FDA CDER Pharmaceutical Quality Metrics Program Panel Discussion

Where Are We Now?

What Does It Mean?

Path Forward: What Should We Do Now?

FDANEWS

FDAnews Inspections Summit
4 – 6 November 2015

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Panel Objectives and Focus

- To provide up-to-date information on the status of the FDA's Metrics Program and related industry initiatives
- To discuss and provide commentary on various aspects of FDA's program and explore impacts of the related industry initiatives
- To provide an opportunity for panel discussion and audience questions & answers about the program

Expert Panelists

Denyse Baker, Senior Advisor, Scientific and Regulatory Affairs, PDA

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Executive Vice President, Global Quality & Compliance
Perrigo
(GPhA Quality Technical Group)

Karthik Iyer,
Acting Branch Chief
Quality Intelligence Branch (QIB)
Office of Surveillance (OS)
Office of Pharmaceutical Quality (OPQ), CDER, FDA

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School of Chemical & Pharmaceutical Sciences
DIT

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Compliance Architects LLC
Moderator

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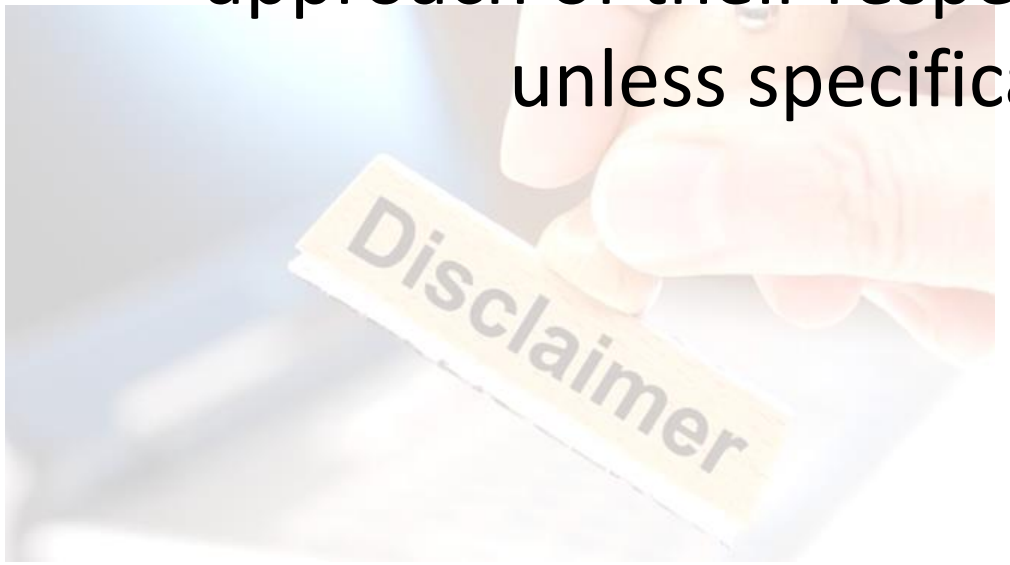

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Panel Discussion Structure

Where Are We Now?

- Brief Presentations
- Brief Panel Structured Q & A / Discussion

What Does It Mean?

- Panel – Structured Q & A / Discussion

Path Forward: What Should We Do Now?

- Panel – Structured Q & A / Discussion
- Open Audience Q & A

Should the Medical Device Folks Leave to Get Some Coffee??

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Part 1:
Where Are We Now?

Jack Garvey
Denyse Baker

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Interested / Involved Parties

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Multiple Industry Organization Metrics Proposals

ISPE

PhRMA

GPhA

PDA

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Our Journey

1980s – Today: Ever Increasing Use of Metrics in Business

2000 - 2005	Quality by Design, 2003	Process Analytical Technology, 2003 - 2005	GMPs for the 21st Century, FDA, 2004	ICH Q9, 2005
2006 - 2010	QS Approach to GMPs, FDA, 2006	ICH Q10, 2008/9	ICH Q8, 2009	
2012	**FDASIA, 2012**	FDA Announces Office of Pharmaceutical Quality		
2013	FDA Proposal and Request for Public Input on Metrics, 2013	PDA Quality Metrics Conference, 2013; PDA Issues Points to Consider	ISPE-FDA Conferences, 2013; ISPE Task Force Created	ISPE Annual Meeting, 2013; ISPE Status Report Issued 12/2013

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Our Journey (Contd.)

