The Past, Present and Future of Quality Culture

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Distinguished Fellow
Regulatory Compliance Associates

November 11, 2021

Topics for Discussion

The Past:

- Quality Metrics Journey

The Present:

- Regulations
- Potential Models for Measuring Quality

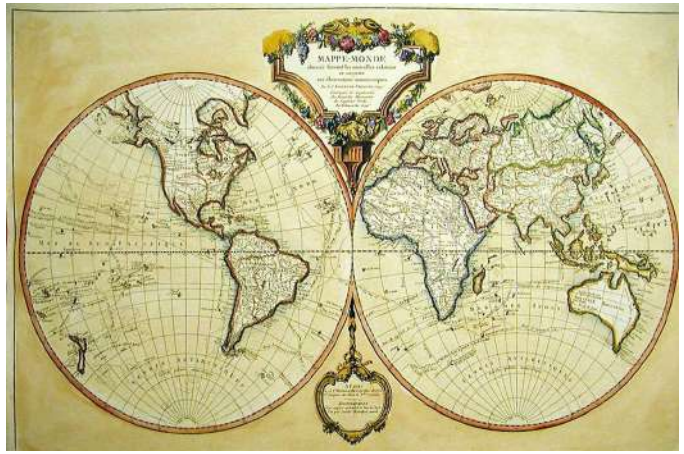
The Future:

- Data Integrity & Quality Culture
- Expectations of Regulators

The Past

"Progress, far from consisting in change, depends on retentiveness. Those who cannot remember the past are condemned to repeat it."

George Santayana (1863—1952)



In the Beginning….

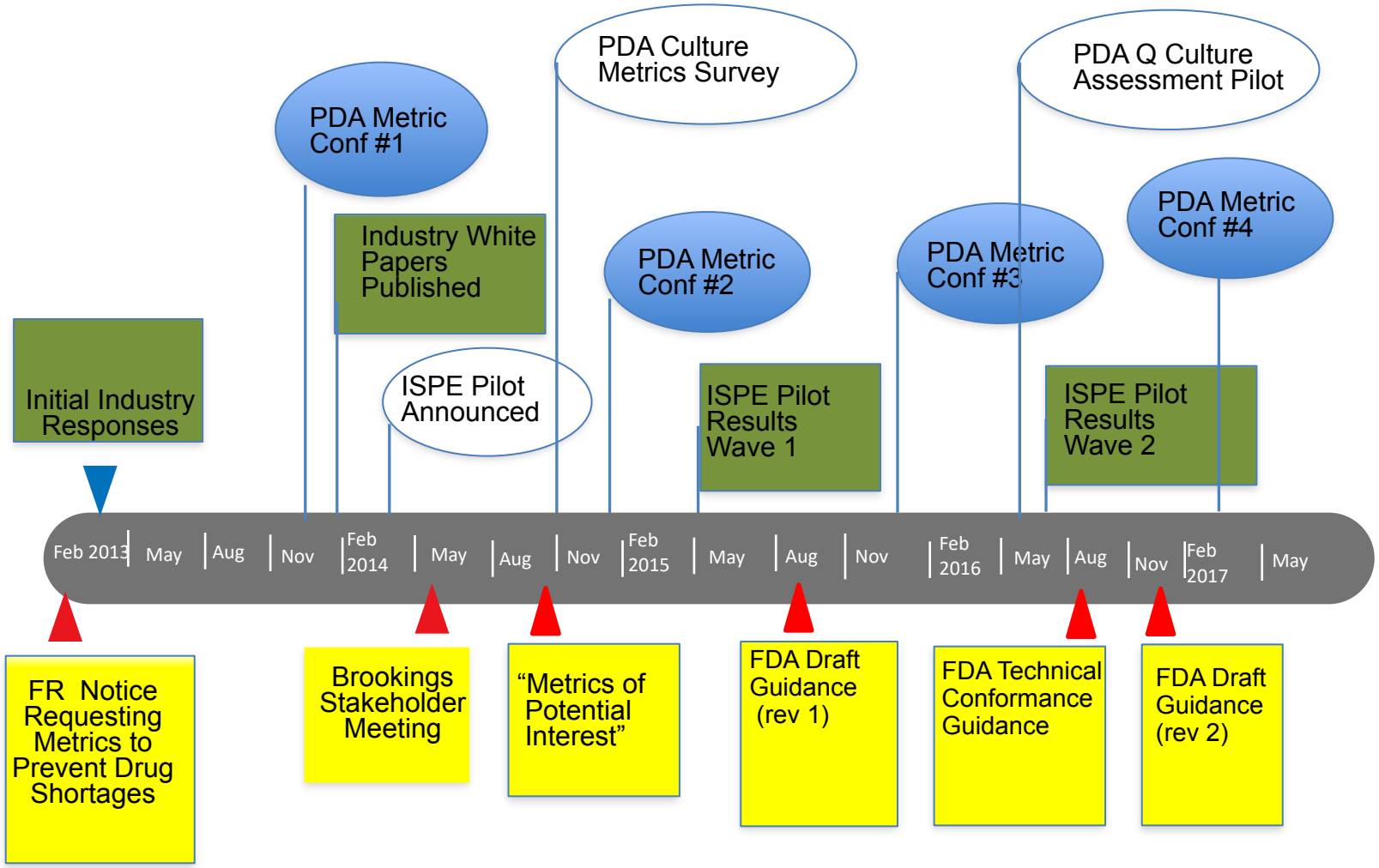
A maximally efficient, agile, flexible, pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight.

