WHY DR. HAMBURG NEEDS HER DEAN'S LIST[1]

ABSTRACT: the quality metrics debate needs to recognize the paramount importance of quality culture over and above the mere compliance that results from meeting a quality system. What is needed is a simple reward system that identifies role models. An FDA's Dean's List will solve many problems: it will reward those producers that do the right thing for the patient, it will encourage innovation in pharmaceutical manufacturing, it will allow inspection resources to be applied wisely, it will make quality an effective differentiator at a time when the vast majority of manufacturing is done through outsourcing. This paper flags the responsibility of the CEO in driving the organization's quality culture: the final safety net that assures patients only get good medicines.

It is now more than a year since FDA brought out its Federal Register Notice asking input from the industry on quality metrics. The goal is ambitious: to stratify along increasing levels of quality all the manufacturing sites regulated by FDA.

When implemented Quality Metrics will put quality of manufacturing sites on the agenda like never before. It will be yet another example of FDA pushing our industry forward. Exhibit 1 in the last page exemplifies the current view on the matter. This paper argues that while the direction is right and the need is pressing, the current approach is too complex and unnecessarily detailed, and two major ingredients are missing from the debate. First, quality culture is barely addressed. FDA, CEOs, and regulators in general have not devoted much attention to this primary driver of product quality. What is uppermost in their mind is the verification of compliance (i.e., the effect of quality), and the current debate seems limited to measuring quality system performance. Second the willingness to learn from others is absent. There is no evidence that anyone wants to go beyond their comfort zone.

Over the years, FDA has been shown repeatedly to be a thought leader. For example, FDA demanded GMPs for APIs 40 years before such a requirement became law in Europe[2]. FDA has also been behind process analytical technologies (PAT) and quality by design (QbD). Major medicine breakthroughs, such as Vertex's Kalydeco (ivacaftor) for the treatment of cystic fibrosis patients, would not have been possible without FDA's innovation of the breakthrough therapy designation. The stratification that FDA is seeking to implement must happen, but it needs a leap of faith and major innovative thinking in a direction that is different from current proposals.

FDA's thermometer is one that only measures negative temperatures. FDA, as well as other regulators, tends to focus on the "floor" with medicine agencies explicitly defining a threshold level below which quality performance is deemed unacceptable.

What does FDA issue when it wants to say "Well done!"? Presently there is no FDA form for *Well Done*. Yet FDA is keen that we move in the direction of its 21st century vision with concepts like process understanding[12], risk management and supply reliability. FDA has nothing in its arsenal to encourage the proactive pursuit of greater manufacturing quality and reliability. At the same time, sanctions for non-compliance, especially when non-compliance is a business strategy, are insufficient to be an effective deterrent. Because the type of sanctions hurt primarily shareholders and not management, rogue behavior is encouraged by positive payback. Because non-compliance pays, rogue players often win. For example, has anyone been caught (let alone jailed) for causing hundreds of deaths in the heparin tragedy?

[1] See the author's editorial in the Chemical & Engineering News issue of 22nd April 2013.
[2] GMPs for APIs became an FDA requirement in the USA in 1964, in 1971 in the UK the Orange Guide – Good Manufacturing Practice, but 2005 was the deadline of the EU directive that brought ICH Q7a into Law across all member states.

Safety and quality have much in common, with both being crucial aspects of industrial activity. Both depend directly on constant management attention and require the right tone at the top. Yet in terms of metrics, safety is easy (while quality is complex). The number of deaths, lost time due to accidents, the gravity and frequency indices are well-established metrics and are sufficiently comparable across all sectors. What we are trying to measure is simple. Research has also taught us to expect correlations between near-misses and accidents.

OSHA VPP Star program

The Occupational Safety and Health Administration (OSHA) is the USA's authority that enforces safety and health in the workplace. It performs regular compliance surveillance through surprise inspections. OSHA's voluntary protection program (VPP)[3] rewards workplaces that have consistently no lost time accidents by removing them from the inspection roster. VPP Star program recognition drives appropriate behaviors—a reduction in insurance premiums is a financial benefit, but paramount is the pride workers have in a safe workplace, and no effort is wasted in maintaining that status.

