Pfizer Global Manufacturing **CONFIDENTIAL**

Meeting Minutes

Participants

Bob Grillo; Bernadette Mauser, Niek Hombrouckx, Katrien DePooter, Stan Danowski, Les Van Alstine, and John Wydila

Summary

No data points contained in the FDA inquiry histogram were greater than the upper specification limit. The drop size is not a medical dosing issue because the human eye can absorb only 7 µl of fluid. The critical dosing parameter is the API concentration. Both the manual and Xal-Ease drop size qualification methods will be maintained. Puurs will develop a new manual testing method employing a constant pressure source on the container to form the drops. A revised response to the New Tip FDA inquiry will be reviewed at the next team meeting prior to regulatory submission. Development of a Xalatan and Xalacom regulatory submission timeline is in progress. The tip test water and drug product drop rates were proven to be statistically equivalent.

Discussion

- Drop size histogram data - response to FDA new tip inquiry

	Min (µl)	Max(µl)
Purrs, 45°	25.7	31.3
Purrs, 90°	24.1	30.8
Cardinal Health, 45°	24.7	31.4
Cardinal Health, 90°	26.9	31.2

  - Drop size normal distribution is not appropriate
  - Max data will round to 31 µl - Question 4 response
    - No data points from the histogram data are outside the specification
- Medical and regulatory implication of dispensing drops > 31 µl
  - Summary of Bernadette's discussion with Mike Lynch, Pfizer internal documents, and ophthalmic literature.
    - Some of the new tip drop size data is > 31 µl

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- Drop size is not a medical issue
  - The human eye can absorb approximately 7 µl of fluid. The remaining drop fluid beyond 7 µl is not absorbed by the eye.
  - Pharmacia reports – no medical reason for accurate measurement of drop size
  - API concentration is the dosing critical parameter.
- Ophthalmic market drug product drop size range
  - 25 -56 µl, average = 39 µl
- NDA review – drop size in not a tip specification. Drop size is found in the NDA development section
- Drop size will affect the volume of drug product fluid in container available for dosing.
  - If drop size is too large, then there may be insufficient drug product in the container to provide required 30 doses
  - Calculations demonstrate that a drop size of 32 µl will result in approximately 1 ml of drug product fluid remaining in the container at the end of the dosing period.

- Broaden US specification?
  - Drop size is a tip qualification test
  - Do not set a tip specification for drop size
- Employ Xal –Ease device for drop size testing?
  - Current manual method, operator dependent, some drops > 31 µl
  - Team decision:
    - Maintain current manual drop size method and Xal-Ease drop size method
    - Puurs will develop a new manual method using a controlled, constant force device instead of human technicians to conduct the manual test.

- Response to the New Tip FDA inquiry
  - Bernadette will compose a revised response to the FDA document which will be sent to the team.

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- Les will prepare a table containing the percentage of drop size measurements >31 μ that will be included in the response to the FDA inquiry.
- The response to the FDA document will be reviewed during the next team meeting. After review, the final document will be sent to Regulatory for submission.

- Statistical analysis on drop rates, water versus drug product
  - Water and drug product drop rates are statistically equivalent.
  - Les will send report to the team.
- Close in time Xalacom New Resins and Xalacom New Process Regulatory submissions with Pfizer Regulatory colleagues during the next team meeting
  - Regulatory submission sequence
    1. US Xalatn new resin
    2. EU Xalatan new resin
    3. Xalacom improved process
    4. Xalacon new resin
  - Niek will create a timeline for the regulatory submission after discussions with Puurs colleagues
  - Les will complete the statistical analysis of the new resins tip data and send the report to the team..
  - The team will discuss the regulatory submission timeline during the next team meeting.

Action Items

1. Review the Xal-Ease device submission for drop size and drop size specifications by 4/8 (Katrien and Valja)
2. Send a table containing percentage of drop sizes > 31 μl by 4/1 (Les)
3. Send a response to the FDA revised draft document to the team by 4/11 (Bernadette)
4. Review the response to the FDA document at the next team meeting (Team).
5. Send water versus drug product statistical analysis report to the team by 4/1 (Les)
6. Create a timeline for the Xalatan and Xalacom regulatory submissions by 4/11 (Niek)

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7. Send the News Resins Tip data analysis report to the team by 4/1 (Les)

8. Review the regulatory submission timeline during the next team meeting (Team)/

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