



Food and Drug Administration
Center for Biologics Evaluation and Research
Division of Manufacturing Product Quality

To: Administrative File, STN 125613/0 for Kamada

From: Pankaj (Pete) Amin, Senior Reviewer, OCBQ, DMPQ, MRB II

Through: Qiao Bobo, OCBQ, DMPQ, MRB II, Branch Chief

CC: Damaris Lopez-Rosario, CSO, OCBQ/DIS/PSB

Subject: Review memo for Kamada Ltd., responses to the 483 Observations made during the PLI (March 26 to April 05, 2017). The inspection covered the manufacturing operations of Rabies Immune Globulin (Human) drug substance and drug product at Kamada facility in Beit Kama, MP Negev, Israel.

Action Due: 8/29/2017

Review Recommendation:

CBER conducted a pre-license inspection (PLI), under BLA STN 125613/0, at Kamada Ltd., manufacturing facilities in Beit Kama, MP Negev, Israel from March 26 to April 05, 2017. This joint inspection (Center for Biologics Evaluation and Team-bio) was initiated in association with Biologics License Application (BLA) 125613/0 for the new product Rabies Immune Globulin, Human (HRIG) and for the CGMP inspection for the licensed product Alpha-1 Antitrypsin (AAT), licensed in 2010.

The inspection team consisted of Pankaj Amin (CBER), Ewa Marszal (CBER) and Arie C. Menachem (Team bio/ORO). At the conclusion of the PLI, CBRE issued a Form FDA 483 Inspectional Observations containing six observations.

On May 04, 2017, the sponsor submitted the initial written response to the 483 observations where they discussed their action plans and time frame for completing the corrective actions. Kamada provided additional response on June 5, 2017.

The inspection team reviewed the sponsor's 483 responses and the updates. Overall, the responses to the 483 observations appear to be acceptable and the inspectional issues are considered resolved.

We recommend confirmation of the corrective actions to the 483 observations in the next GMP inspection.

Background Information

Kamada inspection was performed for the following DS and DP facility:

Facility (DS/DP)

Kamada Ltd.

Beit Kama

MP Negev 8532500

Israel

(b) (4)

Kamada-HRIG (b) (4) is manufactured from human hyperimmune plasma of healthy adult donors who have been immunized with rabies vaccine and have developed high titers of rabies antibody, and is fully compliant with FDA and EU regulations for human blood products. The manufacturing process includes a (b) (4) and three viral inactivation steps (solvent-detergent (S/D) treatment, heat treatment, and nanofiltration).

Drug Product

Kamada-HRIG drug product is a sterile, non-pyrogenic liquid preparation enriched with antirabies immunoglobulins (not less than 95% protein as IgG). It has a labeled potency of 150 IU/mL. Kamada-HRIG is supplied in 2 mL and 10 mL (b) (4) glass vials as a ready-to-use solution.

REVIEW OF 483 RESPONSES

The original 483 Observations (in bold italics), Sponsor's responses (in plain text) and commitments (bold), and Inspector's comments (underlined) are reported below.

Observation 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not followed. Specifically,

1a) The current aseptic process is not adequate to prevent media fill failures or disqualifications. (b) (4) media fill failures and (b) (4) disqualification occurred between 2014 and 2017 were attributed to the same organism - (b) (4), identified in some of the contaminated vials and EM excursions in the personnel monitoring and production areas including the ISO (b) (4) filling room. Although numerous corrective actions were implemented, (b) (4) was identified in the contaminated vials during the February 2017 media fill.

Kamada Response 1a:

Kamada provided a brief summary of the media fill program for the (b) (4) as follows: The (b) (4) current design was implemented as part of a manufacturing facility upgrade in 2007. Glassia, the Alpha-1-Proteinase Inhibitor (Human) intravenous (AAT) drug product for the US Market and of Kamada-HRIG [Human Rabies Immune Globulin], is produced by aseptic processing in (b) (4). The aseptic filling processes for Kamada's drug products are routinely validated and re-qualified in accordance with SOP N-2C-001, *Validation of aseptic filling process (media fill)* (version 10, effective date

06.04.17), by performing (b) (4) [redacted]. The environment of (b) (4) [redacted] aseptic filling operations is monitored for physical parameters ((b) (4) [redacted]), non-viable particles, and for microbial attributes, according to SOP N-2G-009, *Microbiological and physical monitoring of filling rooms* (version 14, effective date 30.04.17).

Kamada stated that the contamination rates of the microbial environmental monitoring of (b) (4) [redacted] are very low ((b) (4) [redacted]), based on the calculated results of the last two years (2015-2016).