Just like FDA, OSHA has defined where the "floor" lies. Below such minimum acceptable safety level, sites get closed down and fines are levied. But OSHA's thermometer also measures positive temperatures—the VPP Star program identifies the role models. OSHA thus has a three-level stratification of the safety performance of all the sites it regulates. The VPP Star program is an effective reward mechanism and a confirmation of a sound and vibrant safety culture.

The metrics used to assess the safety of workplaces exhibit the attributes that FDA is looking for, which include "not amenable to gaming, objective, cross all sectors, are non-intrusive and relevant". It is simple, has virtually no cost and enables the deployment of inspections of resources where they are really needed. The quality metrics currently under discussion involve setting up systems that are complex, require annual data input, need supervision and funding, and will necessarily introduce behaviors focused on improving "the site's position in the league table" rather than just doing the right thing for the patient.

In accidents, harm to the worker is a simple common denominator. No comparable measure exists in quality. All the metrics that have been proposed may be objective and may ultimately correlate with recalls and adverse events, and elegant mathematics may make them comparable across sites and across all sectors of the pharmaceutical industry. Such metrics, however, are unable to measure whether the CEO is really committed to developing and nurturing a quality culture in his or her organization.

Sections 705 and 706 pf the FDA Safety and Innovation Act (FDASIA) mandate that metrics be made available so that FDA can deploy its inspection resources appropriately. It does not say it needs to be complicated or costly, or that FDA cannot get inspiration from an OSHA-type VPP star program. FDA could publish a simple list of manufacturing sites that are role models. When this list is published, FDA will have done enough to define the right behaviors and will have done so at a low cost.

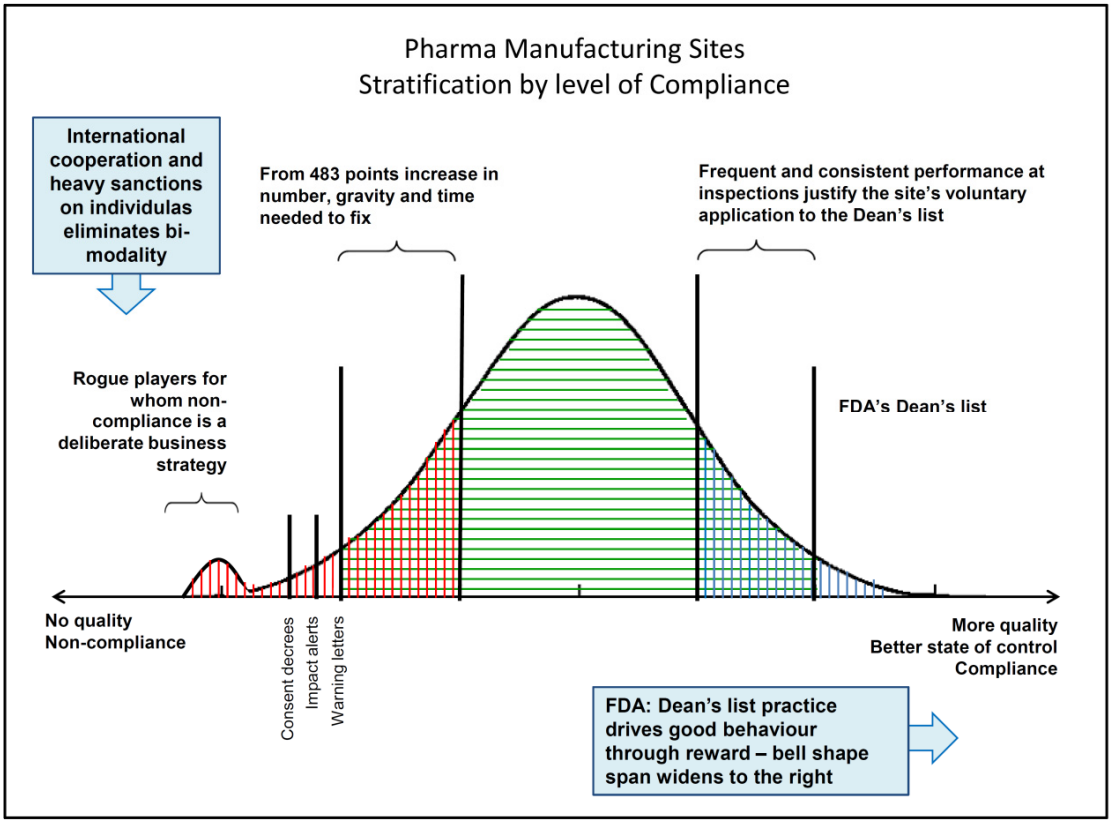
The metrics being discussed tend to focus on all the deciles from the bottom all the way to the top, which is both costly and an unnecessary level of detail. The only stratification the industry has today is a well mapped-out lower level, below which quality is unacceptable. What is needed now is just a definition of an upper level, beyond which the quality performance is in the right direction and deserves recognition and applause (see Figure 1).

