While this document was created as an outcome of the 2014 FDA/Xavier University PharmaLink Conference, its content remains relevant to the on-going metrics work and new FDA inspection protocol discussed during the 2015 FDA/Xavier Univerisity PharmaLink Conference.

FDA/Industry Collaborative Approach to Quality: With the Patient in Mind

A proposal submitted by Xavier University for FDA and Industry consideration

Based upon presentations and dialogue during the FDA/Xavier University PharmaLink Conference March 19-21, 2014

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Executive Summary

During the FDA/Xavier University PharmaLink conference[1], Russ Wesdyk (Scientific Coordinator, CDER, Office of Pharmaceutical Science) presented "FDA/CDER's Evolving Approach to Quality and the Use of Metrics". The goal of this initiative from the perspective of FDA is for industry to achieve and be rewarded for quality results, without extensive regulatory oversight. This outcome would be incorporated into FDA's work on: (1) identifying predictors for drug shortage vulnerability; (2) establishing a site inspection schedule based on risk ranking; and (3) developing an enhanced inspection paradigm.

The 4-step Xavier University proposal presented herein builds upon the premise of the 2004 Risk Based Inspection Program established by FDA,[2] but focuses more heavily on the clinical relevance of the impact to the patient. The Xavier proposal then goes beyond the 2004 program by outlining not only an enhanced inspection paradigm but also an impactful reporting of inspection findings that will prove to be a useful tool for FDA and industry alike. Importantly, this proposal takes into consideration the limited resources of FDA, as well as the desire by industry to level the playing field with their un- and under-regulated competitors, all while remaining focused on the needs of the patient.

Introduction

Xavier University proposes that the FDA inspection frequency program be based on Total Patient Risk, which is comprised of a combination of Inherent Patient Risk factors and Quality Patient Risk factors as depicted in Figure 1. The Inherent Patient Risk factors include clinically relevant product impact to the patient, process impact to the patient, and facility complexity that could result in impact to the patient. Quality Patient Risk factors are considered controllable and include data already in the hands of FDA that can be assessed quickly and objectively (such as inspection history and geographical location) matched with industry self-reporting data provided to FDA through the CDER Quality Metrics Initiative.

[1] FDA/Xavier University PharmaLink Annual Conference: Leadership in a Global Supply Chain. March 18-21, 2014. www.XavierPharmaLink.com.

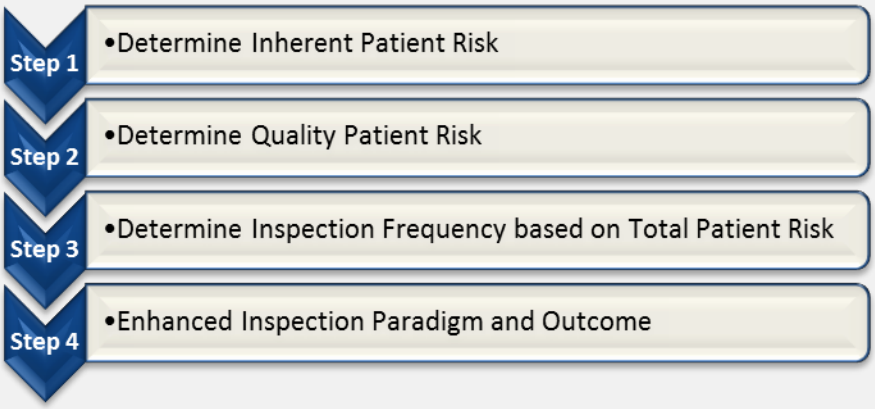
[2] "Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites — A Pilot Risk Ranking Model." September 2004.

Figure 1. Determination of Total Patient Risk

Ultimately, the Total Patient Risk has to be put into context through an enhanced inspection program that focuses inspection activities on determining the strength of the corporate quality culture surrounding the most clinically critical products and processes at the facility being inspected. A proposal on how this enhanced inspection approach can be accomplished is provided herein.

As a result of the enhanced inspection program, Xavier University proposes that the inspectional outcome include a risk reporting of inspectional findings based on a combination of Quality System Strength and Clinical Relevance to give an ultimate rating of Total Patient Impact. This type of inspectional outcome approach would then become a useful tool for industry and regulators alike.

Figure 2. Steps involved in the Xavier Proposal



The 4-step Xavier Proposal, as depicted in Figure 2, will be discussed herein. Together, industry and regulators should ensure all activities are commensurate with impact to the patient.

It should be noted that the Xavier proposal highlights the importance of collaboration between industry and regulators in order to increase trust, and therefore, increase the likelihood of success. A lack of trust is often borne out of avoidable misalignment. It is known that three major reasons for misalignment are: (1) "data": the parties are working from a different set of data and don't realize it; (2) "definition": the parties have different interpretations of the same words and don't realize it; (3) "drivers": the parties have different drivers which are influencing the direction of the outcome.[3] Collaboration does not require total alignment, which is often not achievable in any relationship. Instead, collaboration is strengthened by alignment where possible and an understanding of where and why misalignment exists. Collaboration that minimizes avoidable misalignment is recommended throughout this proposal, which again, increases the chance for successful impact of this program.