Kamada discussed EM isolates found in the (b) (4) [redacted] and probable root cause for this isolate found in the filling suite. Kamada identified [redacted] on all contaminated samples from the filling rooms, as per SOP N-1P-0001-06, *Microorganisms concentration determination* (version 14, effective date 13.03.17). Most of the contaminated air samples (total of (b) (4) [redacted] deviations in 2 years) and personnel monitoring samples ((b) (4) [redacted] contaminated samples in 2 years) were identified to be (b) (4) [redacted]. According to Kamada, there is no evidence from the scientific literature to suggest that (b) (4) [redacted] strain is likely to have adverse effects on human health. According to Kamada, (b) (4) [redacted] is generally considered harmless, non-pathogenic, commensal organism. It is mesophilic (optimum growth at (b) (4) [redacted]).

As all equipment in the room is sterilized or depyrogenated prior to introduction to the room (filling apparatus and primary packaging materials), or (b) (4) [redacted] sterilized in place prior to use ((b) (4) [redacted]), it is highly likely that (b) (4) [redacted] is introduced into the room by operators.

Kamada discussed additional detail on the media fill investigation. The effectiveness of (b) (4) [redacted] solution was studied on various microorganisms according to report VL-100586-AM, *Effectiveness test of (b) (4) [redacted] on various microorganisms* (version 2, effective date 06.04.16). The effectiveness against (b) (4) [redacted] was tested among others. All tested bacteria showed at least (b) (4) [redacted] log reduction after (b) (4) [redacted] minutes contact time in both (b) (4) [redacted] (working dilution) and (b) (4) [redacted] (worst case) (b) (4) [redacted] solutions. The effectiveness of (b) (4) [redacted] solution was established also when applied on surfaces composing the controlled environments in Kamada, against various microorganisms, according to Rep-VL- 100708-AM, *Effectiveness Test of (b) (4) [redacted] Against Various Microorganisms on Surfaces Composing Kamada's Clean Rooms* (version 2, effective date 06.04.16). (b) (4) [redacted] showed a reduction of at least (b) (4) [redacted] logs.

Based on the data presented above kamada concluded that the source of the (b) (4) [redacted] appearance in the room was not in the equipment / surfaces in the room, which are cleaned using the above mentioned disinfectants. In addition, repeated monitoring of the same sampling point on three consecutive days showed no growth. Kamada concluded that the appearances of (b) (4) [redacted] in the room are most likely isolated events, introduced by the operators during that specific entrance to the room.

Kamada provided summary of past media fill failure and related corrective actions taken as follow:

Media fill failure – May 2014

In accordance with SOP N-2C-001, *Validation of aseptic filling process (media fill)*, on May 2014 a media fill run for Heparin 10 ml was done as part of the initial validation for a change to the filling process of that product. The Heparin 10 ml media fill failure of May 2014 consisted of (b) (4) contaminated vials out of over (b) (4) vials that were filled (deviation MDR- 7292). The bacterium was identified as (b) (4) - a spore forming Gram-positive bacterium from an environmental source.

Kamada concluded that this contaminant had penetrated the filling room via uncontrolled entrance of contractors and company employees without proper procedure for entering and returning from work in the room during the (b) (4) -week period prior to this media fill performance. These entrances were not referred to as "shutdown" activities, and therefore procedures to return to control were not adequately followed. As a corrective action, a new procedure was written (N-3F-340 Form 3, *Entrance and behavior (b) (4) for unqualified persons* (version 1, effective date 14.07.14)), for the procedures which need to be followed for each entrance of an unqualified person to the filling room, or for qualified operators for non-routine activities.

Media fill failure – December 2014

In December 2014, a routine media fill run mimicking Glassia (AAT 50 mL) filling resulted in an Action result of (b) (4) contaminated vials. This media fill failure was reported and investigated under MDR-9009. The contaminants identified were (b) (4).

The probable root cause of the contamination was a leaking (b) (4) that was not reported by the operators during the filling operation, combined with interventions in the area where the media was present and inadequate aseptic technique while performing intervention in the critical area during the adjustment of the filling needles.

Additional possible root causes, all related to the specific filling operation, were also analyzed and various corrective and preventive actions were implemented. In terms of aseptic technique, corrective actions included an update of the filling SOPs, the operators conduct SOP, and the media fill SOP. Kamada conducted significant re-training to the entire filling team, including theoretical and actual technique demonstration tests for each operator. After all operators passed the re-qualification session, and the (b) (4) was rejected, (b) (4) repeat media fill runs were performed successfully in March 2015.

