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Hybrid Pharma Responses to Form FDA 483 Inspection Dates 7/27/2021-9/3/2021

OBSERVATION 1

Investigations of an unexplained discrepancy did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.
Your firm does not conduct adequate investigations of unexplained events or occurrences. Specifically,
A. During the 100% visual inspection of Magnesium Chloride 200 mg/mL, Lot 210226A, the operator found 5 of 148 vials containing particles. Possible sources of contamination included fibers from gowning sleeves and dust from carrying bins, resulting in a change of gowning procedures (remove sleeve covers during filling), wiping of bins, and rewashing vials. However, the investigation was not comprehensive in that it did not consider other sources of contamination such as the bulk drug, personnel contribution, or the routine movement of vials. Additionally, the investigation did not extend to other batches.

Response: Yes, we did not do the investigation on the bulk drug, Magnesium Chloride, from another supplier and/or another lot number. That might have given extra input.

Though personnel contribution, routine movement of vials contribution(s) variables are insignificant, we will include them to be more comprehensive.

Hybrid Pharma affirms its investigation was extended to other batches. We do particle check as part of our 100% visual inspection of all the vials in all batches Hybrid Pharma compounds. It means that subsequent batches and all finished drug vials were always checked for particles, and none were found. Please see Attachment 1 for an updated copy of the

Investigation Form that includes other root causes and extends it to other batches.

Corrective Action: In the future we will include contribution from the raw materials (both API and non-API), Personnel, movement of vials, and closure integrity, and we will write a more comprehensive investigation report with possible root causes and the exclusionary list.

Attachment 1: Investigation Report Form QA-01F2 version 2 [6 pages]

B. A complaint of particles found in 9 vials of Magnesium Chloride 200 mg/mL, Lot 200417A, BUD 10/17/20, was received on 08/21/2020. You contacted recipients of Lot 200417A and relied on customer testimony to determine that other vials contained no particles. According to the CAPA investigation, you reviewed retain samples "at the time of complaint" and found no particles and then reviewed the samples again "after a few months" and found particles; the investigation does not provide dates of events. In addition, the documentation does not specify how the investigation extended to other batches.

Response: On 08/21/2020, one customer asked for replacement of nine vials of Magnesium chloride, #200417A with precipitation. The customer stated they were stored in the fridge mistakenly. Hybrid Pharma received the vials and replaced them with new vials of the same product.

At that time we analyzed the commercial Mylan product and their label with a note “WARNING: DO NOT USE IF A PRECIPITATE IS PRESENT,” and we concluded this is the nature of the product. We also added an auxiliary label with same warning as the commercial product.

Looked at the solubility and solubility product of magnesium chloride in water and that was very high at room temperature. Whatever may be we will follow through date of events for thorough investigation.

Hybrid Pharma affirms its investigation was extended to other batches. We do particle check as part of our 100% visual inspection of all the vials in all batches Hybrid Pharma compounds. It means that subsequent batches and all finished drug vials were always checked for particles, and none were found.

During the FDA inspection, the investigator found particle in other lots of magnesium chloride injection made after this batch and from the commercial drug product made by Mylan. The investigator sent Hybrid Pharma samples to FDA laboratories. Mylan requested that we send Mylan samples to Ireland for their investigation. Till today (9/20/21) we did not receive any result(s) from FDA and/or Mylan.

The very fact that drugs made from both Hybrid and Mylan have the same type of particles present eliminates variables such as raw materials, container closure, storage condition, manufacturing, as they are independent of the manufacturing facility. This leads one to conclude the nature of the drug itself. A thorough investigation may solve this problem, and hence expecting a detailed test result(s) from both FDA and Mylan.

Corrective Action: We are expecting the test results from both FDA and Mylan to continue/conclude the investigation. In the meantime, we are sterilizing the Magnesium Chloride 200 mg/ml injection at least two times with 0.2 micron filter after a pre-filtration with 0.45 micron filter.

Hybrid Pharma will follow through date of events whenever it is needed for thorough investigation.

C. A complaint of wrong label concentration identified for Combo Drops Lot 210301C was received on 03/02/21. Corrective actions involved relabeling of the vials and updating the label tracking form to include the review ingredient strength. However, a root cause was not investigated or determined. The investigation did not extend to other batches.

Response: The root cause was identified as the Other Ingredients % was missing in the Label Tracking Form checklist.

The Revised form 101F, Rev.6 [created march 2021) includes the % calculation matching the formula sheet and the same updated version of Label printing, Tracking, and Verification Log is extended to other batches.