Step 1: Determination of Inherent Patient Risk

FDA has already developed a risk ranking methodology that includes an assessment of facilities based on products manufactured at that facility, processes employed at that facility, and facility type.[4] One clear outcome of this methodology is wide recognition that FDA does and should consider a sterile product, process and facility to be of higher risk than a non-sterile product, process and facility. This methodology has been the foundation for determining inspection frequency based on risk, and has offered a great avenue for FDA to begin to triage its resources.

Now that the initial FDA risk ranking methodology has been established and implemented with success, Xavier proposes that the timing is right for an enhancement to the existing program through collaborative discussions with industry. The product, process and facility risk being assessed in this step is referred to as "inherent" based on the following rationale:

- The clinical relevance of the products manufactured at the facility either are or are not inherently of higher risk based on the clinical need of the product to sustain patient life. The risk decreases as the product becomes necessary to sustain patient comfort, and then finally to treat non-life threatening symptoms.
- The need for compliance to any of the manufacturing processes at the facility either is or is not inherently of higher risk to patient life. The level of need drives commensurate

[3] Based on the research of Nobel laureate, Thomas C. Schelling, http://www.schellingpoint.com/ao-pedia/

[4] "Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites — A Pilot Risk Ranking Model." September 2004.

activities to determine the robustness of studies supporting the critical process parameters (CPPs). Clearly, a breach of sterility can have high risk to patient life.

- The complexity of the facility either is or is not inherently of higher risk of impact to the patient. Complexity is viewed in light of the inherent impact the facility can have on the product, which could then impact patient life. One clear example is potential cross-contamination of a penicillin-based product in non-penicillin based products.

How the "facility" factor is assessed in this proposal is a different approach from the 2004 Pilot Program, in that it focuses on the complexity of the facility which increases the risk of contamination or error. Questions for the scorecard could therefore include the number of products manufactured, volume of products manufactured, types of products manufactured (non-sterile, sterile, vaccine, biologics, penicillin based, etc.), % of dedicated equipment per number of products and then specifically for the highest risk products, etc. The inspection history types of questions are included in the Quality Patient Risk factor determination since it is not viewed as inherent, but rather, controllable.

Each inherent risk to the patient from product, process and facility impact can be determined based on predefined criteria established collaboratively between industry and regulators. Since facilities often involve manufacturing operations for multiple products, it is suggested that the highest risk product based on clinical relevance and highest risk process based on potential impact to the patient be used for the risk ranking exercise. Figure 3 offers a view of the outcome of this exercise, where "Low", "Medium" and "High" for each inherent risk would have a list of factors to assess in order to determine the appropriate ranking. A collaborative exercise between industry and FDA would result in the most robust and relevant list of factors to include. This is an additional distinction from the approach used in 2004 in that previously, only FDA officials were involved in establishing the risk ranking program.

Figure 3. Determination of Inherent Patient Risk Score

Example of Inherent Patient Risk Determination			
Risk of Patient Impact	Clinical Relevance of Product	Relevance of Process Compliance	Facility Complexity
Low			L
Medium	M		
High		H	

Example of how the Overall Inherent Patient Risk Score can be determined:

- Low: no medium or high scores in grid
- Medium: at least one medium and no high scores in grid
- High: automatic whenever there is any high score in grid

Overall Inherent Patient Risk Score of Example above, would therefore = **High**

The overall Inherent Patient Risk factor would then be used in determination of Total Patient Risk described in Step 3 of this proposal.

Step 2: Determination of Quality Patient Risk

In addition to known inherent risks to the patient based on product, process and facility factors discussed in Step 1, there are numerous risks to the patient induced by quality factors. It is important to contextualize quality factors with impact to the patient, which is the basis for the "Quality Patient Risk" concept presented in this proposal. Quality Patient Risk factors can be identified and scored from two main sources:

1. Data already in the hands of FDA that can be assessed quickly and objectively, such as inspection history and geographical location.
2. Data to be provided to FDA from industry through the self-reporting CDER Quality Metrics Initiative.

A scoring matrix of quality risk factors for each of the two sources noted above will be demonstrated within this section. The final score will provide the overall Quality Patient Risk factor to be used in combination with the Inherent Patient Risk factor from Step 1 to determine

the Total Patient Risk discussed in Step 3. At this point, examples of quality risk factors to assess from each of the two main sources noted above will be explored in turn.

A. Data in FDA Possession

FDA has a plethora of data in its possession that provide insight to the risk level of product, process and facility based on quality factors. It is recommended for this proposal, however, that FDA consider data that can be assessed quickly and objectively, while verifying and contextualizing on inspection (as discussed in Step 4). By setting up a score card with clear criteria and measures, FDA can maximize the review of important indicators with minimal FDA resources. As noted throughout this proposal, Xavier recommends industry and FDA work together to identify the most impactful information to include in this scorecard.

Figure 4. Example Scorecard of Quality Risk factors in FDA Possession.