[3] https://www.osha.gov/dcsp/vpp/all_about_vpp.html

Commissioner Hamburg's Dean's List

For FDA to establish a stratification of its sites in at least three classes, such as OSHA, it will need to define the border between "being in compliance" and "being ahead." And those sites that make it beyond that threshold join what has been described as Commissioner Hamburg's Dean's List.

Figure 1: Pharmaceutical manufacturing sites stratification by level of compliance.



It is unlikely that the shape of the distribution today approximates a normal distribution because there is nothing defining the right side of the bell shape. Once a driver of behaviors, such as a Dean's List, exists one could expect a normal distribution.

Figure 2: What areas under the curve matter?[4]

Costly sanctions region	Red flag regions	Bulk of sites are compliant	Motivation to-do-better region	Valuable reward region

[4] Regulators should only be interested at extremes of the distribution: the unacceptable and the role-models – what is in-between is OK so needs no attention. This insight is owed to the late Antonio Borges, Dean of the INSEAD business school for many years, who always reminded his students of the imperative of public recognition of good work. He felt applause had a superior contagious effect in driving the right behaviors. He wanted them to do the same when they led their organizations.

There would be no need for supervision by the regulator if all manufacturing sites were compliant. The reality is very different especially on the left hand side of the curve. A large portion of sites do the bare minimum to remain "approvable" - this is reflected by the high number of manufacturers that avoid client audits. This is the region of weak or no compliance, or where deliberate non-compliance becomes a competitive advantage. Fortunately the regulators focus on this area and exert a healthy tension that ensures no-one stays complacent. However regulators have ignored the blue area thereby failing to reward role-models and also failing to provide drivers for doing better than just "remaining in compliance".

Have any Pharma quality champions been promoted to CEO? Quality is today perceived as a minimum to be met, not as a differentiator at the high end. This state of affairs explains why the efforts to innovate in manufacturing seldom come from Industry. Unlike the regulators in the automobile, aviation, tourism and many other industries ours have done a stellar job at introducing innovation in our manufacturing. This probably came from exasperation from seeing API and tablet producers displaying little initiative to embark in step-changing innovation. FDA in particular has been prolific at shining light of what should making medicines in the 21st century look like (see page 1).[5]

Regulators have emphasized compliance to the detriment of quality. They sanction non-compliance but they do not applaud quality. By not rewarding good behavior they ensure that the industry that makes billion dollar bets in Science has conservative risk-averse manufacturers. It is crucial that FDA changes it message so we have a clear inflexion in the drivers of pharmaceutical manufacture.

This paper argues that metrics pulled from a quality system alone will not help define where Commissioner Hamburg's Dean's List starts. The industry and regulators need to start acknowledging that what genuinely assures compliance and then takes an organization to levels of quality beyond the minimum is the organization's quality culture. An organization's quality culture is embedded in the values of the people that make any site function. A quality system will only assure quality if it is backed-up by a well-nurtured quality culture that permeates the entire manufacturing organization. Without a culture of quality, a quality system assures nothing[6]. An article from Fortune magazine, "Dirty Medicine," provides a good description of an organization where incidents of fabrication of compliance evidence were endemic. In other words, in an organization that has no culture of quality, it is not a system of controls and documents that will safeguard quality.

The large number of warning letters and import alerts issued to sites based in India in the last two years may not be statistically significant given the very large number of FDA sites in that country. What is both significant and of concern is that they are all related to data-integrity issues. The chief executive of an Indian drug maker was recently quoted as saying, "When a company is small, it can be managed by strong supervision. As companies get bigger, supervision can break down… You need systems and a culture to maintain proper supervision—and we are in that process of growing up, I think".[7] Indian generic companies' grew at a rate so fast that the nurturing of such quality culture needed to be miraculous.