As a preventive action, in order to maintain a good state of aseptic technique practices, a new SOP, *Periodic Qualification in the Filling Department N-3T-022* (original version 1 became effective on 08.02.15), was written. During the periodic qualification, the filling room operators will be required to perform different aseptic activities, e.g., gowning, media fill run, annual training on the SOPs and a quarterly review of their aseptic operations by watching and discussing recorded video-films of their operations in the rooms, which are saved for this purpose.

Four Media fill Disqualification (2014 to 2017)

After the December 2014 routine media fill failure (mimicking AAT 50 mL filling), (b) (4) media fill runs were performed in (b) (4), starting with the (b) (4) repeat media fills of AAT 50 ml. Kamada disqualified (b) (4) media fill runs in accordance with the media fill SOP (N-2C-001) as not

representing a product fill or due to a deviation / equipment malfunction. These runs were stopped during filling or before incubation.

Summary- Media Fill Failure 2017 (Most Recent MF)

On February 2017, at the end of the Glassia (AAT 50 mL) product filling campaign, a routine media fill to mimic this product was performed, as the next campaign was planned after the April shutdown. This media fill run (lot (b) (4)) resulted in (b) (4) contaminated vials out of almost (b) (4) vials filled – and was therefore defined as a media fill failure.

Deviation MDR-19528 was reported, investigated, corrective actions were taken, and repeat media fill runs are currently being performed. All of the bacterial identifications indicate that the source was human. (b) (4) out of the (b) (4) contaminated vials were found contaminated with (b) (4), the most common bacteria found in the clean room.

Kamada performed detailed review of batch records, including video-film records viewing and operator interviews. In addition, a review of participating operator qualification files was also performed. Internal and external experts repeatedly performed video film review sessions. Kamada noted that an unfortunate event had occurred during the (b) (4).

During the set up - for (b) (4) from the (b) (4), a sprinkle of media occurred. This sprinkle splashed across the far side of the machine (barrier) and left media droplets on the barrier surface. This barrier is close to where the operator works. This event went unnoticed in real time by the operators performing the setup. The sprinkle and splash was only observed in re-runs of the video film in slow motion, during the video film review done as part of the investigation.

While watching the video film, it was noticed that the operator, on the way to perform the (b) (4), nearly tripped over the connected transfer line. Therefore, it is most probable that he was startled or was nervous; leading to the movements, he made which caused the sprinkling of media during the (b) (4), and to the fact that he did not notice the splashing.

Droplets of media were present on the barrier where, in need to perform an intervention, the operator works. Even though the review of films shows that interventions were performed according to procedure, these operations caused the operator to position himself closer to the barrier where the media was splashed. Any isolated microorganism on the operator gown could have then contaminated the media on the barrier. The vibration of the filling machine during filling and the airflow velocity of (b) (4) through the filling machine could have sporadically swept particles with microorganisms from the contaminated (b) (4) media into the open vials located on the conveyor and contaminated them.

Following this finding, video footage for all product lots from the last successful media fill run of November 2016 and other media filling runs were observed specifically at this stage of (b) (4) during set up. No recurrence of media / product sprinkling was observed.

Review of operators' qualification, during the current media fill failure investigation, showed that all operators and the maintenance technician participating in this media were all qualified and trained according to the SOPs, and passed all training tests successfully. The interventions and operations

within the critical area were also reviewed and found to be in accordance with good aseptic practices.

Routine review of environmental monitoring data, and data reviewed during the investigation has shown a negative trend of increased events of gown monitoring contaminated samples (alert or action). This increase was already investigated and several corrective actions were implemented during 2016.

A change was also issued to improve the gown sterilization procedure, in terms of wrapping and (b) (4) unloading procedures (CC #19943, due date 31.12.17).

As the media contaminants were of human origin, and in regards to this elevated trend of gowning contamination, with the same type of microorganisms, Kamada concluded that gowning issues might have been a contributing factor to the media contamination. More preventive actions related to the handling and control of gowning items will be implemented, including improved control of gown shelf life (see answer to 483 observation 1c below), and further improvement in the handling of goggles (see answer to 483 observation 1b below).

According to Kamada, aspects related to aseptic operations in the clean room have also been addressed and implemented in production SOPs as detailed in answers to 483 observations 1d and 4c below. According to the media fill SOP N-2C-001, *Validation of Aseptic Filling Plan (Media Fill)* version 10, effective date 06.04.17. After implementing corrective actions, Kamada will performed three repeat media fill runs to identify the root cause and verify corrective actions effectiveness.