Quality Risk Factors	Low Risk (1)	Medium Risk (2)	High Risk (3)
1. Has the facility been inspected by FDA? (Yes = 1 and skip to Step 3, No = Step 2)	1		
2. Has the facility been inspected by recognized foreign regulatory authority (Yes = 2, No = 3)			
3. Inspection history outcome: (OAI= 3, VAI = 2, NAI = 1). List "3" if never inspected by FDA.			3
4. Number of years since OAI (0-3 = 3, 4-7 = 2, 8+ = 3). Leave blank if no OAI. List "3" if never inspected by FDA.		2	
5. Facility ever under consent decree? (Yes = 3, No = 1). List "3" if never inspected by FDA.			3
6. Number of years since coming out of consent decree (0-3 = 3, 4-7 = 2, 8+ = 3). Leave blank if never under consent decree. List "1" if never inspected by FDA.	1		
7. Is the company headquarters, mfg operations, or CMO located in un- or under-regulated regions of the world? (No = 1; Yes = 3 (unless verification of systems by inspection, then 2)	1		
8. Has the company, its contract manufacturers, or API manufacturers ever delayed, denied or limited FDA inspection? (Yes = 3; No = leave blank)			3
Sub-Score	3	2	9
Total Score (range = 3 – 19)		14	

Importantly, the examples of data that could be assessed by FDA in Figure 4 are objective and do not require contextual information to understand the validity of potential patient impact. The total score from the Quality Risk factors scorecard based on the data already in the possession of FDA will be combined with the total score from the Quality Risk factors scorecard based on data submitted by industry to FDA (discussed in Section B below).

B. Industry Self-Reporting Program

Congress has given FDA authority through the FDA Safety and Innovation Act of 2012 to request information from industry prior to an inspection. Through the CDER Quality Metrics initiative, FDA would like to request data and information that could feed into the determination of risk ranking for inspection frequency purposes. FDA has been considering stakeholder input on product and process specific metrics; however, to date, the metrics recommended require intensive contextual information to understand the relevance to potential patient impact. Appendix I explores the limitations of a few of the examples under consideration.

It is important to note as Wesdyk conveyed to the PharmaLink delegates that "industry has ultimate responsibility for the product it manufacturers". Therefore, industry needs to monitor the product, process, and facility data complexity and trends along with business tolerance against impact to the patient. In order for industry to take "ultimate responsibility for the product it manufacturers", each organization has to accept this responsibility and surround the responsibility with a strong commitment to a corporate quality culture. The result of having FDA perform granular monitoring of product and process metrics would signal to industry that FDA is responsible for this activity, rather than industry, which is certainly a shift in the wrong direction.

Xavier University recommends that quality risk factors that signal the strength of the corporate quality culture be submitted by industry to FDA through the self-reporting program.

Why focus on data and information that will assess the strength of the corporate quality culture instead of product, process or facility specific metrics? First of all, a strong corporate quality culture enables an organization to properly prevent and/or address the failures CDER desires to eradicate, including but not limited to drug shortage. Consider how each of the following examples would be avoided in organizations with a strong corporate

quality culture: poor product development; poor linkage of product and process risks to clinically relevant outcomes; poor understanding of critical process parameters that affect critical quality attributes; poor understanding of critical quality attributes; poor development of specifications for incoming materials, in-process controls and finished product; poor selection of supply chain partners; lack of drive and curiosity to identify root cause for unplanned events/failures; ineffective corrective and preventative actions; lack of commitment to implement corrective actions; inability to sustain preventative practices; inconsistent documentation practices; ineffective quality system controls; lack of reporting field alerts; lack of completion of annual reports; product recall avoidance…and the list goes on. (Appendix II provides quotes from industry executives and FDA officials attesting to the importance of corporate quality culture).

Secondly, recognizing FDA resources are limited, the submission of detailed product and process metrics that require intensive contextual information would likely not be possible for FDA to review. Furthermore, since the selection of product and process metrics would be the result of industry agreement to the lowest common denominator metrics, the metrics would offer little risk-related insight. And finally, using product and process metrics afford the opportunity for "gaming" to make the numbers look better than they really are. (Appendix III provides responses to questions asked of the PharmaLink delegates regarding concerns they had for potential use of the metrics discussed to assess the quality mindset of their companies).

What objective, meaningful information related to corporate quality culture could be reported? Figure 5 provides an example scorecard of data that could be submitted to FDA to provide indicators related to corporate quality culture – the level of senior management oversight, involvement and governance of corporate quality. Figure 5 is provided as an example of the types of data that could be submitted, however, it is recommended that FDA and industry work together to finalize the list. It should be noted that there is considerably more information and data that could be submitted, but the detail and rigor of review and contextual information required would be better suited for review upon inspection. Step 4 of this proposal recommends the linkage of inspectional activity with Inherent Patient Risk and Quality Patient Risk, which therefore, includes verification of the self-reported data provided by industry in Figure 5. It is important to note again that through FDASIA, FDA has the authority to request this information in advance of inspection.

As noted above in Section A, the total score from the Quality Risk factors scorecard based on the data already in the possession of FDA (Figure 4) needs to be combined with the total score from the Quality Risk factors scorecard based on data submitted by industry to FDA (Figure 5).