2014 to 2015 – Organizational Activity

FDA	December 2014: FDA Announces Consideration of New Inspection Scoring System
	January 2015: Commencement of Office of Pharmaceutical Quality
	June 2015: FDA Offers Grants Funding Quality Metrics Research
	July 2015: Draft Guidance: Request for Quality Metrics
	August 30, 2015: Public Meeting; Comment Period to Close 9/30/15
	September 2015: Comment Period Extended to 11/27/15
ISPE	June 2014: ISPE Phase 1 Metrics Pilot
	October 2014: ISPE Program Update / Metrics Pilot Early Feedback
	December 2014: ISPE Metrics Pilot Wave 1 Complete
	June 2015: ISPE/FDA/PQRI Meeting: ISPE Wave 1 metrics presented
	June 2015: ISPE Phase 2 Metrics Pilot Begins
OTHER	May 2014: Engelberg Center for Health Care Reform at Brookings Meeting
	December 2014: PDA Conference – Focus on Quality Culture Metrics
	September 2015: 2015 PDA/FDA Joint Regulatory Conference

Our Journey (Contd.)

FDASIA Authority for Metrics Program

(From Title VII of the Act: Drug Supply Chain)

Section 705 of FDASIA, *the Food and Drug Administration Safety and Innovation Act* , signed into law on July 9, 2012, requires drug facility inspections be performed
"in accordance with a risk-based schedule established by the Secretary."

Section 706 of FDASIA requires
"records or other information … be provided … in advance or in lieu of an inspection…"

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Highlights of the Last 12 + Months

- FDA Guidance Published
- ISPE Pilot Wave 1 Results
  - Wave 2 Results to be announced soon
- FDA Public Meeting
- Extension of Comment Period
- Regular articles, webinars and conference panels on the topic

PDA Active in Dialogue with FDA on Metrics Program

- Metrics Program for all sites and products will yield the best information. Plan for an assessment period.
  - Are defined metrics predictive and discriminatory ?
  - Are definitions well understood?
  - What unintended consequences have arisen?
- Metric trends are more comparable than absolute results.
- Quality culture matters more than data and it's hard to measure.
  - December 2014 Direct Feedback to FDA about challenges of a culture metric
  - PDA Quality Culture Survey Report Sept/Oct 2015 volume journal.pda.org
  - Assessment Tool for Culture Maturity based on existing models November 2015 Conference

Coming Soon

- Each company should be informed of their own relative risk.

ISPE Key Messages- *Start Small, Learn, Evolve*

- **ISPE supports FDA's effort to implement a Quality Metrics program** in collaboration with industry to meet the intent of:
  - Risk-based inspection scheduling (near term)
  - Potential as early indicator of drug shortage (longer term)
  - Risk-based principles for reduced post-approval manufacturing change (longer term)
- ISPE supports the need for the program to start with a **small, targeted approach**, to enable industry and FDA to learn and evolve the approach over time.
- Recommend a **phased introduction**

- *ISPE is supportive of **starting with 3 of the proposed metrics***
  - *Lot Acceptance Rate (report by site, differentiated by product)*
  - *Product Quality Complaints (report by product only)*
  - *Invalidated OOS (report by site, differentiated by product)*
- *ISPE recommends to **defer as potential future metrics** APR on Time Rate and Optional Metrics*
- *Start with **reporting by site, differentiated by product***
  - *More representative of how industry currently gathering data*
  - *May reduce burden for start up of program*

What About Medical Devices?