Kamada additional Response (dated June 5, 2017)

In order to address the root cause of the contamination in the investigation and minimize the risk of re-occurrence, improvements were made to the relevant SOP for performing the release of (b) (4) before they are reconnected to the filling manifold. In addition, the aseptic technique of the operators within the filling room was addressed. All of these changes were implemented before the initiation of new repeat media fills. All operators were trained. The training session included; SOP reading, discussion and simulation by the trainer and each trainee.

Kamada made following revision to their SOP and aseptic procedures:

1. The following SOPs were updated N-3F-570/4 rev. 15, N-3F-570 version 15 and N-3F-340 version 15 to emphasize the required actions in case media is spilled on the conveyor or the working surfaces.
2. Following review of the filling video films, the following SOPs were updated: N-3F-570/4 rev. 15, N-3F-570 version 15 and in N-3F-340 version 15: to improve the aseptic techniques:
3. When the operator's hands went below (b) (4), he should exchange gloves. Passing over the transfer line while connected – is forbidden. Except from tools, any other equipment that fell down should not be reused during filling (nor touched by the operator).

4. If during media fill, media spilled on the working surfaces or on the filling machine, the filling should be stopped, surfaces should be cleaned, and reported to QA representative before proceeding with filling.

5. Lying (fallen) vials should be discarded. Removing lying vials should be performed only in certain point on the conveyor, where intervention can happen and avoiding passage of the operator hands over opened vials.

6. Angular conveyor should be cleared from vials before opening it, and after entering the closed area, the operator should wait (b) (4) min before reoperation of it. Before performing aseptic operation, operator A should exchange his gloves.

7. Addition of documentation of (b) (4) ml sterile (b) (4) – lot number and expiration date.

8. Aseptic connection technique improvements of the transfer line to manifold and manifold to (b) (4).

9. Air release technique improvement to avoid solution spill during (b) (4) release.

10. Rubber stoppers (b) (4) technique improvement

11. Updated the SOP N-3C-520 version 10, this SOP perform cleaning of the filling rooms ceiling (b) (4).

Upon implementing all the required immediate corrective actions and training performance, (b) (4) additional 50 ml media fills runs were conducted in (b) (4) in order to requalify the aseptic process. The (b) (4)-repeat media fill runs re-qualifying the (b) (4) for Glassia (50 ml configuration) were executed successfully. Summary is provided in the table below:

Media Lot	Simulated Product	Fill Volume	Filling Date	Production Quantity Incubated*	Visual Inspection Date	Number of Contaminated Vials	Result
(b) (4)							

*All integer vials that were filled were incubated.

1. (b) (4) media fill run (b) (4) was stopped at the (b) (4) sterile (b) (4) from formulation to filling (b) (4) as the (b) (4) and media could not be filtered. Filling could not be done, the media run was discontinued.
2. (b) (4) During filling room setup prior to filling media (b) (4) un-identified stains were observed on the rubber stoppers (b) (4). (b) (4) was disqualified for filling, and therefore filling could not be done. Media run was discontinued.

Review comment: Kamada's response is acceptable. We noted that (b) (4) media fills were performed successfully in the (b) (4). All corrective actions were completed. (b) (4)

Observation 1b

b) The goggles used during aseptic processing in the ISO (b) (4) filling room are processed as follows:




- **Goggles are sterilized (b) (4)**
- **Prior to use, goggles are sanitized and exposed to (b) (4) for (b) (4) minutes**
- **After use, goggles are sanitized**

While the manufacturer's specifications have established a maximum of (b) (4) sterilization cycles, no evidence is available to indicate that exposure to (b) (4) does not affect the longevity of the goggles. Similarly, no evidence is available showing that the sterilization of goggles is effective or consistent.

Kamada Response 1b:

Kamada provided Kamada's current goggle sterilization process information as follow:

(b) (4)



Review comment: Kamada response is acceptable based on the proposed corrective actions. These (b) (4).

Observation # 1c

The supplier of ISO (b) (4) gowning and associated laundry services has stated that the gowns can undergo approximately (b) (4) washings prior to replacement and has halved that number for washings when combined steam sterilization. No evidence is available to show that these gowns remain an effective barrier against viable or non-viable human generated particulates after (b) (4) cycles of washing, steam sterilization, and use.

Kamada Response #1C

Kamada provided a brief summary of the current gowning sterilization process as follow: (b) (4)

(b) (4)

(b) (4)

(b) (4)

Observation #1d

The following departures from aseptic technique were observed during review of GLASSIA setup activities:

An operator was observed to place his gloved hand on the underside of the bottom shelf of a cart to move the cart; the operator subsequently handled the bulk formulation transfer hose without sanitizing his hands.