The agency should consider whether an organization that has a culture of fraud instead of a culture of quality can ever be reformed, or whether it should be given a second chance[8]. The

[5] Generalizations are usually dangerous but the author believes that the promised land of QbD in the shape of more freedom over changes has not been seen by many. Yet it exists: in a 2011 full QbD filing Hovione was able to get a 2nd site approved on a CBE30 simply by showing compelling data.
[6] Readers of Fortune have also seen how greed in the banking industry has drawn circles around compliance officers and their central bank supervisors. These are clear examples of leadership failure as a result of poor values. This trend, in the author's view a sign of Western's society decline, is at odds with the growing demand for transparency in our society where young people give increasing value to doing the right thing.
[7] Reuters, 13 March 2014 - FDA bans imports from Sun Pharma plant in India crackdown. The growth of Indian firms has been spectacular: The author's first job at Hovione in 1984 was selling APIs made in Europe to Indian Pharma companies.
[8] IPQ – "FDA integrity concerns continue in India as three more firms draw GMP warning letters"– January 2014 issue.

agency should also consider whether drug shortages are not inevitable when unscrupulous companies compete unfairly in the market through systematic non-compliance and destroy the competitiveness of compliant firms. A regulator's job is not limited to the oversight of the quality of drugs. Regulators must take decisive action when non-compliance becomes an obvious competitive advantage that hurts the fabric of the Industry. "A firm can have all the SOPs, systems and controls required but, without a quality culture, product quality and business continuity are not assured"[9].

A culture of quality

A quality culture is not the result of procedures, specifications, audits, a quality unit or enforcement by regulators. Although some of these elements do help establish a quality organization, by themselves, they are insufficient. Henry Ford said, "Quality means doing it right when no one is looking."

Is it not time we gave more weight to people and their values than to paperwork?

It is surprising that of the 128 comments to FDA's docket, only Pfizer's refers explicitly to quality culture as preeminent: "The indicators mentioned above are only useful when coupled with a strong quality culture, which we believe is the foundation of consistent quality performance"[10].

Those responsible for Pharma manufacturing operations know how complex their activity is, that not all parameters are under their full control, that knowledge is sometimes imperfect and that it may even be lost over the life of a drug – the challenge is such that a quality system alone does not give 100% certainty that all drugs will always be good for the patient. Those that live their responsibility for making good APIs and medicines want to make sure their drugs have a safety net; our safety net is the quality culture we build into our plants. It is the combination of a good quality system and people that display a vibrant quality culture, good science and sound engineering that allow responsible CEOs and boards to sleep at night.

The conditions where a quality culture[11] will develop are likely to include:

- the right tone at the top, a focus on the right values
- a constant display of concern for quality, for putting the patient ahead of everything else
- an organization that consistently "walks the talk"
- an organization with great people skills and strong values
- shareholders who expect more than just financial rewards

The indicators of a strong quality culture include:

- quality-driven productivity brought about by sustained change through the introduction of improvements and innovation
- adoption of and investment in technology including IT to ensure a better state of control over systems and timeliness of event follow-up
- prompt adoption of best practices, promotion of change and continuous improvement in the quality system itself
- pro-active and transparent behavior with regulators leading to a rich relationship with regulators based on dialogue, sound science and mutual respect
- intense participation in the standard setting-process
- good performance in other areas such as safety, business conduct, and sustainability
- low staff rotation