- Don't feel left out!

- Joint program being developed by FDA and Xavier Health (2015)
  - Adopted by Medical Device Innovation Consortium (MDIC)
  - *Problem Description:*
    - Lack of harmonized, well-defined, stakeholder-verified (FDA, Industry, Payor) product quality metrics impedes the ability of all stakeholders to continuously and predictively assess evolving confidence in product quality.
  - *Objective:*
    - To convert the top predictive product quality measures identified through the FDA/Xavier Device Quality Measures Initiative into actual metrics that can be implemented, piloted, and validated for potential FDA and broader stakeholder use.
  - *Timing:*
    - Pilot in late 2015 / early 2016
    - June 2016: Results to be reported at MDIC Case for Quality forum
  - What Are the Metrics? Unknown, but "17 measures" are currently being considered that will need to be "converted" into metrics

http://xavierhealth.org/pharma-quality-metrics-initiative

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DISCUSSION:

Where Are We Now?

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Before We Begin…
What *Are* the Proposed FDA Metrics?

DATA TO BE COLLECTED

1. Number of attempted product lots;
2. Number of specification-related rejected product lots, rejected either during or after manufacturing;
3. Number of attempted lots pending disposition for greater than 30 days;
4. Number of out-of-specification product results, including stability testing;
5. Number of product lot release and stability tests conducted;
6. Number of OOS results for product lot release and stability tests that are invalidated because of a lab error;
7. Number of product quality complaints received;
8. Number of lots attempted that are released for distribution or for next stage of manufacturing;
9. Number of product annual product reviews or product quality reviews that were completed within 30 days of their annual due date; and
10. Number of APRs or PQRs required for the product.

FDA-CALCULATED METRICS

1. Lot Acceptance Rate;
2. Product Quality Complaint Rate;
3. Invalidated Out-of-Specification Rate; and
4. Annual Product Review *or* Product Quality Review *On Time Rate.*

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… And a Few Optional Metrics…

Proposed Optional Metrics for Quality Culture & Process Capability / Performance

1. Was each APR / PQR reviewed and approved by the following:
   - the head of the quality unit;
   - the head of the operations unit;
   - both; or
   - neither?

2. What percentage of corrective actions involved re-training of personnel? (i.e., a root cause of the deviation is lack of adequate training.)

3.
   a) A “yes” or “no” value of whether the establishment’s management calculated a process capability or performance index for each critical quality attribute (CQA) as part of that product’s APR or PQR.

   b) A “yes” or “no” value of whether the establishment’s management has a policy of requiring a corrective action or preventive action (CAPA) at some lower process capability or performance index.

      i. If “yes” to the above question – what is the process capability or performance index that triggers a CAPA?

      ii. If “no” to the above question – please do not respond.

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QUESTION(s):

Are there any updates on the topic from information discussed at the FDA / PQRI Meeting in Bethesda on October 5-7?

Is there going to be an Organization "consensus document" and is there any clarity on what that looks like?

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QUESTION(s):

Did FDA go far enough with the Guidance and the metrics proposal?

Why or why not?

QUESTION(s):

Why did FDA make the “Quality Culture & Process Capability/Performance” metrics optional?

Is there something fundamentally different about the “optional” metrics from the ten primary, required data elements?

QUESTION(s):

What are the primary drivers of FDA's Metrics Initiatives?

What is missing in the current regulatory oversight framework that this new initiative is necessary?

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QUESTION(s):

Does industry yet have sufficient understanding about Guidance relative to what FDA expects, and potential risk from fulfilling FDA's requests for information?

If not, what should they know?

QUESTION(s):

Are CDER and CDRH collaborating at all on their respective initiatives??

If not, why not?

Do the FDASIA metrics authority provisions pertain only to pharmaceutical manufacturers?

Part 2:
What Does It Mean?

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QUESTION(s):

Is FDA's Guidance "binding" on Industry?