An operator was observed to transfer multiple pieces of small equipment to the bottom tray of a cart; the operator did not immediately sanitize his gloved hands after this activity.

During the addition of stoppers to the stopper bowl, an operator's gloved hand was observed to be directly above exposed stoppers.

An operator's gloved hand was observed to be directly above the opening of the formulation transfer hose immediately prior to connecting it to the filling manifold apparatus.

Kamada Response #1D:

Kamada provided following summary for the proposed improvement:

Aseptic techniques performed during the setup and filling activities were either improved or further detailed in the appropriate procedures for performing the release of the remaining (b) (4) from the filling (b) (4) before re-connecting to the filling machine manifold to minimize the risk of contamination. In addition, the aseptic technique of the operators within the filling room was addressed. Revised instructions were developed as an outcome of a brainstorming session with the operators, consulting with advisors and specialists in aseptic processing, reviewing films from past media / product fillings and regulatory comments. Revisions were made to the operating procedures and to the filling operator qualification procedure.

Improvements in the following procedures were implemented (see details below) before the initiation of a repeat media fills:

(b)
(4)

[REDACTED]

(b)
(4)

All operators were trained as part of the media fill investigation corrective actions. The training session included SOP reading, discussions and simulations by the trainer and each trainee.

Review comment: Kamada response is adequate based on corrective actions taken.

Observation 1e

Studies performed to evaluate disinfectants are deficient in that they do not reflect current practice in manufacturing. For example, there is no evidence available to assure that (b) (4) can effectively eliminate spores from (b) (4) surfaces. Similarly, disinfectant efficacy studies for (b) (4) and (b) (4) do not include the contact time between the disinfectant / sporicidal and the surface under test.

Kamada Response 1e:

Kamada provided summary of disinfectants effectiveness study that was performed:

Kamada's validation of the effectiveness of disinfectants was conducted based on the principles set in VL-100095-AM, *Validation for the effectiveness of surface disinfectants* (version 3, effective date 20.04.17). According to SOP N-2M-003, *Controlled materials* (version 9, effective date 08.01.17), introduction of a new cleaning / disinfectant into Kamada is managed under change control, and includes effectiveness and compatibility studies. The effectiveness of (b) (4) on various surfaces is summarized in Rep-VL-100691-AM, which includes effectiveness studies on (b) (4).

Kamada describes proposed corrective actions as follow:

Following 483 observations, the effectiveness study of (b) (4) of (b) (4) surface will be completed under CAPA 19859. Protocol VL-100095-AM (version 3, effective date 20.04.17) was updated to include (b) (4) surfaces. The surface challenge test for effectiveness of (b) (4), will be repeated to include verification of effective contact time and effectiveness study on (b) (4) surface. While an effective contact time of (b) (4) minutes was established in the disinfectant effectiveness studies, Kamada's SOPs N-3C-520, and N-3F-340 require a contact time of at least (b) (4) minutes. At the surface challenge test, the disinfectant effectiveness was established after complete drying of the disinfectant on the surfaces.

Following 483 observation, the effectiveness studies will be completed to include effective contact time on the various surfaces under CAPA 19859. The surface challenge test for the effectiveness of

(b) (4) and (b) (4) will be repeated to include verification of effective contact time. In addition to the above, a thorough review was performed for all studies performed, to evaluate disinfectants and the following improvements were introduced. Rep-VL-100382-AM, *Effectiveness Test of (b) (4) for Disinfection of (b) (4) Surfaces*, Rep-VL-100809-AM, *Effectiveness Test of (b) (4) Against Various Microorganisms on (b) (4) Surfaces* (version 1, effective date 03.04.17), a (b) (4) log reduction was proven for the viability of (b) (4), due to low inoculum of the bacteria for the test. The studies will be completed to prove at least a (b) (4)-log reduction. The due date for completion of studies is 30.09.2017.

Review comment: Kamada response is considered adequate based on the proposed corrective actions. All corrective actions should be verified during the next cGMP inspection.

Observation 2

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its cleaning and maintenance.

a) The media fill failure in December 2014 identified a (b) (4) as the most likely root cause. In addition, media fills (b) (4) (03/04/2015), and (b) (4) (08/25/2015) were disqualified due to various equipment malfunctions, including, in one case, the (b) (4) controller.

b) While the current (b) (4) maintenance procedure requires routine (b) (4) maintenance, records reviewed indicate that (b) (4) unplanned maintenance operations were performed for the (b) (4) month period between June 2016 and March 2017. On 03/27/2017 multiple stoppages were observed during a filling demonstration due to failure of the (b) (4) element to reach its' required temperature. The (b) (4) 2ml, 10ml, (b) (4) vials.

