MEETING MINUTES

SUBJECT: FDA-GPhA Board of Directors (BOD) Quarterly Meeting

DATE: May 28, 2014

FDA ATTENDEES:

Janet Woodcock - Center for Drug Evaluation and Research (CDER)
Richard Moscicki - CDER
Kathleen (“Cook”) Uhl - Office of Generic Drug (OGD)
Mary Dempsey - OGD
Keith Flanagan - OGD
Thomas Hinchliffe – OGD
Michael Jones – OGD
Denise Toyer Mckan - OGD
Robert Lionberger – OGD
Linda Park – OGD
Robert West - OGD
Carol Bennett - Office of Regulatory Policy (ORP)
Grail Sipes – ORP
Lawrence Yu – Office of Pharmaceutical Science (OPS)
Edward Sherwood – OPS
Theresa Mullin - Office of Strategic Programs (OSP)
Hilmar Hamann – OSP
Andrew Kish – OSP
Russell Wesdyk – OSP
Katherine Yang – OSP
Ellen Morrison – ORA
Carol Bennett – Office of Compliance (OC)
Michael Levy - OC

SPONSOR ATTENDEES:

GPhA Member Company attendees:

Momenta                      Craig Wheeler – President and Chair of the GPhA Board
Teva                         Allan Oberman – President and Vice Chair of the GPhA Board
Zydus                        Joe Renner – President
Lupin                        Paul McGarty – President
Mylan                        Marcie McClintic Coates – SVP Regulatory
Impax                        Marcy Macdonald – VP Regulatory Affairs
Perrigo                      Richard Stec – VP Regulatory Affairs
Fresenius-Kabi               Molly Rapp – VP Regulatory Affairs
Sandoz                       Nicholas Tantillo – VP Regulatory Affairs
Hospira                      Lisa Zboril – SVP Global Regulatory Affairs
Apotex                       Kiran Krishnan – VP Regulatory Affairs
Ranbaxy                      Robert Femia – VP Regulatory Affairs
Amneal                       Candis Edwards – SVP Regulatory Affairs
Heritage                     Pablo Davila – VP Regulatory Affairs
**GPhA attendees:**
Ralph Neas
David Gaugh
Lisa Tan
Mark Hendrickson

**Agenda (for reference):**

I. Introductions
II. OGD New Personnel
III. Target Action Dates
IV. Documentation of communications between industry and FDA
V. OGD Policy Update
   - Quality of Submissions
   - Other Policy items
VI. Regulatory Science Part 15
VII. Stability – Finalizing the Q&A Guidance
VIII. Quality Metrics
IX. Industry Updates
   - GDUFA Goals
   - Inactive Ingredients Database (IID)
   - First Generics
   - Inspections
   - Challenges faced by supply chain partners
X. OGD move to White Oak
XI. Wrap-up and Next Steps

**Topics Discussed/Action Items:**

1. Denise Toyer Mckan was introduced as the Director of Project Management for OGD
2. Target Action Date implementation in OGD was overviewed (slides 5 & 6) by Keith Flanagan
   
   GPhA understood and strongly supported the TAD initiative.
3. Documentation of communications between industry and FDA
   
   Any and all communication directed to an OGD member by applicants will be archived in the administrative record.
4. OGD Policy update was provided (Slide 8 & 9)
5. Regulatory Science Part 15 (slide 10)
   
   Part 15 meeting was held on May 16, 2014. David Gaugh from GPhA was the only ANDA industry participant in attendance. FDA encouraged industry companies to provide any comments on the open docket by the June 13, 2014 deadline.
6. ANDA Stability guidance and Finalizing the Q&A Guidance was discussed by Dr. Yu (slides 12 – 16)

   The implementation date is June 20, 2014.

7. Quality Metrics update was provided by Russell Wesdyk (Quality Metrics slide deck attachment)

8. GPhA Update (slide 18)

   GPhA directed questions to FDA to which FDA responded as follows:

   GDUFA Goals
   
   i. FDA is on target with year 2 hiring numbers – no exact numbers were provided.
   
   ii. Year 3 metric goal is 60% of original ANDA applications will have an Action in 15 months. FDA will strive for Action on 100% in 15 months. 100% is very unrealistic, but striving for it makes achieving 60% more likely.