Janet Woodcock, FDA, Center for Drug Evaluation and Research October 5,2005

Drug Shortages to Quality Metrics to Quality Culture

- FDAISA (7/12)
  - Title VII, Section 705
    - risk based inspections
- Title VII, Section 706
  - allows for records to be requested in advance or in lieu of inspections
  - Title X, Section 506C-1
    - FDA annual drug shortage report to Congress
- Federal Register 12 Feb 2013
  - Assist in drafting strategic plan on drug shortages

Quality Metrics Journey

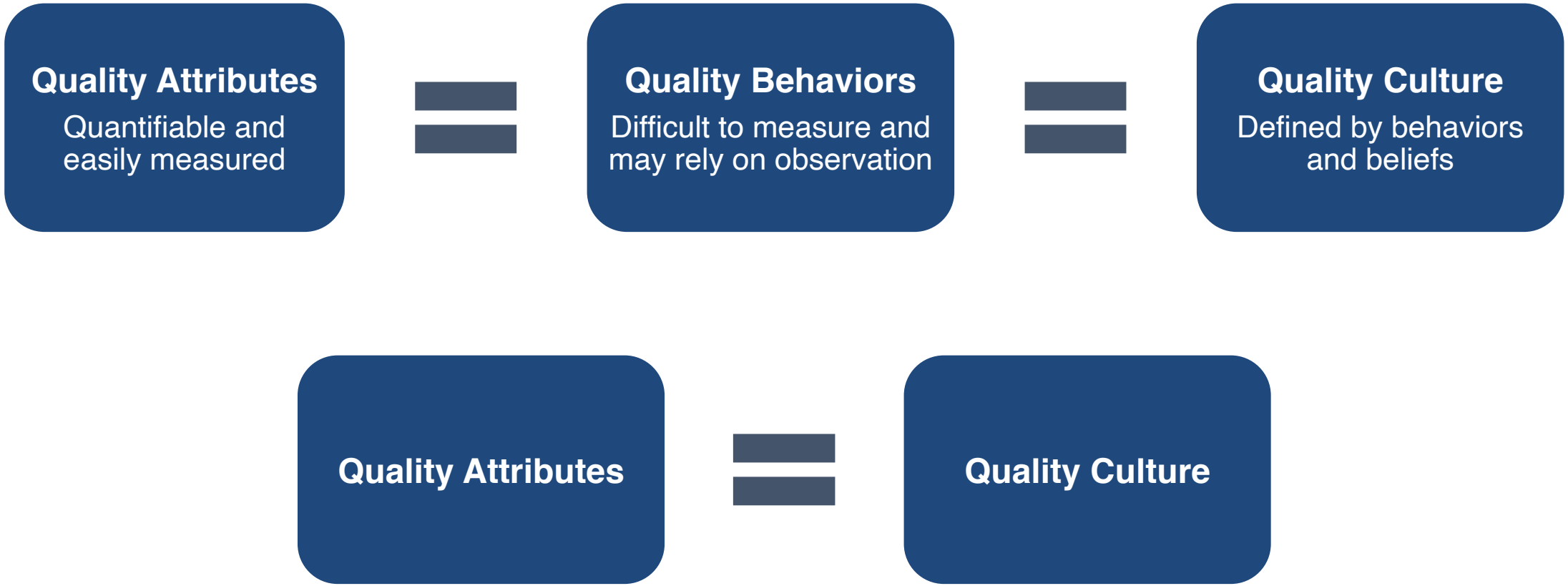


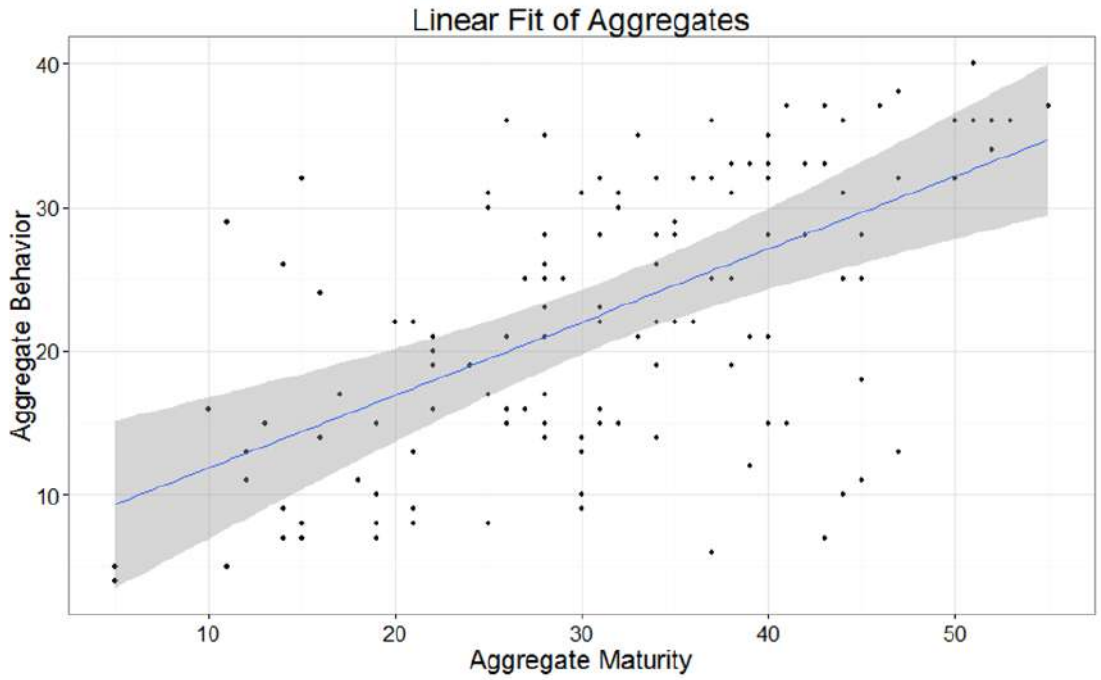
Developing a Standard

Is there a set of Mature Quality Attributes that are a surrogate for Quality Culture Behaviors?

1. Is there a relationship between Quality Culture Behavior scores and Mature Quality Attribute scores?
2. Which Mature Quality Attributes relates to Quality Culture behavior?