Kamada Response Observation #2:

Kamada describes current equipment maintenance program as follow:

Equipment is periodically monitored and maintained according to SOP N-8G-040, *Technical Department General SOP* (version 13, effective date 15.04.17). According to this SOP, periodic maintenance is performed on equipment, according to a pre-approved plan. The periodic maintenance is documented. In addition, equipment repair (unplanned maintenance) is also performed and documented according to this SOP. The SOP N-2P-020, *Annual Quality Systems Review* (version 4, effective date 14.06.16), requires unplanned maintenance occurrences for equipment at the site to be reviewed yearly to reveal any trends and re-occurring events. These are analyzed and corrective actions are introduced, for example: changing frequency of preventive maintenance, changing existing equipment, changing operational instructions, or addition of preventive maintenance measures.

The preventive maintenance plan for the filling machine S-42 (which includes the filling (b) (4) that were mentioned in the 483 observation) incorporates the following:

- (b) (4) preventive maintenance, involving mechanical checks ((b) (4));
- (b) (4) preventive maintenance, including check of crimping heads (b) (4)), mechanical cleaning, mechanical checks as well as parts disassembly and replacement.

Furthermore, as part of the media fill investigation corrective actions from 2015, the (b) (4) preventive maintenance for the filling machine (b) (4) was updated to include a visual check for scratches / bumps and check for leakage of the filling (b) (4). This is in addition to the replacement of aging filling (b) (4), which was performed during 2015. Since 2016, no filling (b) (4) used for production runs or media fills have required repairs.

Following 483 observation, the preventive and unplanned maintenance history for the filling machine (b) (4) was reviewed for the period of January 2014 - April 2017. A total of 24 preventive maintenance activities were performed during this period. No malfunctions were documented in the preventive maintenance documentation. During this period, a total of 67 unplanned maintenance occurrences were documented.

- Following the analysis performed for the filling machine (b) (4), Kamada concluded that the (b) (4) preventive maintenance required additional maintenance for tightening of the conveyor alignment screw. The preventive maintenance was updated on 24.04.17.

The preventive maintenance plan for the (b) (4) incorporates the following:

(b) (4)

(b) (4)

(b) (4)

In follow up to the inspection and 483 observation 2(b) [i.e. regarding (b) (4) unplanned maintenance operations performed in the (b) (4) month period between June 2016 and March 2017], Kamada reviewed the preventive and unplanned maintenance history for the (b) (4), for the period January 2014 - April 2017. During this period, 50 preventive maintenance activities were performed and no malfunctions were documented, and 46 unplanned maintenances occurred. Following the analysis, it was concluded that the preventative maintenance plan for the (b) (4), warranted the following modifications:

A change to the (b) (4) preventive maintenance plan to include a check of (b) (4). The preventive maintenance plan was updated on 24.04.17; and A change to the (b) (4).

preventive maintenance plan to include the addition of cleaning of the (b) (4) that was observed during the FDA inspection). The preventive maintenance plan was updated on 24.04.17 In addition to the above, due to the (b) (4) encountered during the inspection, (b) (4)

Review comment: Kamada response is acceptable

Observation 3

Biological product deviations were not reported within the 45-calendar day timeframe. Specifically, during review of the 16 Biological Product Deviation Reports filed between January 2014 and March 2017, ten (approximately 63%) were not received by the Agency within 45 days of discovery of the deviation.

Kamada's Response Observation 3:

BPDR reporting to CBER is performed according to SOP N-2C-013, *Deviation Reporting to CBER* (version 4, effective date 30.10.16). On April 2016, training was carried out for Kamada's management by a Baxalta representative (distributor of Glassia in the US) regarding BPDR reporting. Following this training, Kamada clarified within its SOP the types of events that should be reported to CBER. SOP N-2C-013, *Deviation Reporting to CBER*, was revised (version 4, effective date 30.10.16), to clarify the FDA requirement for BPDR reporting.

Prior to the training, Kamada's approach for reporting BPDRs to CBER was to wait to submit a complete investigation after concluding the potential risk to the lots marketed, rather than submitting an incomplete investigation within the required timeframe. This approach is reflected in the extended timeframes between identification of the deviation events and the submission of the complete investigations to CBER. In order to correct this approach, specific BPDR training was carried out for relevant departments and employees in the company (QA, QC, Validations, RA), to ensure future BPDRs are reported correctly and in compliance with BPDR reporting standards.