When FDA requests the information, does the company, by law, have to provide it?

If so, what could the penalties be for non-compliance?

Could a Notice of Refusal be issued for failure to provide requested information?

QUESTION(s):

How might FDA use the provided information?

Could FDA issue a FDA Form 483 based solely on the information provided?

Is this an opportunity or a risk for the industry?

QUESTION(s):

What if a company provides incorrect or inaccurate information?

Do data integrity principles apply to data provided?

Will FDA question *definition differences* from company to company?

QUESTION(s):

Do the optional “Quality Culture & Process Capability/Performance” metrics provide sufficiently meaningful information to potentially “merit a reduction in inspection frequency” as stated in the guidance?

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QUESTION(s):

Are the definitions of data FDA requests sufficiently detailed and unambiguous to provide meaningful data when viewed across multiple companies?

For CMOs, what if site metrics for the site do not align with product metrics reported by the application holders?

QUESTION(s):

Will FDA set action limits or thresholds for the calculated metrics? If so, will they be internal thresholds or available to Industry?

Could thresholds differ from District to District?

Could threshold levels be adjusted based on product or site portfolio risk?

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Part 3:
Path Forward:
What Should We Do Now?

QUESTION(s):

Should a company now have a formal procedure on Quality Metrics Reporting? A Policy? A Standard?

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QUESTION(s):

How should a company prepare for FDA's first request for data?

What form should the submission take?

Who should author and sign the submission?

QUESTION(s):

How should companies with *paper-based* quality systems approach the data gathering and reporting process?

Are there inherent data integrity problems with reporting metrics from paper-based quality systems? If so, how can they be mitigated?

Will computer-based tools need to adhere to 21 CFR Part 11 and principles of computer systems validation?

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Audience Questions

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Comments Close in 23 Days: 27 November 2015

As of 10/21/15, 26 comments submitted.

Agency/Docket Number:
Docket No. FDA-2014-D-2537

Original Federal Register Notice: 80 FR 44973 URL: https://federalregister.gov/a/2015-18448

To submit electronic comments, visit: http://www.regulations.gov and enter docket number.

To submit written comments, mail them to:

Division of Dockets Management (HFA-305)
Food and Drug Administration
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Rockville, MD 20852

All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions:
(CDER) Tara Gooen Bizjak at 301-796-3257 or
(CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 240-402-7800.

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A Closing Thought…

Data provide the promise of certainty. However, in business, certainty is not too dissimilar from a desert oasis; pursuing it typically results in disappointment.

Is There Room for Intuition in the Era of Big Data?
Mark Mallinger, PhD and Matt Stefl
Graziadio Business Review
Graziadio School of Business and Management
Pepperdine University
2015 Volume 18 Issue 2
http://gbr.pepperdine.edu/2015/10/big-data-decision-making/

Detailed Timings

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Detailed Timings

Part 1: Intro & Where Are We Now?

				End Time
Introductions, Disclaimer & Agenda	Jack	5 slides	5 minutes	Slide 7 — 8:50
Where Are We Now: Background	Jack, Nuala, Denyse	9 slides	20 minutes	
Where Are We Now: Discussion	All	8 slides/ 6 questions	20 minutes	Slide 17 — 9:10
		Total Time Part 1:	**45 minutes**	

Part 2: What Does It Mean?

What Does It Mean: Discussion	All	6 questions	20 minutes	Slide 26 — 9:30
		Total Time Part 2:	**20 minutes**	

Part 3: Path Forward / What Should We Do Now? Q&A / Closing Thoughts

Path Forward / What Should We Do?: Discussion	All	3 questions	15 minutes	Slide 33 — 9:50
Audience Question & Answer	All	N/A	10 minutes	Slide 37 — 10:05
Guidance Comments Due Slide / Closing Thoughts	Jack	2 slides	2 minutes	Slide 38 — 10:15
		Total Time Part 2:	**27 minutes**	

Total Projected Time: 1hour, 32 mins

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