PUBLIC CONSULTATION PAPER
REVIEW OF THE VARIATIONS GUIDELINES

REGULATION (EC) No 1234/2008 ARTICLE 4:
REVIEW OF THE VARIATIONS GUIDELINES

S. No 1
A.7 Deletion of manufacturing sites:
Condition 3: At least one batch control/testing site remains within the EU/EEA or in a country where an operational and suitably scoped GMP mutual recognition agreement (MRA) exists between the country concerned and the EU, that is able carry out product testing for the purpose of batch release within the EU/EEA.

Ranbaxy Comments:

Condition 3 should be modified to

At least one batch control/testing finished product site remains within the EU/EEA or in a country where an operational and suitably scoped GMP mutual recognition agreement (MRA) exists between the country concerned and the EU, that is able carry out finished product testing for the purpose of batch release within the EU/EEA.

S. No 2
B.I ACTIVE SUBSTANCE
B.I.a) Manufacture

B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier

Ranbaxy Comments:

This variation should be modified to

B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control release sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier

Reason: As testing can be performed at contract lab being controlled through company SOP

S. No 3

B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier

Documentation 8: Proof that the proposed site is appropriately authorised for the pharmaceutical form or product or manufacturing operation concerned, i.e.: For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice. For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority. For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice.

Ranbaxy Comments:

EU GMP certificate should not be necessary for filing variation for filing alternate sterilization site. Text to modified to cover that Variation can be filed without EU GMP certificate with a commitment that site will be audited by EU Agency prior to release.

S. No 4

B.I.a.2 Changes in the manufacturing process of the active substance
e) Minor change to the restricted part of an Active Substance Master File

Ranbaxy Comments

This variation should be modified to

e) Minor change to the restricted part of an Active Substance Master File
(Except in case of point B.I.a.2 a) & B.I.a.2 f)

S. No 5

B.I.a.2 Changes in the manufacturing process of the active substance
f) Change to non critical processes parameters, where the process has been developed and optimised using an enhanced development approach for the particular manufacturing step(s)

Ranbaxy Comments

This variation should be applicable only for the APIs which have been originally developed by enhanced development approach

S. No 6

B.I.a.2 Changes in the manufacturing process of the active substance

Condition 4: The change is fully described in the open ("applicant's") part of an Active Substance Master File, if applicable.

Ranbaxy Comments

This condition should be deleted as process is described only in Restricted Part of DMF.

S. No 7

B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance

Condition 8: The currently approved batch size was not approved via a Type IA variation

Ranbaxy Comments

This condition should be deleted as increase in batch size will not have any impact on the quality of the drug substance as specification of API will remain same. Accordingly, conditions to be fulfilled in B.I.a.3.a should be updated to delete "8"

S. No 8

B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance

g) Change to the limits of non critical processes parameters, where the process has been developed and optimised using an enhanced development approach for the particular manufacturing step(s).

Ranbaxy Comments

This variation should be applicable only for the APIs which have been originally developed by enhanced development approach

S. No 9

B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance

Condition 7: The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.

Ranbaxy Comments

This condition should be modified to

"There should not be any change in the specification of active substance"

S. No 10

B.I.b) Control of active substance

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance

c) Addition of a new specification parameter to the specification with its corresponding test method

Documentation to be supplied :1, 2, 3, 4, 5, 7

Ranbaxy Comments

Documentation to be supplied :1, 2, 3, 4, ~~5~~, 7

Documentation no 5 should be deleted as this variation will just be an addition of new parameter in an already approved specification and there will be no change in the manufacturing process.

S. No 11

B.I.b) Control of active substance

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance

d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter e.g. odour)

Conditions to be fulfilled: 1,2, 8

Ranbaxy Comments

Conditions to be fulfilled: 1,2, ~~8~~

Condition no 8 should not be applicable for variation category B.I.b.1.d) for Starting Material/Reagents/Intermediates as API specification will remain same

S. No 12

B.I.b) Control of active substance

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance

Condition 8: The specification parameter does not concern a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing..

Ranbaxy Comments

This condition should be modified to

"There should not be any change in the Active Substance specification"

S. No 13

B.I.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of
the approved dossier

c) Change to an approved stability protocol

Ranbaxy Comments:

This variation is already covered in variation category a) Re-test period/storage period & b) Storage conditions; as any change in re-test period will change the stability protocol, hence, suggest to delete this category.

S. No 14

B.III CEP/TSE/MONOGRAPHS

B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability:

a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.

6. New certificate for a non sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free.

Ranbaxy Comments:

As BET is a limit test hence substance should not be claimed as endotoxin free. Modify that BET in Active Substance to meet requirement of Drug Product

S. No 15

B.III CEP/TSE/MONOGRAPHS

B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability:

a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.

Condition 11: If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.

Ranbaxy Comments:

This condition should be modified to

Condition 11: If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must meet limit of Bacterial Endotoxins as per the requirements of Drug Product