On 27.12 2016, CAPA 18332 was issued to improve the BPDR reporting process at Kamada. As part of the CAPA, a review was carried out in the (b) (4) system for all events reported since 2012, which may potentially be BPDRs that were not reported to the FDA.

During the inspection, Kamada presented its revised approach to reporting BPDRs to FDA, including the use of (b) (4) to enable timely reporting of these events. Training for all involved personnel was performed on 30.04.17. With the implementation of this revised approach, all future BPDRs will be reported within the 45-day time frame.

Review comment: Kamada response is acceptable based on the proposed corrective actions.

Observation 4

The master production and control records are deficient in that they do not include complete manufacturing and control instructions and specifications. Specifically, the Master Batch Record for GLASSIA is deficient in that:

a) The lot and expiration date of (b) (4) used to lubricate (b) (4) that dose vials in the filling machine is not specified.

b) A statement for theoretical yield or established a maximum or minimum specification for final yield of drug product is not included as part of the batch record.

c) The process for aseptically connecting the (b) (4) apparatus is not adequately described as part of the batch record or other manufacturing or training documentation.

Kamada's Response 4:

Kamada explained that documentation of the lot number and expiration date of (b) (4) that dose vials in the filling machine were added to SOP N-3F-570/4, *Product Filling in (b) (4)* (for AAT to USA, Heparin, Kamacaine and Kamada HRIG), section 3.8, version 15, effective date 04.04.17.

According to Kamada, the (b) (4) is defined as a key parameter, therefore monitoring of the (b) (4) is performed on an ongoing basis, according to SOP N-2C-010, *Policy for Performance of Production Trend Analysis* (version 8, effective date 14.07.16). The (b) (4) of each specific lot is calculated and trended by the Product Line Supervisor upon review of the batch record. Trend limits for the Glassia (b) (4) were set based on statistical calculation ($\text{Avg} \pm 3\sigma$) of data from (b) (4) lots, as summarized in report Rep-N-2C-010/9. Where an Out-of-Trend (OOT) result is obtained, an investigation is issued in order to identify the root cause. In addition to the routine monitoring, the data is analyzed (b) (4) a year in the Annual Product Review Report.

In response to the 483 observation Kamada proposed the following corrective actions: 1) a new form, N-3F-353, *Calculation of the (b) (4) for AAT* (version 1, effective date 10.05.17), was established (see attachment No. 4-b) and (b) (4) limits of theoretical and actual drug product (b) (4) are now incorporated into Form N-3F-353. The new form will be included in the batch record. 2) A detailed description of the process for aseptically (b) (4) apparatus was added to form N-3F-570/4, *Product Filling in Filling Room (b) (4)*. 3) In addition, training documents SOP N-3T-002/7, *Complementary Training for a New Filling Dept. Employee - Stage I*, section 2.2 (version 2, effective date 24.04.17) and SOP N-3T-008, *Training of a New Filling Room Employee - Stage II*, section 3.2, 3.4.2 (version 03, effective date 24.04.17), were revised to include training on performing the revised procedure.

Review comment: Kamada response is adequate, (b) (4).

Observation 5

Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without performing at (b) (4) specific identity test on each component and establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. Specifically, (b) (4) in the filling machine is not tested after receipt. This material comes into direct contact with drug product.

Kamada's Response, Observation 5:

Kamada provided following justification regarding this observation:

- All chemical raw materials that are used in the production process that are components of the product (drug substance and drug product) and primary packaging materials are received, sampled, tested in QC and released by QA according to SOP N-1G-009, *Testing and release of controlled materials- Chemical Raw Materials and Primary Packaging Materials* (version 12, effective date 18.04.17). These materials are tested in the QC laboratory with acceptance criteria according to the relevant (b) (4) monograph (and (b) (4) monograph). In addition, the manufacturer's COA for the incoming lot is verified.
- Other critical auxiliary materials used in production are released by QA based on comparison to a controlled reference specification document, according to SOP N-1G-008, *Testing and release of Controlled Critical Auxiliary Materials used in production*.

As stated in the above 483 observation, the (b) (4) of (b) (4) used to lubricate (b) (4) in the filling machine are released by comparing their detailed COA to the reference COA included in specification S-180/1, (b) (4). So far, it was not deemed necessary to perform QC testing because Kamada evaluated the risk of the (b) (4) being a component of the final product as extremely low.