The Culture Equation





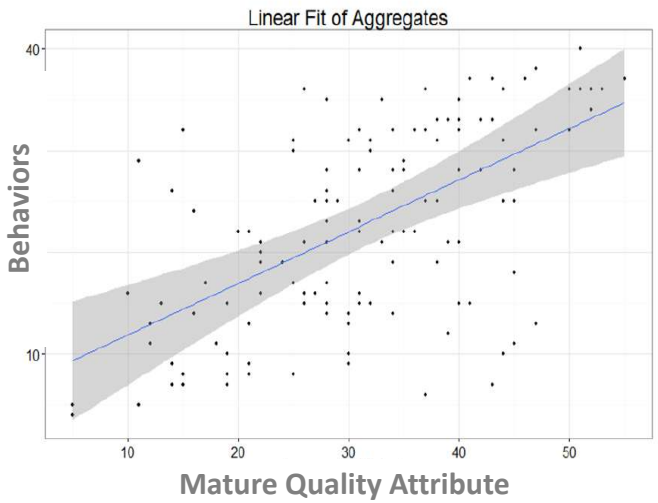
PDA Quality Culture Survey analysis
http://journal.pda.org/content/69/5/631.full.pdf+html?sid=1d68365b-c441-4c68-943f-eb0f39ce084e

- Higher MQA score the higher the behavioral score
- Given this is a Social Science Analysis, this is a strong relationship

Yes! There is a relationship between Quality Culture Behavior and Mature Quality Attribute

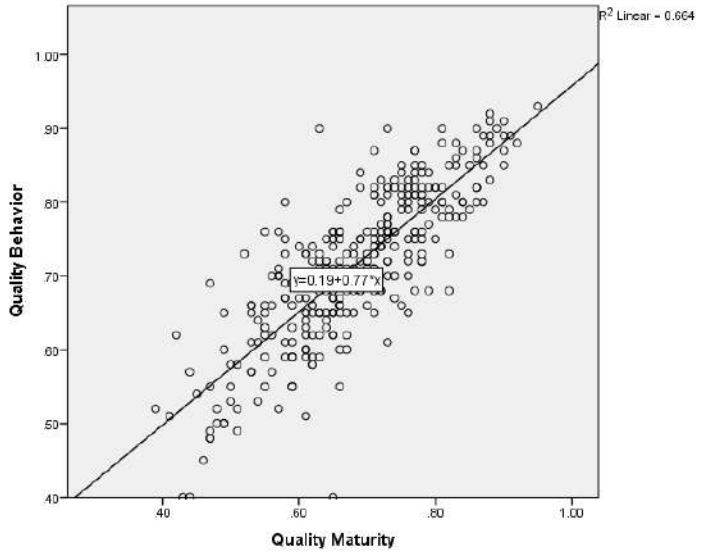
St.Gallen confirms PDA's Quality Culture Survey outcome

PDA Survey Analysis 2014



$R^2 = 0.34$

St.Gallen Analysis 2017



$R^2 = 0.66$

- 326 pharmaceutical sites of different size and focus within St.Gallen database confirm PDA

Dr. Thomas Friedli, Measuring Quality Systems & Quality Culture February 2017

Most Impactful Attributes Identified

1. Participation at conferences to stay current
2. Collecting Error Prevention Metrics
3. Management Communication that Quality is Everyone's Responsibility
4. Utilization of new proven technologies
5. Clear performance criteria for feedback and coaching
6. EH&S Environmental Program with trained staff (risk assessments, emission controls, spill prevention and response)
7. Site has formal quality improvement objectives and targets
8. Quality topics included in at least half of "all hands" meetings
9. Collecting Management Review Metrics
10. Collecting Employee Turn Over Rate Metrics

11. Program to show how employee's specific goals contribute to overall quality goals
12. Program to measure, share and discuss product quality performance and improvement from shop floor to executive management.
13. Continuous Improvement Program / Plans with active support of CEO and Corp Management of QMS
14. Program that establishes quality system maturity model and action plan and tracking to measure progress
15. Internal survey measuring a company/ site quality culture

Voted by ~225 Conference Participants, Dec 2014

The Attributes

PDA Connecting People, Science and Regulation®

PDA Quality Culture Guided Assessment Tool

TABLE OF CONTENTS

The ANSI Standard Development Process

*Re Work -> the document goes back to the technical team/consensus body to re work if:
There are substantive changes;
There are outstanding objections to the approval;
There are less than two thirds of the votes in the affirmative with all members voting.

