VIATRIS

Flex Field Report

Division:	Specialty Formulation Facility	**Project:**	Deviation
PR ID:	64869	**PR State:**	Closed - Done

Cause Detail:

After the discovery of the deviation the observation has been discussed with concerned personnel involved in the activity.
Discussion reveals that, the personnel involved in the compounding & sampling process has misinterpreted the sampling plan as " Sampling to be drawn after mixing for 3min , 5min & 7 minutes respectively" instead of sampling at 3rd min, 5th min & 7th minute respectively with a mixing time of 2min each between the sampling duration.
As a result, Stirring has been performed for a total duration of 15 minutes against the requirement of 7 minutes as per the sampling plan defined in the PVP.

Comments:

Subject batch is the first process validation batch and mixing time, sampling plan were not followed as per the approved protocol; an additional batch was added to the process validation. Product is a liquid injection and additional mixing performed after 100% volume make up may not pose any impact on the product quality. Results of related substances verified, found within the specification limits and no impact on the quality of the product. Results obtained for the batch were compiled along with the other three batches and no variation observed in the results. In-process and finished product results found complies with the specifications and satisfactory. Retraining has been imparted to relevant personnel on the concepts of process validation and sampling plan requirements. CAPA initiated for enhancement of PV sampling plan to provide better clarity on sampling requirements and training to applicable personnel on templates of process validation protocols and sampling plans. CAPA ref. No.: SFF-CAPA-2014-312.
Deviation closure review report attached.

Description:

During review of compounding process print out for B.No. 7602313, Observed stirring time after 100% volume make up was not done as per PVP (Process validation protocol) and the bulk sample were not drawn as per the sampling duration specified in the PVP.
Stirring has been performed for a total duration of 15 minutes against the requirement of 7 minutes as per the sampling plan defined in the PVP. (Mixing time as per the BMR is 5min)
Back Ground :
As per the requirement of process validation protocol (Protocol No.: PV/200342/950.0L/S2/P0), Bulk samples after 100% volume make up has to be drawn from top & bottom locations after 3rd minute, 5th minute and 7th minute of stirring. But samples were drawn from top & bottom locations after 3rd minute, 8th minute and 15th minute of stirring.
Note : Sampling has been drawn after the each stage of stirring completion by stopping the stirrer as per the practice followed.
Product: Dexamethasone Sodium Phosphate Inj. USP 4mg/mL [30mL], B. No.: 7602313
BMR reference No.: 2000342/950.0L/S2/V0, Batch size: 950 L.
Personnel Involved: Mr.Manjunath GR (QA), Mr.Kotresh (PDN) & Halaswamy (Operator)
Observed By : Manjunath M
At the time of observation compounding process was completed and awaiting for 1st filtration.

Details of Follow-up Actions:

08/13/2014 02:57 PM (GMT+5:30) added by Vijay S (PID-000669):

The samples drawn after 100% volume make up is tested as per the In-process specification and found complying with the specification.
To assess the impact of impurities due to additional mixing performed for the bulk solution, the samples drawn from the bottom locations after 3rd, 8th & 15Th minutes of mixing were tested for related substances in addition to the test parameters of in-process specification. The results of all the test parameters including related substances found meeting with the specification (refer attached annexure).
As per the recommendation stated under resolution action, the 4th batch of the campaign run is considered as an additional process validation batch and the samples were drawn as per the sampling plan of process validation protocol. The results obtained for the samples drawn as per the protocol were found meeting with the acceptance criteria.
All four process validation batches executed and sample withdrawn at different stages of manufacturing were compiled and compared (See attached annexure-1) and found results of the B. No.: 7602313 is comparable and complying to the pre-determined specification.
The results obtained for the batch under deviation is compiled along with the results of other 3 process validation batches executed in campaign . Review of comparison results reveals no significant variation between the batches and all the results were meeting with the specification.
The batch under deviation is loaded for the stability study since it is a process validation batch. Stability study Protocol Reference No.:1090-SS-140198.
As an immediate corrective action, the concerned personnel involved in compounding & sampling of the B. No.: 7602313 are trained on the concept of process validation approach and sampling plan requirements.
As a preventive measure, the existing template of process validation sampling plan shall be revised to provide better clarity on the sampling collection between the mixing intervals. Refer CAPA No.: SFF-CAPA-2014-312.
Based on the evaluation of all the actions and review of results it is concluded that the observed deviation has no impact on the quality of the batch processed. Hence the batch can be released for distribution.**********
*08/09/2014 04:51 PM (GMT+5:30) added by Vijay S (PID-000669):
As part of the investigation sample withdrawn during process validation for the subject batches (B. No.: 7602313, 7602314, 7602315 & 7602316) has been evaluated and results are tabulated below.
Evaluation of process validation batches at compounding stage:

Process Steps / Stage

Tests
Acceptance criteria
OBSERVATION DURING BATCH NUMBER
7602313
7602314
7602315
7602316
Bulk Sample for analysis after 3 minutes stirring.
Description
Clear, colorless solution free from visible particles.
Top
Clear, colorless solution free from visible particles.
Clear, colorless solution free from visible particles.
Clear, colorless solution free from visible particles.
Clear, colorless solution free from visible particles.
Bottom
Clear, colorless solution free from visible particles.
Clear, colorless solution free from visible particles.
Clear, colorless solution free from visible particles.
Clear, colorless solution free from visible particles.
Identification by HPLC
In the test for assay, the retention time of the major peak in the chromatogram of the assay preparation should correspond to that in the chromatogram of the standard preparation.
Top
In the test for assay, the retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation.
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Bottom
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Details of Remedial Actions:
08/09/2014 05:15 PM (GMT+5:30) added by Vijay S (PID-000669):
Not applicable

Follow-up Actions:
Impact of additional stirring, if any on product impurities to assessed as per proposal.
Since the mixing time and the sampling plan is not followed as per the approved protocol, additional batch shall be considered for the process validation (4th batch planned in the campaign run) and the samples shall be drawn as per the PVP.
Inprocess and finished product analytical result to be verified.
Retraining shall be imparted to relevant personnel on the concept of process validation and sampling plan requirements.

Immediate Actions:
Reviewed the batch record and compounding process print data against the sampling plan of PVP, to verify any other issues during the compounding and sampling process. No abnormality was observed except for the error in mixing time & sampling of bulk solution as per the sampling time specified in the PVP.
Review of the records revealed the following information:
On 12.06.2014 after 100% volume make up, stirring is done for 3 minutes from 03:57 Hrs. to 04:00 Hrs and bulk samples were drawn for the 3rd minute sample.
Further stirring is done for 5minutes from 04:05 Hrs. to 04:10 Hrs (instead of 2minutes to draw the 5th minute sample) and bulk samples were drawn. (This actually represents 8th minute sample instead of 5th minute sample).
Further stirring is done for 7minutes from 04:13 Hrs. to 04:20 Hrs (instead of 2minutes to draw the 7th minute sample) and bulk samples were drawn. (This actually represents 15th minute sample instead of 7th minute sample).
The status of samples drawn was verified and found the samples drawn were submitted to quality control department.
The observation is discussed with the CFT (Production, QA & QC) members. Based on the outcome of the discussion, 1st filtration activity is initiated and actions as referred in the resolution actions were taken.

Impact Details:
The batch under execution (B.No. 7602313) is the first process validation batch and the incident of mixing & sampling error is observed only in this batch, hence there is no impact on subsequent batches executed.
Since the mixing time and the sampling plan is not followed as per the approved protocol,

additional batch shall be considered for the process validation (4th batch planned in the campaign run) and the samples shall be drawn as per the PVP.
Since the product batch is non-suspension product, additional mixing performed after 100% volume make up may not pose any impact on the product quality. However results obtained for the samples drawn shall be assessed after completion of the testing.

The samples drawn from the bottom locations after 3rd, 7th & 15Th minutes of mixing shall be tested for related substances in addition to the test parameters of in-process specification. This is to assess the impact of impurities due to additional mixing carried out.
The results obtained for the batch under deviation shall be compiled along with the other 3batches and variation in results obtained if any shall be assessed.
The batch shall be considered for release, if the test results of the batch complies with the specification.

Investigation Details:
Not applicable

Proposal for Resolution:
Filtration & filling activity to be initiated and samples shall be drawn as per the sampling plan defined in the PVP
The samples drawn after 100% volume make up has to be tested as per the In-process specification. The samples drawn from the bottom locations after 3rd, 7th & 15Th minutes of mixing shall be tested for related substances in addition to the test parameters of in-process specification. This is to assess the impact of impurities due to additional mixing carried out. (Note : Additional samples are not drawn for testing, since the sample volume drawn as part of the sampling plan is sufficient to perform the test for related substances)
The batch under execution (B.No. 7602313) is the first process validation batch for Suite-2 proposed for validation due increased batch size. Since the mixing time and the sampling plan is not followed as per the approved protocol, additional batch shall be considered for the process validation (4th batch planned in the campaign run) and the samples shall be drawn as per the PVP.
The results obtained for the batch under deviation shall be compiled along with the other 3batches and variation in results obtained if any shall be assessed.
The batch shall be considered for release, if the test results of the batch complies with the specification.
The concerned personnel shall be retrained on the concept of process validation and sampling plan requirements.

Remedial Actions Proposed:
Not applicable