At the initialization of a filling procedure, it is necessary to introduce a (b) (4) filling (b) (4) to avoid high friction of (b) (4) surfaces of the (b) (4) and the (b) (4). This is done by aseptically adding (b) (4) (produced by (b) (4), Kamada cat. no. (b) (4)) onto a (b) (4), thereby lubricating it. The (b) (4) is discarded and the lubricated (b) (4) is inserted into the (b) (4). A new (b) (4) is used to lubricate each (b) (4). Following the lubrication of the (b) (4), at least (b) (4) of product are pumped into all (b) (4) and (b) (4) (approximately (b) (4) is pumped into each (b) (4)). This procedure essentially (b) (4) used for (b) (4) lubrication. To summarize, the amount of (b) (4) that will actually be introduced into the product is negligible and has no potential effect on the final product delivered to the patient.

However, following the above 483 observation, Kamada has decided to include QC acceptance tests for the (b) (4) used to lubricate (b) (4) in the filling machine.

The material "(b) (4)" ((b) (4)) used to lubricate (b) (4) in the filling machine) was included in appendix N-1G-008/4, Controlled materials that are significant for production which require sampling before their release.

SOP for release tests of (b) (4) used to lubricate (b) (4) in the filling machine was prepared: SOP N-1G-064, *Release tests for* (b) (4). This SOP includes tests for (b) (4).

Kamada has initiated the preparation for qualification of tests for (b) (4) in (b) (4) used to lubricate (b) (4) in the filling machine. Upon qualification of these tests, they will be added to SOP N-1G-064.

Preliminary tests of the currently used (b) (4) (batch 1(b) (4)), Kamada catalog no. (b) (4)) for (b) (4) conducted on (b) (4) used to lubricate (b) (4) in the filling machine showed that the components are within the required acceptance criteria.

Review comment: Kamada response is acceptable. (b) (4)

Observation 6

Validation of certain analytical methods used for product release is incomplete. Specifically, the hold time of samples used for determination of Residual TnBP, and Residual Tween-80 in Glassia Drug Substance has not been properly validated.

Kamada's Response Observation 6:

Kamada provided the following additional detail regarding method validation as follow:

- As part of Glassia release tests, the (b) (4) is tested for residuals of three substances. These three substances are: (1) Residual Tri n Butyl Phosphate (TnBP); (2) Residual Tween 80 according to SOP N-1P- 5182-05; and (3) Residual (b) (4) according to SOP N-1P-5182-07. Validation studies for the three analytical methods complied with Kamada's SOP N-1G- 032, *Validation and Qualification of Analytical Methods*.
- SOP for testing residual TnBP, N-1P-0001-32, instructs to perform the testing within (b) (4) weeks from sampling, based on report Rep-VL-08507-AM, *Hold Time Study for AAT IPC Samples Tested for TnBP Limit Test* (version 1, effective date 15.06.14). SOP for testing residual Tween 80, N-1P-5182-05, instructs to perform the testing within (b) (4) weeks from sampling, based on Rep-VL-08505-AM, *Hold Time Study of AAT IPC Samples tested for Tween 80 Limit Test* (version 1, effective date 15.05.14). Those two hold time limits from sampling to testing were not properly validated and therefore will be repeated after improvement of the study protocols.

- Currently, hold times for testing AAT samples is up to (b) (4) weeks. This hold time, though not properly validated, is not expected to affect the test results. This is because all samples are kept in closed containers, at a controlled temperature, protected from light, and because the substances are known to be chemically stable.
- In addition, following evaluation of this observation, all hold time studies for Glassia drug substance testing were reviewed and it was found that there was no hold time study from sampling to testing of residual (b) (4) .

To remediate these deficiencies, three studies (residual Tween 80, residual TnBP and residual (b) (4)) will be completed under CAPA 19960 according to the following protocols: VL-103071-AM, *Hold Time Study from Sampling to Testing of Residual TnBP within AAT Samples* (version 01, effective date 01.05.17) and VL-103073-AM, *Hold Time Study from Sampling to Testing of Residual (b) (4) within AAT Samples*.

In addition, SOP N-1G-032, *Validation, Qualification and Hold time studies of Analytical Methods*, was updated (version 4, effective date 15.05.17) to include a section that requires performance of hold time studies from sampling to testing. Due date for completion of studies (under CAPA 19960) is 31.10.2017. This due date allows production of the drug substance samples to be used in the studies and the hold time of (b) (4) weeks to be examined.

Review comment: Kamada response is adequate. (b) (4)