The Proposal

Title of Proposed Standard:

Quality Culture Assessment Tool

Stakeholder Category being represented:

X **General Interest**

X **Producer Interest members**

X **User Interest members**

X **Regulatory Interest members**

Project Description:

The U.S. FDA continues to focus on the use of quality metrics to modernize pharmaceutical quality systems and advance innovation. In a recently published document, FDA has called for routine assessment and management oversight of quality culture. In addition, MHRA, PIC/S and the WHO have all issued guidance on data integrity that specifically call for companies to address the issue of quality culture. There is currently no agreed-upon standardized way for companies to effectively measure their quality culture. PDA has already designed a comprehensive *Quality Culture Assessment Tool and Training*, designed to guide companies to a better understanding of quality culture, how to assess it, and what actions to take to improve it. The tool helps a company effectively collect verifiable data that will help them to assess their culture at all levels of their organization. The tool allows the company to facilitate positive culture changes and continuous improvement within their organization. This tool will serve as the basis for the development of a consensus standard to guide quality assessment and facilitate benchmarking both within and across organizations.

Project Details

Project Need:

Provide a data driven assessment approach to allow companies to effectively measure quality culture and its importance in providing high quality medicinal products to patients.

Project Intent:

This proposed American National Standard (ANS) is intended to:

- address the challenges associated with establishing and maintaining a quality culture that meets the expectations of the regulators;
- Provide a reasonable and effective way to collect and evaluate quality culture;
- Provide a way for companies to benchmark their culture through data gathered through the use of the tool.

Project Details (cont.')

Scope, Summary or Abstract of Project:
The U.S. FDA continues to focus on the use of quality metrics to modernize pharmaceutical quality systems and advance innovation. In a recently published document, FDA has called for routine assessment and management oversight of quality culture. In addition, MHRA, PIC/S and the WHO have all issued guidance on data integrity that specifically call for companies to address the issue of quality culture.
PDA has designed a comprehensive *Quality Culture Assessment Tool and Training*, designed to guide companies
to a better understanding of quality culture, how to assess it, and what actions to take to improve it.
The tool helps a company effectively collect verifiable data that will help them to assess their culture at all levels of their organization. The tool allows the company to facilitate positive culture changes and continuous improvement within their organization.
The goal is to ensure that a quality mindset and behaviors are embedded into the daily work of the individuals involved in all functions to ultimately ensure the delivery of high-quality product to patients.
The current tool enables companies to collect vital feedback in the following key areas:

- Employee Ownership and Engagement
- Continuous Improvement
- Technical Excellence
- Leadership Commitment
- Communication and Collaboration

PDA (Parenteral Drug Association)
Contact: Christine Alston-Roberts, (301)-656-5900-, roberts@pda.org Bethesda Towers, 4350 East-West Highway, Bethesda, MD 20814
New Standard
BSR/PDA Standard 06-201x, Quality Culture Assessment Tool (new standard)
Stakeholders: Quality assurance, quality control, quality engineering, operations, production, manufacturing, general interest, regulatory interest members.
Project Need: Provide a data-driven assessment approach to allow companies to effectively measure quality culture and its importance in providing high-quality medicinal products to patients.
A comprehensive Quality Culture Assessment Tool and Training, designed to guide companies to a better understanding of quality culture, how to assess it, and what actions to take to improve it. The tool helps a company effectively collect verifiable data that will help them to assess their culture at all levels of their organization. The tool allows the company to facilitate positive culture changes and continuous improvement within their organization.

PDA® Standards Development: Call for Volunteers:

Standard 06-201x, Quality Culture Assessment Tool (new standard).

