Safeguarding public health

Workshop – Deficiency Points

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Question 1

The limits for residual solvents, in particular for toluene should be tightened in line with batch and stability data. Simply applying the ICH limits without due regards to the data is not acceptable.

API specifications

Question 2

Unless otherwise justified, the release and shelf life specifications for the individual known (≤0.1%), individual unknown (≤0.1%) and Total related substances (≤0.5%) should be significantly tightened to the corresponding limits specified for Fenofibrate in the corresponding Ph Eur monograph, in line with reported batch analytical and stability data.

API specifications

Question 3

It is stated that residual solvents are tested once every 10 batches or annually which ever is sooner. This is unacceptable in principle. Proposals for reduced testing of active substances require review in the context of the manufacturers audit programme, historical data and risk assessment within the GMP inspection. The suitability of any reduced testing schedule should be considered during the next GMP inspection.

UK position

API specifications

Question 4

Justification for absence of a test for benzene in the drug substance should be provided.

API specifications

Question 5

Drug-excipient compatibility data should be provided for all the excipients used in the final formulation.

Development

Question 6

The F2 similarity factor for the test product and reference product dissolution profiles should be provided and discussed, unless otherwise justified.

Development

Question 7

Certificates of analysis for the excipient lactose monohydrate should be provided.

Routinely?

Question 8

The functions of the coating components should be stated.

How important? Obvious?

Excipients

Question 9

Declarations should be provided from excipient suppliers that no materials of animal/human origin were used in the manufacture of the excipients.

Excipients

Question 10

Purified water should be confirmed as being produced on site; the method of production should be described. The source of purified water should also be confirmed as being suitable for human consumption, in line with local regulations.

Excipients

Question 11

Confirmation should be provided that the same excipients specifications are used at the two product manufacturing sites.

Excipients

Question 12

A written assurance should be provided that no significant changes in the manufacturing method have taken place following the grant of the Certificate of Suitability.

Manufacturing process

Question 13

Confirm that the European packaging sites will not be involved in any aspects of finished product manufacture (including any drying steps).

Manufacturing process

Question 14

In section 3.2.P.3.5. in the IPC table it is stated the following: compression step, average weight, frequency: ‘50 tablets are taken from BME of the compression and 10tablets are taken every 30min’ whereas in section 5. Statistical Analysis of Results and Discussion it is stated as ‘50 samples are taken at the beginning, middle and end of compression process and 10 samples are taken every 20 min of the compression process.’ Clarification is required.

If both are acceptable, why does it matter?

Manufacturing process

Question 15

It should be stated whether any reprocessing of materials takes place. Conditions that would necessitate reprocessing should be stated and the steps described and justified.

Manufacturing process

Question 16

For an orodispersible tablet :

The manufacturing process has been described. However, conditions such as mixing time and temperature are missing and should be provided.

Manufacturing process

Question 17

Explanation for the different batch numbering system, from the batches used in the stability study should be provided.

Manufacturing process

Question 18

Unless otherwise justified, the final blend before compression should be routinely tested for homogeneity.

Manufacturing process

Question 19

The intended testing frequency for identification of colour should be specified as one batch in every ten or annually whichever is the more frequent.

Finished product specification

Question 20

Specifications should be marked by indicating the version number.

Finished product specification

Question 21

Test for subdivision of tablets should be included in the finished product specifications, unless otherwise justified.

Finished product specification

Question 22

It should be clarified why impurities have been specified in the release specification and shelf life specification which are considered synthesis by-products coming from the active substance source.

Finished product specification

Question 23

The tablets are uncoated tablets and should conform with Ph. Eur. disintegration test, unless otherwise justified.

Finished product specification

Question 24

Specification includes test for uniformity of dosage units – by mass

Test for uniformity of mass in accordance with Ph. Eur. should be included in the drug product specifications, unless otherwise justified.

Finished product specification

Question 25

Specifications and certificates of conformity should be provided for all packaging components used by Teva for the micronised Fenofibrate.

How important?

Packaging

Question 26

Confirmation should be provided that packaging components in direct contact with the bulk drug material are certified as being in compliance with EC Directives on accepted safety standards for materials in contact with foodstuffs.

Packaging

Question 27

Certificate of analysis for the HDPE bags should be provided.

Packaging

Question 28

It should be confirmed whether the intermediate precision covers different analysts, days and equipment.

I don’t see why there should be any doubt

Analytical methods / reference standards

Question 29

Precision (repeatability and intermediate precision) should be calculated for the other impurities stated in the specification (imp 1, 2, 3 & 5).

Analytical methods / reference standards

Question 30

It is noted that the reference standard is not tested for optical rotation or heavy metals. These tests should be included.

Analytical methods / reference standards

Question 31

The working standards should be standardised against the EPCRS standard.

Analytical methods / reference standards

Question 32

Confirmation should be provided on whether or not the dissolution testing is operating under sink conditions.

Analytical methods / reference standards

Question 33

A commitment is required that any anomalous results obtained during the ongoing stability studies with the production batches …… will be immediately reported to the Licensing Authority (with course of action).

Stability

Question 34

Film-coated tablets:

Friability should be measured during stability studies.

Stability

Question 35

Stability study: Justification should be provided for why sulphated ash is not determined after time 0.

Stability

Question 36

It should be confirmed that the start of the proposed 36-month shelf life is the date of production defined as the date that the first step is performed involving combining the active ingredient with other ingredients, as specified in CPMP/QWP/072/96.

Stability