Attachment 2:

Label printing, Tracking, and Verification Log 101F Rev.6 [2 pages]

2. Observation: The accuracy, specificity, and reproducibility of test methods have not been established. Specifically, you method validation of ascorbic acid 500 mg/mL assay is inadequate because the validation parameters tested are not performed on the actual method used for release testing. You performed method validation studies on an HPLC method and use a titrimetric method for routine analysis. Comparison studies use one sample (i.e. 1 titration) to measure precision against HPLC results.

Response:

The accuracy, specificity, and reproducibility of titration assay method has been initiated and established for Ascorbic acid 500mg/mL injection as suggested by the FDA investigator. The method validation protocol and data are provided as attachment.

Attachment 3: TR210819 batch record [3 pages]

Attachment 3A: Ascorbic acid assay method Validation studies [7pages]

OBSERVATION 3

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.
Environmental monitoring of personnel is not always performed after aseptic processing. Specifically, microbiological fingertip samples are not collected after the processing of small batches (of approximately less than 20 units). For example, the following products were compounded and no fingertip or sleeve samples were collected:
A. IC/B12/B2/B3/Carnitine/Chromium/Lucine, Lot 210608A, on 06/08/21
B. Buprenorphine HC1, Lot 210510B, on 05/07/21

Response: During the compounding of six units of #210608A and four units of #210510B, the aseptic processing area has been environmentally monitored for non-viable particles, differential pressure, viable air sampling in LFH and viable surface sampling without fail.

However the personnel fingertip sampling is missing. We will improve microbiological fingertip sampling.

4. Observation 4- Laboratory records do not include complete data derived from all tests, examinations, and assay necessary to assure compliance with established specifications and standards.
Specifically, product release testing records from January 2020 to present were reviewed and do not include documentation of all data obtained during the analysis to include, but not limited to:

1. *System suitability determinations*
2. *Standard and sample preparations*
3. *Calculations performed*

Response: Hybrid Pharma will evaluate the system suitability in every experiment and a template containing system suitability determinations, that includes standard and sample preparations, and calculations performed. Please see Attachment 4 form that has been updated information for system suitability.

Attachment 4: System suitability in Analytical testing of the finished drug product. Module 8-13 [5 pages]
Attachment 4A: Methylcobalamin-analytical test method [5 pages]

5. *Observation 5- You did not retain reserve samples for drug products for one year after the expiration dates of the drug products.*
On 8/16/21, you were unable to provide the retain sample for Magnesium Chloride, Lot 210226A, citing it was reviewed as part of an incident/ investigation (dated 03/01/21), and it was misplaced. This product was manufactured on 2/26/21, with BUD 8/26/21. In addition, you did not implement the stated procedure according to your SOP entitled *Protocol for Retention Samples* which states that the retain sample is discarded after the BUD.

Response: Hybrid Pharma was using the five retention samples for an investigation, they somehow got misplaced. Hybrid Pharma has revised its SOP 5-9: Protocol for Retention Samples. The SOP was also revised to state that the retention sample will be kept 30 days past the BUD. Reference: Section 503B of the FD&C Act, Revision 2, p.32, Section M, Line 1219.

Corrective Action: SOP 5-9 Protocol has been revised for retention samples.

Attachment 5: SOP 5-9: Protocol for Retention Samples [3 pages]

6. *Observation-6: Your outsourcing facility did not submit a report to the FDA upon initial registration as an outsourcing facility identifying the drugs compounded during the previous 6 month period.*

Response: Originally, as outsourcing facility we used to submit list of finished drug product report by Microsoft excel sheet with no issue. Hybrid Pharma has always reported drug products in good faith. We need assistance for compounds which shows data error on submission.

During the FDA 483 closing, we expected to get a contact name from FDA about the ESG CDER FDA reporting website, but we have not received yet.

We also emailed the agency for a contact to help us in reporting, and as of today's date, we did not receive any response.

9/10/21- Email was sent to ORAPHARM2_RESPONSES@fda.hhs.gov requesting a contact.

Corrective Action:

1. If we receive any help from the Agency, we will work with them and fulfill the requirement.
2. If we do not get any help from FDA, we will try our level best and document any problems as an evidence.