PDA is very pleased to announce the launch of the Parenteral Drug Association's sixth standard! We are seeking volunteer participants to assist in developing, writing, and fine tuning the following proposal:

Standard 06-201x, Quality Culture Assessment Tool (new standard).
A comprehensive Quality Culture Assessment Tool and Training, designed to guide companies to a better understanding of quality culture, how to assess it, and what actions to take to improve it. The tool helps a company effectively collect verifiable data that will help them to assess their culture at all levels of their organization. The tool allows the company to facilitate positive culture changes and continuous improvement within their organization.

This proposed American National Standard (ANS) was presented by Susan Schniepp, Distinguished Fellow with Regulatory Compliance Associates.

Those individuals involved in Quality Assurance, Quality Control, Quality Engineering, Operations, Production, and Manufacturing, Regulatory, and General Interest are needed.

Nominations/Volunteers to serve as a member of the technical team (consensus body) must have some subject matter expertise, and willing to help write/contribute to this standard. Applicants should apply by contacting the PDA Standards Manager at standards@pda.org.

The deadline to submit notification of interest in serving on the consensus body is **January 14, 2020.**

Why is Culture Important

Data Integrity and Quality Culture: Regulatory Expectations

PIC/S: Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments

- 6.3 Quality Culture
  - Management should aim to create a work environment (i.e. quality culture) that is transparent and open, one in which personnel are encouraged to freely communicate failures and mistakes. Organisational reporting structure should permit the information flow between personnel at all levels.

Data Integrity and Quality Culture: Regulatory Expectations (cont.')

MHRA 'GXP' Data Integrity Guidance and Definitions

3. The principles of data integrity

3.1 The organisation needs to take responsibility for the systems used and the data they generate. The organisational culture should ensure data is complete, consistent and accurate in all its forms, i.e. paper and electronic.

3.3 The impact of organisational culture, the behaviour driven by performance indicators, objectives and senior management behaviour on the success of data governance measures should not be underestimated. The data governance policy (or equivalent) should be endorsed at the highest levels of the organisation.

Data Integrity and Quality Culture: Regulatory Expectations (cont.')

World Health Organization: Guidance on good data and record management practices

1. Introduction

1.4 Examples of controls that may require development and strengthening to ensure good data management strategies include, but are not limited to:

- adoption of a quality culture within the company that encourages personnel to be transparent about failures so that management has an accurate understanding of risks and can then provide the necessary resources to achieve expectations and meet data quality standards:

Data Integrity and Quality Culture: Regulatory Expectations (cont.')

World Health Organization: Guidance on good data and record management practices

4. Principles

4.7 **Quality culture.** Management, with the support of the quality unit, should establish and maintain a working environment that minimizes the risk of non-compliant records and erroneous records and data. An essential element of the quality culture is the transparent and open reporting of deviations, errors, omissions and aberrant results at all levels of the organization, irrespective of hierarchy. Steps should be taken to prevent, and to detect and correct weaknesses in systems and procedures that may lead to data errors so as to continually improve the robustness of scientific decision-making within the organization. Senior management should actively discourage any management practices that might reasonably be expected to inhibit the active and complete reporting of such issues, for example, hierarchical constraints and blame cultures.

Data Integrity and Quality Culture: Regulatory Expectations (cont.')

Data Integrity and Compliance With Drug CGMP
Questions and Answers
Guidance for Industry

Meaningful and effective strategies should consider the design, operation, and monitoring of systems and controls based on risk to patient, process, and product. Management's involvement in and influence on these strategies is essential in preventing and correcting conditions that can lead to data integrity problems. It is the role of management with executive responsibility to create a quality culture where employees understand that data integrity is an organizational core value and employees are encouraged to identify and promptly report data integrity issues. In the absence of management support of a quality culture, quality systems can break down and lead to CGMP noncompliance.