Figure 5. Example Scorecard of Quality Risk factors Submitted by Industry to FDA

Quality Risk Factors	Low Risk (1)	Medium Risk (2)	High Risk (3)
1. Frequency of Quality Management Review meetings (at least annually = 1, less than annually = 2, none = 3)	1		
2. Is there cross-functional representation of senior management at each Quality Management Review meeting? (Yes = 1, No = 2)		2	
3. Are actions resulting from the Quality Management Review meeting included in the CAPA system? (Yes = 1, No = 3)			3
4. % of Annual Product Reviews conducted on-time (90-100% = 1; 80-89% = 2; >80% = 3)		2	
5. Is a year-to-year comparison of annual product review data conducted? (Yes = 1, No = 2)	1		
6. % on-time of completion of preventative maintenance work (90-100% = 1; 80-89% = 2; >80% = 3)		2	
7. % on-time of employee training (90-100% = 1; 80-89% = 2; >80% = 3)	1		
8. Number of Prior-Approval Supplements submitted to address quality failures in the past 5 years (0-1 = 1; 2-4 = 2, 5+ - 3)		2	
9. Significant change in Executive Management, such as CEO, or CEO + Vice Presidents)? (Yes = 2, No = 1)	1		
10. Increasing trend of unexpected adverse events (based on product or process failures = 3, based on new product introduction = 2, all other = 1; no trend = leave blank)			3
11. FDA officials found on inspection that Field Alert reports were not submitted that should have been submitted. (Yes = 3, No inspection = 3, No = 1)	1		
12. Company initiated recalls due to quality system failures. (Yes = 3, No = leave blank)			3
Sub-Score	5	8	9
Total Score (range = 10 – 33)		22	

A simple model can be employed, but needs to be finalized with FDA and industry involvement. As noted in Section A, the range of scores from Figure 4 is 3 – 19, whereas the range of scores from Figure 5 is 10 – 33. Therefore, the range of scores for the Total Quality Patient Risk is 13 – 52. A risk score based on risk tolerance can be established, such as:

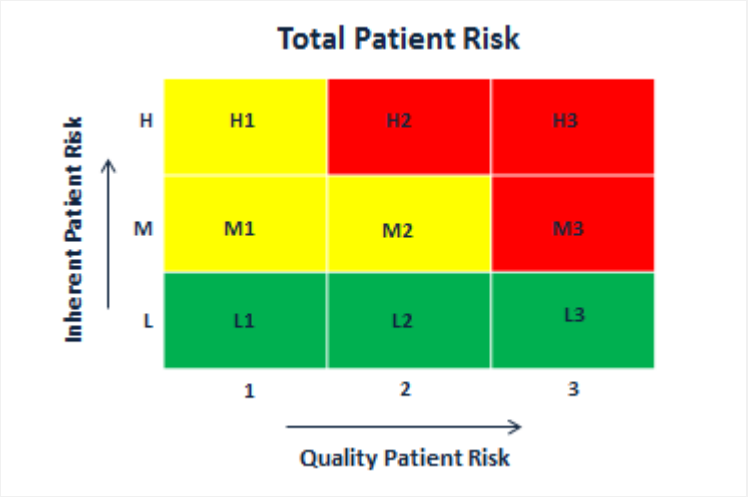
- Combined score of 40 – 52 = Risk Level 3 (Highest Risk)
- Combined score of 23 – 39 = Risk Level 2 (Medium Risk)
- Combined score of 13 – 22 = Risk Level 1 (Lowest Risk)

Based on the example data used in Figures 4 and 5, the Quality Patient Risk would be 14 + 22 = 36, which results in a risk ranking of "2".

Step 3: Inspection Frequency Based on Total Patient Risk

Xavier University proposes that inspection frequency be based on a combination of Inherent Patient Risk (which includes clinical relevance of the product, process and facility impact to the patient), and Quality Patient Risk (which includes data already in the hands of FDA and data submitted to FDA by industry). The risk grid shown in Figure 6 provides a visual for how the two sources of risk can be combined to determine Total Patient Risk. An associated predetermined inspection frequency would be developed for each of the boxes in the 9-box Total Patient Risk grid.

Figure 6. Total Patient Risk grid.



The example data provided within this proposal thus far would result in a ranking of "H2" since the Inherent Patient Risk was concluded to be "H" in Figure 3, and the Quality Patient Risk was found to be "2" as a result of the combination of Figures 4 and 5. Again, a simple model incorporating risk tolerance would need to be developed, as shown in Figure 7.

Figure 7. Inspection Frequency Determination based on Patient Risk

Risk Grid Color	Inspection Frequency
High	ASAP + annually
Medium	every 2 years
Low	2-5 years

Importantly, all of the information that feeds into the Total Patient Risk factor is dynamic and needs to be reassessed on a predetermined frequency, where annually is suggested, and certainly after each new inspection.

Step 4: Enhanced Inspection Paradigm and Outcome

Ultimately, the Total Patient Risk has to be put into context through an enhanced inspection program that focuses inspection activities on the products at the facility in question that have the greatest risk of patient impact combined with verification of the quality system strength supporting the success of these products.

In addition to the self-reported data discussed in Step 2, prior to inspection FDA needs to determine which products manufactured at the facility in question have the highest clinically relevant risk. Whether determined internally by FDA or through a report submitted by the facility in question, FDA can then focus on the products of the highest clinically relevant risk. Once this product-type risk is determined, FDA can ask for the associated annual product review upon initiation of the inspection – and in fact, based on the authority given FDA through the FDA Safety and Innovation Act, FDA can request these annual product reviews in advance in order to begin the assessment, confer with CDER, and plan the inspection based on the

information. It is recommended that FDA start with the annual product review of the highest risk product so FDA can then delve deep into the quality systems while assessing the impact of any findings to the clinical relevance of that highest risk product. Through this approach, major quality systems would still be assessed as typically done today, such as investigation handling, CAPA management and effectiveness, complaint systems, change control, etc. As a result of the enhanced inspection paradigm, quality system failures would be put into context with patient risk.