   Inactive Ingredients Database (IID)

   i. FDA recognizes the need to have a robust and accurate IID. Internal discussions on improvement are happening.

9. OGD Move to White Oak has been completed with success. Our presence on campus alongside all other agency counterparts will exponentially increase our ability to closely collaborate, communicate, and coordinate. This is a positive step towards securing greater program success.

10. Wrap-up

   Action items/Topics for next meeting:

   FDA:

   - OPQ update
   - OGD Division of Quality Management overview
   - IT systems (5 year plan) update
   - Inspection program revisions update (bio site and manufacturing/testing/packaging facility)
   - Investigate feasibility of gathering data concerning issued CR deficiencies for analysis to identify potential commonalities or possible trends in types of deficiencies or factors contributing to failure to respond to CRs.
GPhA:

- Provide industry perspective regarding product launch regulatory challenges.
- Develop additional specific proposals to improve OGD communications transparency.
- Conduct survey of GPhA member companies concerning coordination of inspections and scientific review.

CC:
Janet Woodcock, CDER
David Gaugh, GPhA
FDA/GPhA Quarterly Board Meeting on GDUFA Implementation

Kathleen Uhl, M.D.
Acting Director
CDER Office of Generic Drugs
U.S. Food and Drug Administration

May 28, 2014
Meeting Agenda

I. Introductions All
II. OGD New Personnel FDA
III. Target Action Dates FDA
IV. Documentation of communications between industry and FDA FDA
V. OGD Policy Update FDA
   - Quality of Submissions (FDA & GPhA)
   - Other Policy items
VI. Regulatory Science Part 15

🌟 Break Time🌟 All 2
Meeting Agenda

VII. Stability- Finalizing the Q&A Guidance   FDA
VIII. Quality Metrics   FDA
IX. Industry Updates   GPhA
   • GDUFA Goals
   • Inactive Ingredients Database (IID)
   • First Generics
   • Inspections
   • Challenges faced by supply chain partners
X. OGD move to White Oak   FDA
XI. Wrap-up and Next Steps   All
OGD New Personnel

- Denise Toyer Mckan, PharmD.
Target Action Dates

- FDA will start assigning target action dates (TAD), to a small number of submissions at first.
- A TAD is a date by which we will target “action” on a submission.
- A TAD is an internal, administrative and communications target.
- TAD is not a GDUFA goal date. It is different. Don’t conflate them.
- GDUFA goal dates for original ANDAs start in Year 3 of the program.
- Year 3 starts October 1, 2014.
Target Action Dates (cont.)

• TADs will help us improve coordination of review before Year 3 begins.
• That way we won’t start from a “cold stop”.
• To promote transparency and enhance communications, RPM will notify applicant of TADs. Details to follow.
• This goes above and beyond our GDUFA commitments.
• Does GPhA understand and strongly support TADs? Any concerns?
Documentation of Communications Between Industry and FDA

- Kathleen Uhl
OGD Policy

• Draft Quality of 505(j) Submissions Guidance
• Draft GDUFA Amendment Tiers Guidance
• Draft GDUFA PAS Guidance
• Draft GDUFA Controlled Correspondence Guidance
• Final RTR Guidance
• Prioritization MaPP
• Prioritization Governance MaPP
• Communications with Industry MaPP
OGD Policy

When FDA issues Draft Guidance….

