

10. Please describe the procedures in place at the ranch for insect, vermin and stray animal control.
11. Are any herbicides or pesticides used at the Ranch?
12. Is the water supply monitored for contamination e.g. herbicides, pesticides, bacterial contamination and heavy metals? If so how frequently is the water monitored?
13. Is the horses' feed (all forms) ---(b)(4)----- monitored for contamination? If so how frequently?
14. Are the feed suppliers monitored? If so do you perform on site inspections of the suppliers?
15. Do you monitor the horse's body weight? If so please describe how the body weight is monitored and how frequently.
16. What is the incidence of colic in the production animals? Is there a correlation between immunization and colic?
17. Does immunization affect the horses feed intake? If so please describe in detail the affect and duration of the affect.
18. Do you monitor the horse's body temperature? If so please describe the technique and frequency. Is there a relationship between elevated body temperature and immunization?
19. Do any of the paddocks or pastures have areas of standing water? Please describe the drainage patterns of the pastures/paddocks and provide elevation diagrams of all areas where the horses have access.

Horse prophylactic immunization.

20. Please vaccinate and appropriately booster all horses and other animals on the farm (cats, dogs) with the appropriate rabies vaccine.
21. Please vaccinate and appropriately booster all horses with the trivalent vaccine covering EEE, WEE and VEE.

QC on production serum:

- 22. What considerations are given to withdrawal times in respect to agents administered to the horse, e.g. anthelmintics, antibiotics, analgesics, expectorants, etc. prior to blood collection?

Venom immunization procedure:

23. -----
 -----(b)(4)-----

 -----?

- 24. Please clarify the use of your term "challenges". Do you use the word "challenges" to mean -----(b)(4)-----?

- 25. What is the total volume administered at the time of immunization -----(b)(4)-
-----?

- 26. Post- immunization does the horse experience any more then transient discomfort (pain)? If so is this associated with the ---(b)(4)---and/or the concentration of venom?

- 27. What is the incidence of abscesses at the site of immunization?

- 28. Item 4, D, d mentions after the horses are bled -----(b)(4)-----
-----?

CHEMISTRY, MANUFACTURING AND CONTROLS

- 29. Please provide the assay SOP (SOP M-CB-011), the assay validation protocol, and the assay validation final report, for your ----(b)(4)---- based Identity testing.

- 30. Please provide the assay SOP, assay validation protocol, and the validation final report, for your Sucrose determination test.

- 31. For all steps during manufacture where intermediates may be stored for any length of time, please indicate the maximum hold time and storage conditions.

- 32. Are the ---(b)(4)--- containers used for the collection of horse blood depyrogenated?

- 33. Are the (b)(4) containers used for the collection of horse blood reused? If so, how are they tested for sterility and endotoxin?
- 34. Your batch record directs the operator to "------(b)(4)-----
-----." Where are these mixing steps documented? -----(b)(4)-----
-----?
- 35. Your batch record for plasma collection and -----(b)(4)-----, code DM-PR-001, pages 7 and 8 of 18 have spaces for recording of "------(b)(4)-----", and "-----
------(b)(4)-----". Is ---(b)(4)-- added to the horse plasma before sampling for -----(b)(4)-----?
- 36. Your test methods for horse plasma include -----
------(b)(4)-----

-----?
- 37. How long do you store the horse plasma before use? At what temperature is the plasma stored?
- 38. What are your critical process parameters? Have you set in-process controls at these steps? Please note that a typical manufacturing procedure would monitor bioburden, endotoxin, and protein concentration at several steps during the process.
- 39. -----(b)(4)-----?
- 40. -----(b)(4)-----
-----?
- 41. -----(b)(4)-----

-----?
- 42. Do you perform any assays to characterize your pepsin or pepsin solution?
- 43. How long can the pepsin solution -----(b)(4)-----?
- 44. How many lots (sub-batches) of horse plasma can be mixed per lot of bulk drug product?

- 45. Are lots (sub-batches) of horse plasma tested for adventitious agents prior to use in manufacturing a lot of bulk drug product?
- 46. How is the product solution mixed in the reactor? Where are the mixing steps documented in the batch record?
- 47. Have you set a maximum volume of ---(b)(4)--- that can be used to -----
-----(b)(4)-----?
- 48. What is the minimum/maximum time allowed for the pepsin digest? Do you take samples to monitor the progress of the digestion?
- 49. Do you have data to support that if you "------(b)(4)-----
-----?
- 50. What mixing speeds are used? How are these documented?
- 51. Do you monitor the rate of ammonium sulfate addition? -----
------(b)(4)-----?
- 52. Have you set limits for the amount of time -----(b)(4)-----
-----?
- 53. -----
------(b)(4)-----
-----?
- 54. Have you established limits for processing time -----(b)(4)-----?
- 55. Do you have time limits for -----(b)(4)-----? Is there a maximum hold time ----
------(b)(4)-----? Are samples taken for bioburden, protein concentration, and endotoxin determination?
- 56. -----(b)(4)-----
----- ?
- 57. -----(b)(4)-----?
- 58. What is the maximum amount of time allowed for -----(b)(4)-----?

59. Please provide details on how the -----(b)(4)-----.

60. -----(b)(4)-----

---?

61. Do you have a maximum filtration time for -----(b)(4)-----?

62. -----(b)(4)-----
-----?

63. Have you validated (or are in the process of validating) the maximum number of uses for your -----(b)(4)-----?

64. How many times may the integrity test for the -----(b)(4)-----be repeated?

65. How do you determine the state of -----(b)(4)-----?

66. How often is -----(b)(4)-----?

67. What is the maximum amount of time allowed for the -----(b)(4)-----?

68. How do you determine -----(b)(4)-----?

69. How long may the concentrate -----(b)(4)-----?

70. -----(b)(4)-----
-----?

71. -----(b)(4)-----?

72. What volume of water is used to dissolve the excipients? Is WFI or reverse osmosis water used?

73. How many batches require -----(b)(4)--? How many batches require----(b)(4)-----
-?

74. What is the maximum amount of time allowed for the nanofiltration step?

75. Do you monitor flow rate through the nanofilter?

76. What procedures are followed if the nanofilter clogs?

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77. How many lots have failed the post-nanofiltration integrity test? Did you investigate why these lots (if any) failed?

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission. Please submit this information as an amendment to this file no later than April 24, 2009. Please do not send an advance copy of the response by email unless requested to do so by FDA. If you anticipate you will not be able to respond by this date, please contact the Agency immediately. The action due date for this file is July 24, 2009.

Thank you for your assistance,

Debbie Cordaro
Regulatory Project Manager
FDA/CBER/DBA/OBRR/RPMB

Information provided b/RF/JB /MK Date: 4/13/09 Transmitted by DLC Date 4/14/09

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