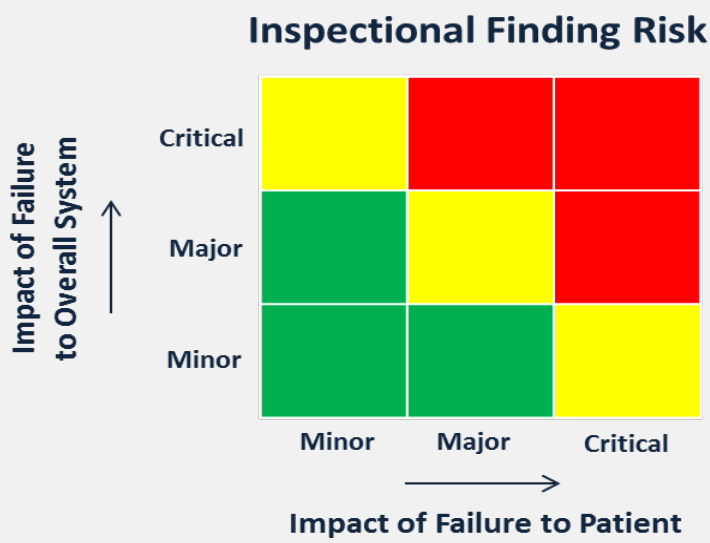
It is also recommended that FDA incorporate into the standard inspectional approach interviewing the highest ranking management members of each functional area across the facility. Questions could be derived that would give an indication of ownership of quality across the organization, as well as how failures and corrections are truly viewed and handled. This inspectional approach could help paint the picture of the quality culture…not just the culture of Quality Department.

In light of the self-reporting program, it is important for FDA to verify on inspection the validity of the data reported to ensure the integrity of the program. Falsification of data would require a commensurate FDA response.

By aligning the inspectional focus with the Total Patient Risk determined in Step 3 (Figure 6), FDA is able to risk rank inspectional findings based upon a combination of Quality System Strength and Clinical Relevance to give an ultimate rating of Total Patient Impact. As stated at the beginning of this proposal, this type of inspectional outcome would then become a useful tool for industry and regulators alike.

Currently inspections are ranked using NAI (No Action Indicated), VAI (Voluntary Action Indicated) and OAI (Official Action Indicated). Also, the findings are supposed to be prioritized. However, neither gives an understanding of the risk ranking of each finding relative to clinical relevance or strength of the quality culture. For example, the highest priority finding at an excellent facility might be of very low *actual* risk. It is recommended that the inspectional findings be ranked by risk (Critical, Major, Minor) based on a combination of impact of the failure to the overall quality system and the impact of the failure to the patient. As depicted in Figure 8, a risk grid can again be utilized as a result of a scorecard exercise to visually demonstrate the risk impact of each finding on the stability of the quality systems relative to patient impact. This effective visual will capture the attention of senior management by expressing in no uncertain terms how significant each finding is relative to potential enforcement and potential impact to the patient.

Figure 8. Risk of Inspectional Findings to Patient



Conclusion

Xavier University proposes a **4 Step Process** by which FDA and industry collaboratively establish with great transparency an "Evolving Approach to Quality". The proposed process takes into consideration the limited resources of FDA along with the desire by industry to have the playing field leveled with their un- and under-regulated competitors. The foundation of the Xavier Proposal is to build an FDA program based on clinical relevance – first objectively, then contextually. The proposal herein can be harmonized across company sizes, geographical locations, product risk types, process criticality and facility complexity.

Based upon the 4 Step process approach, major milestones can be outlined and achieved methodically in a timeframe determined achievable by industry and FDA.

Appendix I

Current Metric Recommendations Submitted to FDA by Stakeholders

The following examples of metrics have been provided by industry stakeholders to FDA as possibilities for consideration in the CDER Quality Metric Program: batch failure rate, right first time, and OOS/laboratory failure investigation rates. The limitations of each example will be explored in turn:

1. Batch Failure Rate

   This metric would have to be put into context based on product and process complexity. It is certainly easier to manufacture a non-sterile tablet than even a non-sterile capsule, let alone a sterile injectable.

   Additionally, business tolerance is a factor that would be difficult for FDA to determine. For example, there are products that were developed decades ago with a very low demand rate. The return on investment cannot be justified to upgrade the process, and also concern that changing the process could not be done successfully. Therefore, the company understands the business impact of having a high failure rate to manufacture the amount needed for distribution.

   Using this metric results in the risk of companies not properly rejecting batches that should be rejected just so the metric reported looks better than it should = industry gaming.

2. Right First Time

   This metric would also have to be put into context based on product and process complexity. Again, it is certainly easier to manufacture a non-sterile tablet than even a non-sterile capsule, let alone a sterile injectable.