- **Would webinars be helpful for your regulatory staff when draft GDUFA GUIDANCE is issued?**
  - Prevent “scrambling” to discern FDA’s approach?
- **What should we expect from GPhA and its members companies?**
  - We welcome feedback.
  - If there are errors or unintended consequences, of course we want to know.
  - It’s good for us to know if you have strong feelings.
  - It’s better if you describe your substantive concerns, and provide constructive options for addressing them. (”Generate light, not just heat.”)
  - Please consider feasibility.
  - If a proposal makes sense, please say so. If we only hear from a few vocal outliers, we won’t know that most people think a proposal is OK.
GDUFA Regulatory Science Initiatives
FY 2014
Part 15 Public Meeting
May 16, 2014

Comments can be submitted to docket until June 13, 2014:

• http://www.regulations.gov/#!documentDetail;D=FDA-2013-N-0402-0019
Break Time
ANDAs: Stability Testing of Drug Substances and Products

Lawrence Yu, Ph.D.
Director (acting), Office of Pharmaceutical Science
FDA Center for Drug Evaluation and Research

May 28, 2014
GPhA Fall Technical Workshop
October 20-21, 2010
ICH Stability Guidance ICH Q1(A)

- In 2010, OGD adopted ICH stability guidance ICHQ1A(R2) to ANDA drug substance sections
  - ICH Q1A(R2)
    - Data from formal stability studies should be provided on at least three primary batches of the drug substance
    - OGD expects impact of such a change to be minimum as almost all submissions provide such stability data

- Whether OGD needs to apply ICH stability guidance ICHQ1A(R2) to ANDA drug product is being explored
Guidance for Industry

ANDAs: Stability Testing of Drug Substances and Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 2013
Generics
Guidance for Industry

ANDAs: Stability Testing of Drug Substances and Products

Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2014
Generics
What is the scope of and implementation date for the FDA stability guidance?

- A1

- The FDA stability guidance covers all new ANDAs under the Federal Food, Drug, and Cosmetic Act, section 505 (j), and DMFs (Type II for drug substances that support the ANDAs). It does not apply to postapproval changes.

- The implementation date is June 20, 2014.
Quality Metrics

• Russell Wesdyk
Quality Metrics Update for GPHA
Stakeholder Feedback, Goals, and Gaps

Russell Wesdyk
CDER/OSP
May 28, 2014
FDA Interest in Quality Metrics

• For purposes of supporting segmentation, an objective measure of the quality - fitness for intended use - of:
  – Products
  – Site
  – Quality systems

• Quality metrics are just one part of the picture
  – Intended to be enhancing FDA’s analysis
  – Not replacing existing measures

• The program will likely need to learn and evolve through continuous improvement
More on Quality Metrics…

• Widely used in industry
  – Benchmarking database
    • Dozens of metrics
    • From ~ 600 sites
    • Common definitions
    • Potential correlations

• Components required under CGMPs
  – Annual Product Review
    • Manufacturing data, SPC charts, process capability output
  – Available to FDA Investigators during inspection

• Potentially collected via FDASIA Title VII, section 706, in part to support section 705
Timeline

Feb, 2013 FRN
Spring-Winter, 2013 Various Conferences
Quality Metrics: Industry FRN Feedback

150 Responses
1 Opposed

Responders include brand, generic, biotech, OTC, and trade/professional associations
Timeline

Feb, 2013
FRN

Spring-Winter, 2013
Various Conferences

Dec, 2013
White Papers
Industry Engagement
(White Papers and Conferences)

- BIO
- CHPA
- GPHA
- ISPE
- PDA
- PHRMA
- Individual Companies
Consensus Goals

• For firms, the use of quality metrics promotes responsible practices and quality driven corporate culture

• For public, a focus on quality leads to fewer recalls and quality related shortages

• For FDA, industry achieves and is rewarded for quality, without extensive regulatory oversight
Consensus Objectives

• Use quality metrics and other risk factors to select sites for reduced inspection frequency.

• Determine when post-market regulatory change filing requirements can be reduced for specific products, processes, or sites.

• Identify products at greatest risk of shortage and recalls.

• Use conventional and innovative quality metrics, including measures of process robustness/capability, to detect and monitor variations in product quality.

• Identify objective measures for quality system effectiveness at manufacturing sites that can underpin structured surveillance inspections.

• Use quality metrics to learn about the state of quality, establish performance goals across industry, and better communicate internally and externally.