Available Information

MHRA GMP Data Integrity Definitions and Guidance for Industry (March 2015)

MHRA: A GxP Data Integrity Definitions and Guidance for Industry Draft version for consultation (July 2016)

FDA Data Integrity and Compliance With CGMP Guidance for Industry Draft Guidance (April 2016)

WHO: Annex 5, Guidance on good data and record management practices (June 2016)

Draft PIC/S Guidance: Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments (August 2016)

Parenteral Drug Association (PDA): Elements of a Code of Conduct for Data Integrity
(2015 – Free on PDA Website)

FDA: Data Integrity and Compliance with Drug CGMP: Questions and Answers, Guidance for Industry (December 2018)

Over 100 regulators from MHRA and USFDA have been trained on PDA's Culture Assessment Tool

Regulator Responses

"[We] can apply the Quality Culture Attributes to improve how we assess firms in non-compliance context"

"As industry becomes aware and comfortable with this tool… it can be a powerful tool for evaluating CMOs and business partners."

"Industry can use the PDA tool as part of internal/self-assessment for improvement of Quality Systems."

"Industry could use the PDA tool to be more open with regulators on quality culture."

"I will consider quality culture when reviewing data from industry."

"Nice to differentiate quality Culture from Quality Systems and emphasize the importance of what we make relative to what we do."

"This course does help identify quality culture issues in a company. This may help [us] to evaluate the quality of a pharmaceutical company."

4.3.3. New Inspection Protocol Project

Inspections have traditionally focused on facility compliance with current good manufacturing practices (CGMPs), with particular attention to process deviations and system failures. Such inspections have not been a reliable predictor of the state of product quality. Consequently, FDA is working to develop a new inspection and reporting paradigm to better assess and record the state of quality in manufacturing facilities; this new paradigm is embodied within an initiative referred to as the new inspection protocol project (NIPP). NIPP is expected to provide a more quality-focused, semi- quantitative approach with streamlined and structured inspection reports. The NIPP protocols utilize expert investigator questions and assessment approaches. NIPP is expected to increase the quality focus of investigator assessments, so that facilities and behaviors found to exceed basic compliance can be recognized as such. Following successful piloting, NIPP-developed protocols will be incorporated into new mobile technology to capture investigator findings and assessments and better support investigators while traveling and during facility inspections.

White Paper: FDA Pharmaceutical Quality Oversight - One Quality Voice

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
19701 Fairchild Irvine, CA 92612-2445 (949)608-2900 Fax:(949)608-4417	7/24/2019-8/2/2019*
	FEI NUMBER 3014617030

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Mark P. Roache, Senior Vice President and Chief Quality Officer

FIRM NAME	STREET ADDRESS
AveXis, Inc.	10210 Campus Point Dr Ste 300
CITY, STATE, ZIP CODE, COUNTRY San Diego, CA 92121-1522	TYPE ESTABLISHMENT INSPECTED Control Testing Lab

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

A. Non-conformance Report NCR-1922 (which was open at the time of the current inspection) was opened on 15 May 2019 due to a report that was made to the CQO (Chief Quality Officer) alleging that data derived from the AVXS-101 In-Vivo Relative Potency Assay Studies 1-10 may have been mismanaged or even potentially manipulated. Aside from evaluations of Studies 1-10 and a planned evaluation of toxicological studies under NCR-2018 there is no documentation in this NCR that an audit of all other potentially impacted data, studies, and reports was conducted or is planned to determine if there was evidence of data mismanagement or manipulation or a justification for not conducting or planning such an audit. Additionally, there is no documentation in NCR-1922 as to why the NCR was not opened until 15 May 2019 when the initial allegation is documented as having been reported on 14 March 2019.

B. Non-conformance Report NCR-409 was opened on 31 Jan 2018 and has an "Event Description" of "On 31Jan2018, during a historical data review of the potency results for Drug Product Lot 600156 per SOP-285, Determination of In Vivo Relative Potency for AVXS-101 Drug Product, it was discovered that the associated assay form (FORM-212) was not completed at the time of CoA generation and approval for Lot 600156…" During the inspection, the associated FORM-212 was reviewed and it was observed that the date/time stamps on the 4 page form are discrepant in that 3 of the 4 pages have a "Generated" date/time of "05 Jan 2018 09:44AM" and 1 page (page 2) has a "Generated" date/time of "04 Jan 2018 09:39AM". There is no documentation in NCR-409 that this discrepancy was noticed or investigated. Additionally, current SOP-381 Version 2.0 entitled "Control of QC Test Forms" does not specifically require verification of consistent date/time stamps on each page of a test form during reconciliation of the form.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Scott T Ballard, Investigator Mihaly S Ligmond, Investigator - Team Biologics X	8/2/2019