   Using this metric results in the risk of companies not properly investigating unplanned events, whether they result in batch failure or not. Additionally, new processes, new products, and/or changes to an existing process could result in unplanned failures due to unfamiliarity. It is often suggested that “Right Second Time” is a better indicator to demonstrate organizations that can learn from mistakes and sustain prevention. Similar

to the Batch Failure Rate metric, this metric runs the risk of industry gaming to make the metric reported appear better than it should.

3. OOS/Laboratory Failure Investigation Rates

Just as a company cannot test quality into a product, testing should not be used to determine the acceptability of a company. The laboratory needs to remain independent of what is desired, and remain true to the scientific results. Therefore, using this metric conveys the wrong message to industry of how laboratory testing can be used to determine anything other than the scientific results of the article tested.

This metric runs the risk of avoidance of reporting and industry gaming mentioned for batch failure rate.

Appendix II

The Criticality of Corporate Quality Culture

Industry executives and FDA officials across the pharmaceutical industry continually point to a flawed corporate quality culture as one facet that leads to company, product and process failures.

- Kathleen Culver (Field Inspector and Drug Pre-Approval Manager, FDA Cincinnati District) presented the top three FDA-483 citations during the FDA/Xavier University PharmaLink Conference and concluded: "The Quality Units in these FDA 483 observations are not equipped to do the heavy lifting required to achieve Dr. Woodcock's vision of having a highly efficient, flexible pharma manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight."[5]

- Michael Davidson (Vice President, Quality Systems and Compliance, Pfizer) indicated that risks exist in contract manufacturing relationships if the contractor has a less mature quality culture and less developed quality systems.[6] The same is certainly true for vertically integrated companies that do not have well developed quality systems.

- Bill Webb (Director, Quality – North America, Aptalis Pharmaceutical Technologies) cited that contract relationships should be developed by Senior Management and driven down to all stakeholders, thus noting the importance of quality culture buy-in from the top.[7] Jaspreet Gill (Vice President Global Quality and Compliance, Baxter) recommended that clients request to attend the management review meetings of their contractor, which signals the importance of understanding the senior management commitment and oversight process.[8]

[5] FDA/Xavier University PharmaLink Conference. Presentation entitled "FDA Inspections Update", slide 5. March 20, 2014.
[6] *ibid.* "Addressing Risk in Partner/Contractor Selection and Onboarding", slide 3. March 20, 2014.
[7] *ibid.* "Contract Manufacturing – Achieving Holistic Success", slide 12. March 19, 2014.
[8] *ibid.* "Contract Manufacturing – An Integrated Approach to a Mutually Beneficial Partnership", slide 11. March 19, 2014.

- FDA National Expert Investigator Rebeca Rodriguez expressed her opinion based on personal observations that contributing industry related factors to inspectional findings and trends include (1) company culture and (2) management oversight.[9]

- MHRA has developed a risk ranking inspection frequency program that cites "It is considered that the scope, frequency and depth of inspections should be dependent on how the regulated [organization] takes responsibility for compliance with the regulations."[10] This clearly indicates an importance placed on corporate responsibility by the MHRA regulators.

Other examples to support the criticality of the corporate quality culture mindset can be cited outside the pharmaceutical industry within other FDA regulated industries:

- In 2013, William MacFarland (Director, Division of Enforcement B, Office of Compliance, FDA/CDRH) indicated during the "Case for Quality" National Forum[11] that "when a firm has constant focus on assuring device quality, why wouldn't compliance be the outcome?" The next day during the FDA/Xavier University Medical Device Conference, Steve Silverman (Director, Office of Compliance, FDA/CDRH) provided the basis for his "Case for Quality" initiative in that "A culture of quality yields benefits: enhanced process stability, cross-functional skills and collaboration, reduced compliance risks and costs, and fewer complaints and investigations."

- During the Xavier Health Cincinnati Chapter meeting on January 8, 2014 Steve Niedelman (former FDA Deputy Associate Commissioner of Regulatory Affairs) pinpointed the number one factor that signals when a company is out of control is the lack of senior management commitment to a culture of quality.

[9] FDA/Xavier University PharmaLink Conference. Presentation entitle "Inspectional Findings and Trends: What Do They ***Really*** Mean?" slide 34. March 21, 2014.

[10] http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/Risk-basedinspections/index.htm

[11] The CDRH "Case for Quality" National Forum was hosted by Xavier University on April 30, 2013.

Appendix III

PharmaLink Conference: CDER Challenge Feedback

March 19, 2014

The PharmaLink delegates were asked the following five questions as a means to provide feedback to FDA regarding the Quality Metrics initiative. Industry concern of "gaming" resonated from the comments provided and during conference discussions. However, if an objective and meaningful process can be identified, industry is genuinely interested in being recognized for good quality performance. Additionally, more direct inspectional reporting is desired by the delegates to provide a clearer understanding of risk ranking of the site operations.