7. Observation 7*-Bulk drug substances used by the outsourcing facility to compound drug products are not manufactured by an establishment that is registered under section 510 as required by section 503B(a)(2)(C). Specifically, the following establishments that supplied bulk substances to the outsourcing facility do not appear to be registered with the FDA:*

A. CoQ10 supplied by Medisca (sourced from Shenzhou Biology & Technology Co., Ltd)
B. Choline chloride supplied by Medisca (sourced from Algry Quimica, S.L)
C. Benzyl benzoate supplied by Medisca (sourced from Phoenix Aromas & Essential Oils)
D. Sodium hydroxide supplied by Medisca (sourced from Atlas Pellet Industries)
E. Inositol supplied by Medisca (sourced from NutriScience Innovations, LLC)
F. Cyanocobalamin supplied by Medisca is sourced from Hebei Yuxing Bio-Engineering Co., LTD.

Hebei is indicated to be in an "inactivated" status with FDA. Also, the cyanocobalamin COA from Hebei states "not for drug use."

Response: We buy API, excipients, and other supplies used in compounding from FDA registered and inspected suppliers from USA/Canada with Vendor Quality Agreements in place.

All the six materials listed in the 483 Form were supplied by Medisca, FDA registered inspected facility, and five of them classified as excipients (inactive ingredient) without any monographs. The cyanocobalamin is often classified as drug with USP monograph and it is also vitamin B_{12}.

The COA of Cyanocobalamin raw material that we produced during inspection had been marked not for drug use. It was pointed out by the FDA Inspector then. Later on, manufacturer clarified "it is for pharmaceutical use".

503B(a)(2)(C):

The 483 citation referenced under the code 503B(a)(2)(C) could not be located in the Law. We e-mailed FDA, and we got a response back from CDR John W. Diehl, M.S. from FDA with two different links, and those links did not talk about the code 503(B)(a)(2)(C). When we e-mailed him for an explanation, he asked us to respond to the 483 in detail.

Please understand the fact the facility and the agency must work together to solve the issue(s). It is damaging to the facility, as the 483/warning letter is in the public domain and anyone can read and interpret their own way, the company's response is within the agency.

Please see Attachment 6 for the email. Let's follow the link CDR John W. Diehl, M.S sent, and it reads "FD&C act provisions that apply to human drug compounding"

Attachment 6: John W. Diehl email dated 9/14/21 [3 pages]

: https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding

1. The law 503B (a)(2)(c)is not cited in the above link.
2. The above link, listing 503A and 503B differences and on page three (3) under the heading bulk drug substances (more relevant to this issue), it

mentions that bulk drug substances must be accompanied by a valid COA and must have been manufactured by an establishment registered with FDA under section 510.

3. There is no mention about the excipients used in compounding in the FDC Act Provisions. On the same page, see section 503B(a)(2) FDA's final guidance describing its interim policy: for compounders using bulk drug substances, while the list of bulk drug substances is being developed. The following link,

https://www.fda.gov/media/94402/download

leads to the article entitled: "Interim Policy on Compounding Using Bulk Drug Substances under Section 503B of the Federal Food, Drug, and Cosmetic Act". On page 2, at the bottom (foot note) of the page, it states:

6 Inactive ingredients are not subject to section 503B(a)(2) or the policies described in this guidance because they are not included within the definition of a bulk drug substance. See 21 CFR 207.3. Pursuant to section 503B(a)(3), inactive ingredients used in compounding must comply with the standards of an applicable United States Pharmacopeia or National Formulary monograph, if a monograph exists.

These are the guidelines the FDA registered supplier/Vendor of the raw materials and the reason(s) provided to us. We are willing to listen and work with the Agency with proper guidelines. Again, proper communication must be important to solve all the issues.

Corrective Action:

1. Hybrid will try to get API, with the USP monograph used for compounding from FDA registered suppliers.
2. We will also try to get the manufacturer's COA.
3. If such a monograph is not available, and we classify them as excipient or inactive ingredients, we will try to get them from FDA registered suppliers. If not, we will use the COA provided by the suppliers meet the USP/NF specifications as per Interim Policy.
4. If the Agency believes differently, kindly communicate with us, and we will follow that.
5. Please avoid issuing a warning letter.

Details of the Attachment Documents:

Attachment 1	Investigation Report Form QA-01F2 version	6 pages
Attachment 2	Label printing, Tracking, and Verification Log 101F Rev.6	2 pages
Attachment 3	TR210819 batch record	3 pages
Attachment 3A	Ascorbic acid assay method Validation studies	7 pages
Attachment 4	System suitability in Analytical testing of the finished drug product. Module 8-13	5 pages
Attachment 4A	Methylcobalamin-analytical test method	5 pages
Attachment 5	SOP 5-9: Protocol for Retention Samples	3 pages
Attachment 6	John W. Diehl email dated	3 pages