FORM FDA 483 (09/08) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 1 of 4 PAGES

August 23, 2019

Via Electronic Mail
Confidential

Office of Regulatory Affairs
Office of Biological Products Operations (OBPO)
US Food and Drug Administration
orabioinspectionalcorrespondence@fda.hhs.gov

Re: AveXis, Inc.'s Initial Response to the Form FDA 483
Issued on August 2, 2019 to the San Diego, CA Quality Control Laboratory
FEI: 3014617030
Investigators: Scott T. Ballard and Mihaly S. Ligmond

Dear Sir or Madam:

Enclosed please find AveXis, Inc.'s (AveXis or the company) initial response to the Form FDA 483 (483) issued at the conclusion of FDA's July 24 – August 2, 2019 inspection (the July/August 2019 Inspection) of the company's quality control laboratory located in San Diego, California (FEI: 3014617030).

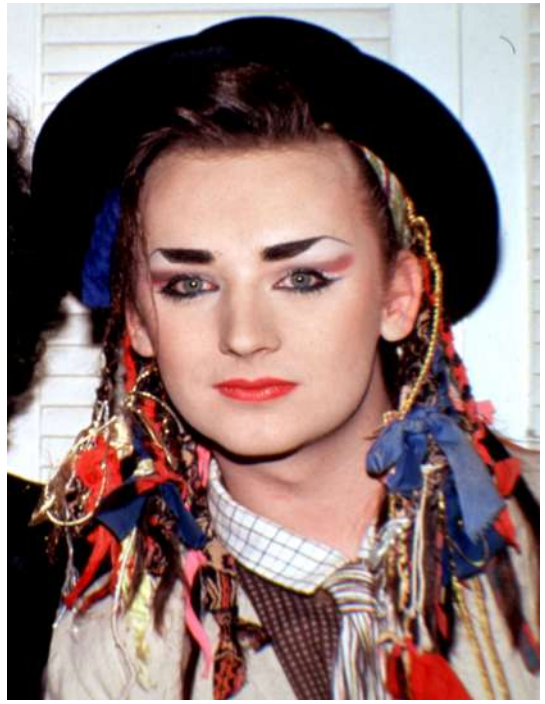
As FDA is aware, the July/August 2019 Inspection followed AveXis's June 28, 2019 self-reporting to the agency of data manipulation issues involving a mouse potency assay—known as the *in vivo* relative potency assay (IVRPA)—used as a product release test during the early clinical phase of Zolgensma® (onasemnogene abeparvovec-xioi).[1] Specifically, it was alleged that two AveXis senior executives altered or instructed others to alter a small amount of raw data used to run the IVRPA. Such conduct is unacceptable, and the two AveXis senior executives have been terminated.

[1] Zolgensma®, Biologics License Application (BLA), STN 125694, is the first gene therapy approved to treat children less than two years of age with spinal muscular atrophy (SMA), the most severe form of SMA and the leading genetic cause of infant mortality.

AveXis takes the feedback contained in the 483 seriously and is committed to comprehensively addressing the noted observations. The company's goal moving forward is to ensure a robust culture of quality and sustainable GxP compliance across AveXis. In light of the data integrity issues mentioned above, and the 483, AveXis, with significant input and oversight from the Novartis Group of companies (Novartis), has developed-and is in the process of implementing-a company-wide Compliance Action Plan (the CAP). As detailed in **Section** II **(pp.** 10-20) of the enclosed response, the core elements of the CAP are (A) the Quality Integration Plan and (B) the Data Integrity Remediation Plan.

Final Thought:

“Quality is always fashionable.”



Boy George (George Alan O’Dowd), Lead Singer of Culture Club
1961 - present