• Operationalize the quality metrics program in a manner to that
  – minimizes potential for unintended consequences,
  – assures data integrity,
  – incorporates learning and continuous improvement, and
  – realizes efficiency, i.e., it minimizes the reporting burden on industry and the regulatory duty of FDA.
Consensus Stakeholder Metrics

• Lot acceptance rate

• Product quality complaint rate

• OOS rate

• Recall rate
Site Monitoring

Binomial Process Capability Analysis of Lots Rejected

Tests performed with unequal sample sizes

- **Proportion**
  - P Chart
  - UCL: 0.05927
  - P: 0.01943
  - LCL: 0

- **Rate of Defectives**
  - Sample Size: 120, 130, 150
  - UCL: 0.04
  - LCL: 0

Summary Stats
- 95.0% confidence
- | % Defective | Lower CI | Upper CI |
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- **Histogram**
  - Sample: 2, 4, 6, 8, 10, 12, 14
  - Frequency: 0, 2, 4, 6, 8
  - Cumulative: 2, 4, 6, 8, 10, 12, 14
  - Process Z: 2.0657

Binomial Process Capability Analysis of OOS

Tests performed with unequal sample sizes

- **Proportion**
  - P Chart
  - UCL: 0.002174
  - P: 0.000721
  - LCL: 0

- **Rate of Defectives**
  - Sample Size: 2000, 2500, 3000
  - UCL: 0.3
  - LCL: 0

Summary Stats
- 95.0% confidence
- | % Defective | Lower CI | Upper CI |
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- **Histogram**
  - Sample: 2, 4, 6, 8, 10, 12, 14
  - Frequency: 0, 2, 4, 6, 8
  - Cumulative: 2, 4, 6, 8, 10, 12, 14
  - Process Z: 3.1861

Product Comparison

Lot Reject Rate
- **Lot Reject Rate**
  - Application, License or Master File # - if applicable
  - UCL: 0.05
  - LCL: 0.019

OOS Rate
- **OOS Rate**
  - Application, License or Master File # - if applicable
  - UCL: 0.0007

40% reject rate
Different product rejects vs OOSs
Timeline

Feb, 2013 - FRN
Spring-Winter, 2013 - Various Conferences
Dec, 2013 - White Papers
May, 2014 - Brookings
Categories for “Qualifying” Metrics

• Assess sites

• Assess products

• Assess systems

• Operationalize
  – Efficiency
  – Avoid unintended consequences

• Adequacy for downgrading
Potential Gaps

- Lot acceptance rate
- Product quality complaint rate
- OOS rate
- Recall rate

- Assess sites?
  - Are these relevant for all types of site

- Assess products

- Assess systems?

- Operationalize?
  - Potential for unintended consequences?
  - Efficiency

- Adequate for downgrading?
Ideas?

- Unconfirmed OOS rate?
- Failures on stability?

- Right first time?
- Lot disposition rate or time?
- Yield?
- Number of products made by site?

- Media Fills?
- Environmental monitoring?

- Product type?
- Facility type?
- Establishment size?
- Time since last inspection?
- Inspection history?

- Complementary metrics?
- Balancing metrics?
- Sector specific metrics?
- Some available factors?
Feedback

- Choose the right metrics
  - The consensus metrics and others on the discussion set were broadly supported
    - There is a need to tweak some definitions such as RFT, and address scope issues/questions
  - There may be higher level metrics but start simple
    - A balanced scorecard of metrics, beyond the robustness measures in the consensus set and compliance focus of existing FDA data would be ideal (ie include quality system measures)
  - There was widespread support for high risk vendors also submitting metrics

- Get started, build trust and employ checks and balances
  - Transparency of how metrics will be used
  - Technical engagement
  - There was interest in pilots
    - FDA made clear we supported all pilots and agreed there would be a learning period
    - FDA’s program launch would not be limited to a sub-set population

- Stakeholder debate around how much metrics data should be public
Conclusion

• Received significant input and support from stakeholders

• Progress on identifying potentially useful metrics and path forward

• Continued feedback welcomed
THANK YOU

Are there questions?
GPhA Update

GDUFA Goals
Inactive Ingredients Database (IID)
First Generics
Inspections
Challenges faced by supply chain partners
OGD MOVES TO WHITE OAK

COLLABORATION   COMMUNICATION   COORDINATION
Wrap-Up and Next Steps