1. What concerns do you have about FDA wanting to recognize quality performance beyond compliance?

- Ensuring the harmonization of the standard across the board.
- "Backing into Quality" Concerns
- Defining the key quality performance characteristics (measurable, meaningful, credible, objective, translational (across industry sectors) and getting everyone to align to them→ don't favor one group vs. another, can adapt/reflect changes over time. How many metrics do you truly need to really be holistic, meaningful, and relevant to true "Quality" performance and culture.
- Metrics being skewed for potential reward/penalty outcome.
- Understanding the metrics and some of the disincentives that might go with a focus away from compliance.
- Standardization-level playing field for all.
- Gaining consensus around the standards.
- Consultants-game of consultant-"looks good" multiple gold stars (less efficient)
- Making a moving target-GMPs are always moving
- Fraudulent Metrics-are the performance displayed easily justified. Does it provide the bigger picture of the site/product for quality performance?
- Selecting the correct metric to report.
- Equity of the measures-positively recognized firms based on faulty data.
- Better storytellers don't equal a better story
- Companies that highlight good metrics might be viewed as better than companies using metrics to tackle problems.
- Determining metrics→ manufacturing vs QC vs supplier
- It will be added expense.

- It does not solve the fundamental problem of the enormous cost of quality and regulatory compliance.
- When the imperfections of people and preferences takes hold (in areas that may be gray or left to judgment). How this information could be used?
- May generate unfair marketing advantages to companies when compliance weaknesses may be product specific and not site or company specific.
- Gaining consensus among metrics used to ensure that companies are rated fairly.
- Metrics should change over time and be based on what challenges are being experienced at that point in time.
- Set of standards not applicable to everyone.
- What metrics would be useful and requested above and beyond a well written APR that is already available to the FDA (is the FDA reviewing this info?)
- What would be the "weight" assigned to these metrics?
- How does it compare to the product profiles, inspection history, size of firm, market share, etc.?
- That the measurement system is appropriate and does not drive the wrong behavior.
- Focusing on quality is the right thing to do. Concerns are more around how the FDA will do it and will they do it in the right way i.e. focus on clinically relevant parameters and metrics. Will it be "numbers" focused or understand. Will investigators interpret the same across districts?
- Lack of common documented expectations.
- A one size fits all approach.
- Lack of standardized definitions, auditor bias on which performance criteria are more important.
- Consultant Gaming
- Paralysis by analysis
- What benchmarks for "beyond compliance" will be used? How will they be determined? Will they be universal? Can they be universal with the diversity throughout the industry?
- Exceptional Variability
- Loss of focus on core
- Too many changes simultaneously
- Distraction
- Might create a monster, companies who spend a great deal of time trying to be better instead of actually being better.
- Raise red flags where there shouldn't be.
- Will the metrics being used adequately assess what it is intending to assess?
- Blurs between regs and nice to do's
- Force marginal companies out of business
- Coming up with a set of metrics to measure will be difficult and may be too narrow.
- Selection of relevant metrics/evaluations to affect outcome desired
- Changing focus to narrow range of concerns which may not be most important

2. What opportunities do you see related to FDA wanting to recognize quality performance beyond compliance?

- Defining clearly what quality performance is and how/to what extent it differs from the compliance vernacular.
- What does "Quality Culture" bring and how does FDA see this including key characteristics. What does it look like? What is the value equation here?
- More universal standard of quality, less opinionated that is effective over time once metrics based system has proven itself and has become the industry norm.
- Possibility of reduced inspection frequency
- Beginning of addressing quality vs just compliance
- Consultants "gaming" the system for their gain
- Are they driving the right behaviors—driving patient outcomes and managing risk appropriately
- Recognize and learn from other industries (aerospace/automotive)
- Speed to market; accelerate
- Collaboration 1+1=3
- Continuity→reshaping behaviors
- Certificate or prize from FDA
- Investors-great confidence
- Thinking Outside the Box: "Metrics" building consultant firms will be on the rise as pharma companies will be forced to outsource the collection of data to support their metrics.
- Confidence/accreditation
- Predictor of future performance
- Promoting the Brand
- Reduced Inspection Cycles
- Promoting a Quality Culture. Focus on clinical relevant specifications
- Easier to drive Quality Culture when there is a focus on more than compliance
- Forces discussion on Quality goals across the company
- Companies could receive recognition that could be used in marketing
- It is good to positively reinforce high achievements in quality and compliance, but is that the best use of time and effort aimed at resolving critical drug shortages and increasing product quality.
- Commoditization mitigation
- Broader assessment of companies. Positive assessment leads to fewer inspections.
- Marketing advantages.
- Identify best performers and allow others to work. Develop a program that recognizes best performance from regulator, industry/client/patient standpoint
- Less inspections/smaller FDA/ Lower Taxes

- Increased patient outcomes, safer, more effective drugs faster time to market, more innovation.
- True value to patient if we focus on quality vs compliance.
- Reduced non-value added inspections for strong performance.
- Faster approvals of changes for some companies.
- Potentially reduced costs.
- A harmonized set of documented expectations regarding metrics.
- A percentile score to incentivize increased purchasing.
- Drive consistency of measure across industry, outlines the importance of metrics for importance, helps outline the importance of driving improvement through quality to executive management.
- With consistent measure it could be easier to apply risk profile to supplier management program.
- Shifts discussion to positive reinforcement.
- Organizations (hopefully) will be motivated to do more than simply "plodding" up to the compliance line. By looking more deeply/thoroughly, perhaps overall quality increases and outcomes for the patients improves.
- Recognize/Reward
- Eliminate unrealistic competitors
- Commercialize status
- Creates a better relationship between companies and FDA
- Less site overview for high performing sites
- Harmonized measurement tool to ensure quality product is getting to the end user.
- Time for FDA to focus on uncharted areas raise level of overall compliance
- More efficient use of FDA's time due to fewer inspections for performing sites will allow them to focus on areas of higher need.

