impurity not a part of USP specified impurity

.. All the USP impurities controlled as unidentified impurity by Navaratna in-house method

TGA Comment- The response to question 9 of the Clarification request dated November 25, 2006 is considered to be incomplete. It was requested to demonstrate equivalency of in-house HPLC methods -----IMTB-20-IN (Degradation product). ----IMTB-40-IN (assay and content uniformity) to the corresponding USP methods by submitting comparative analytical results obtained by these methods; in the case of impurity method, result should be provided for samples containing or spiked with the USP specified impurities at or near the specification limits. Please note that no such data was included in section 3.2.P.5.6 of the response.

Response:

Navaratna has revised the equivalency report concerning in-house HPLC method----- IMTB-20-IN (degradation products) and ----IMTB-40-IN (assay and content uniformity) and the corresponding USP methods.

With regards to the equivalency of the in-house HPLC method---- IMTB-20-IN (degradation products) to the corresponding USP method, please refer to the response to question 4 above.

The method ----IMTB-40-IN (assay and content uniformity) was also shown to be equivalent to the corresponding USP method.

A copy of the revised justification report for degradation products and assay and content uniformity is provided in section 3.2.P.5.6 of this response.

In the course of our evaluation of the USP methods, some minor issues have been identified and mentioned in the equivalency report provided in Section 3.2.P.5.6. These issues will be addressed with USP in form of a petition.

CONCLUSION

Early approval of drug will be helpful for needy people who are suffering with the concerned disease on which the innovator company is working while in case of generic drugs, people will get the benefits of same drug with cheaper price. For a successful submission drug product manufacturer should engage the authorities early and ensure that communication is clear. If there is multiple back and forth on points or an issue becomes a point of contention, then re-evaluation of the situation is the essentiality.

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Note: The views and opinions expressed in this case are those of the authors and not necessarily those of the institutions at which the authors work or worked earlier. The authors assume full responsibility for this write-up and the accuracy of its contents.

CONFLICT OF INTEREST

Author declares that there are no conflicts of interest.

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