3. What kind of inspectional outcomes would promote "Quality Behaviors," not just compliance?

- Outcomes where sites are heralded as standards for innovation and promoted for industry trends doe to effectiveness and positive inspections.
- Giving "rewards" i.e. certificates, grades, etc….can be abused with time.
- Recognition of process capability, preventative maintenance, and data instead of on-site inspection. Use the leading and lagging indicators.
- Quality Management Meeting (on-time)
- Knowledge Transfer
- CPP Specifications
- Quality culture/Quality Performance metric, synopsis, call-out specifically recognized and/or communicated as part of inspection report/EIR…

- This data/outcome shared with key stakeholders (3rd Party Payers… global Healthcare/Reg Agencies) as a performance measure or differentiator vs peer-groups/competitors.
- Successful outcome that shows "Quality Behaviors" through metrics but may not show HOW those behaviors were rolled out.
- Unintended Behavior→ Successful Outcome→ "Quality Behavior"
- Clean or significantly reduced observations during inspections
- Trend against historical inspection records
- Less frequent inspections for Quality Companies—good quality culture and good QMS
- Better "teaching" for non-finding items (recommendations) around how the FDA would like them to look at the next audit. More feedback on items that they did like.
- Recommendations from investigators or statements of what is working well vs. just 483's
- FDA should not promote- Is a firm compliant with current regulations, that's the FDA's purpose
- Reduced Inspection frequency or duration integrated/updated inspection rating system
- Greater periods between inspections
- New enforcement tools, top 5% Pharma company list
- Non-observational recommendations to address trends seen in industry
- Relaxed inspection schedule
- Ability to submit forms/documents in lieu of or to shorten the on-site inspection.
- A quality compliance index that can be used both internally and externally
- Automatically sharing 483/Warning Letters with owners (contract givers) of all products made/tested within the facility
- A letter of approval, like a gold star rating.
- CPK—Large Range

4. What are some actions you do that would demonstrate you are in control—beyond compliance?

- Transparency to self-inspections and auditing programs to highlight company culture standards and how we risk assess our suppliers. Ex. We monitor supplier CAPAs via Trackwise with CAPA management teams down to each minor observation.
- Quality metrics/results owned and reported by the entire organization not QA/Quality Assurance org demonstrating knowledge and capability is widespread→Regular documented Management Reviews with Action Plans
- Consumer relevant performance is truly moving in proper direction→ Consumer complaints down, Safety Issues down, Health outcomes up, Recalls down, Product/Material rejection rates down (poor practices, poor quality, poor performance vs EMPs)
- SPC and 6-Sigma
- Governance process with regular data and trend review with closed loop actions.
- In house metrics and supplier/vendor metrics (report cards)

- Increased quality control measures/specs
- Robust supplier management programs
- Extensive audit program and deviation remediation
- Accuracy measure and report process capability (CPK); all annual reports are completed on time; PM system is adhered to. Strong supplier management program
- Drive down error rates due to human error. Drive down unconfirmed or lab error OOS's. Recognize analyst level quality culture, quality awards. Feedback to clients illustrating their quality.
- Batch rejection.
- Stop production, or keep production from starting. Knowledge management with respect to technical, process, operations, quality/compliance strategies and tactics.
- Internal Audits
- Change Control
- Regularly assessing process performance and documenting
- APRs Reviewed/Action Taken
- Data Analysis and response on regular frequency data trending, signal generation, assessment, escalation, score cards
- Formal Continuous Improvement Plans (CIPs)
- APR's generating product/project initiatives/programs to improve CPK.
- Robust supplier qualification program
- Asking after each management review meeting for feedback on state of control at the facility.
- KPI measurement and reporting
- Critical quality attribute-process knowledge through to process capability
- New products validated under QbD, learning from competitor warning letters-improvement before observation
- Data Analysis
- End to End Change Control
- RFT, no interruption on supply chain
- Assessing In-process data along with end process
- Fix Repeated Process Failure
- Define quality culture and elements in zero tolerance

5. How can #4 be measured and reported

- Report number of inspections and timelines for CAPAs internally and for 3rd parties.
- Control plans linked with Process/Product FMEA's and active risk management based on leading and lagging data.

- Provide both metrics to the FDA for comparison to the FDA metrics. (Comparison of all report cards).
- Trends go in the right direction, recalls and complaints go down and drug shortages are averted.
- CAPA's effective 1st Time
- Rate reduction for unplanned quality events. Report reduction for repeat events
- TQAs: content/existence
- Culture in a company
- Clear metrics shown in the facility
- Process capability
- Fit for purpose
- Compliance Index. System analysis, score card
- APRs on time. Thoroughness of APR. FDA review them, not just check the box that the firm wrote an APR.
- Typically by improvements in already established metrics. Beyond what is measured, there is an opportunity for regulatory (FDA) inspectors to review CIP plans/initiatives, review broader systems initiatives (i.e. SQM process) vs. just looking at failures
- Management Review Minutes