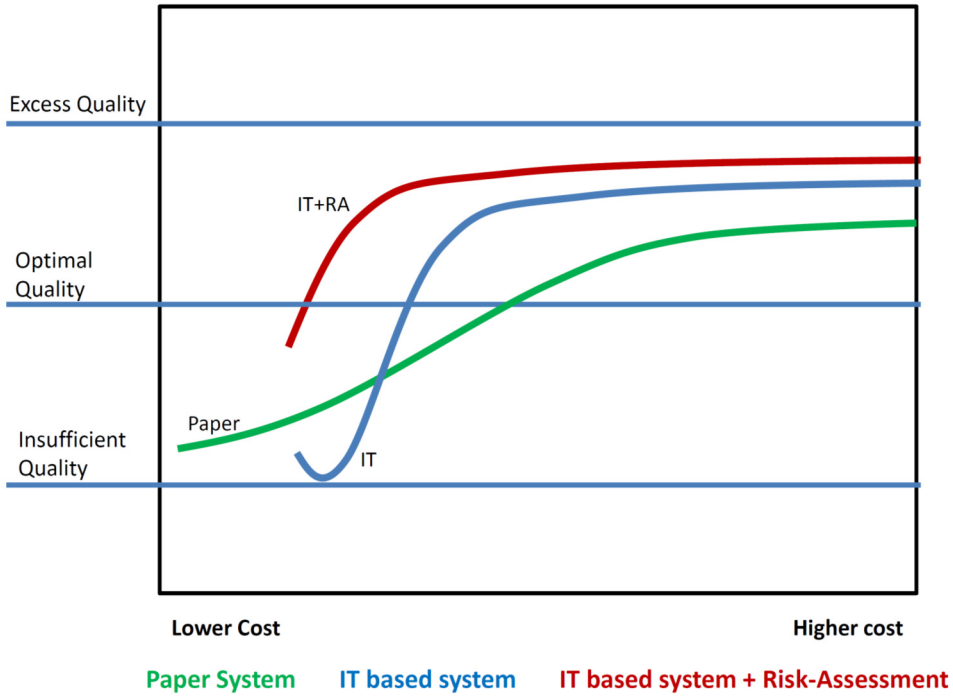
[9] Mary Oates, Vice President, Global Quality Operations, Pfizer Global Manufacturing, November 16 2011 at the APIC Annual Conference in Budapest.
10 Pfizer's March 13 2013, response to Docket FDA-2013-N-2014
11 Hovione's Quality Culture presented at the 2012 APIC Annual Conference

The degree of maturity of the quality culture will correlate directly with the site's quality system in terms of the following journeys:

- an evolving mind-set that accumulates as second nature habits such as deviation recording, change-control, trend analysis, risk management, process understanding12 that defines the space of process capability, and so on
- evolving from a rigid machine organization with inflexible quality systems towards a rationale-based approach that adjusts controls appropriately to each situation

As the quality culture and system of an organization evolve and mature, the cost of quality diminishes and its capability becomes greater and more efficient. Different stages of development of quality systems correlate with different iso-cost curves as per the Figure 3 below.

Figure 3: Quality versus cost iso-curves of different maturity quality systems



A company can move from one iso-curve to the other on its left, and become more cost-effective, by the introduction of more sophisticated and sensible approaches to quality. It is possible to define that imagine that enhanced process understanding[12] and big data systems and next step-change in pharmaceutical manufacture that will give rise to the next iso-curves to the left. These aspects mirror the maturity of the quality culture in an organization. This approach can help map the progress of a quality culture and could be used to define the criteria and boundaries at the right of the bell shaped curve.

An organization with a sound quality culture is easily recognized as it believes in the following two principles[13]:

12 Enhanced process understanding at Hovione – see examples.

[13] To quote a comment from a regulator: "More could perhaps have been made of the importance of risk management and the underpinning principles of product knowledge (how can one make an assessment as to the quality impact of a deviation without knowing the detail of a process and it's variables on the product?) – this is probably the main issue we see on our inspections of QRM systems; poor risk assessments and risk mitigation plans because the foundation of product/process knowledge is absent. This impacts the metrics discussion, as without this underpinning knowledge, a company can't manage its quality system or KPI monitoring effectively, and therefore metrics may be skewed, or the real quality-indicating metrics

- Product and Process understanding[12] – e.g. sufficient depth of science that provides an explanation of why a process deviation has or does not have impact on the quality of the product.
- Sensible business management – Too fast growth and operating at the limit of capacity are often triggers of quality issues or of non-compliance. It is obvious that in many Indian generic companies the product portfolio growth outstripped the company's quality system. Senior management failed in its oversight.

The following additional attributes of a manufacturing site could be used by FDA to set the bar for that site to be listed in Commissioner Hamburg's Dean's List:

- a solid track record of consistent good performance at FDA inspections (frequency of successful inspection in the recent past)
- frequency of filings in the recent past that include a growing pattern of QbD approaches and the application of PAT controls
- providing FDA with IT access to perform at any time and in real-time remote inspection of all quality data related to commercial batch manufacturing and release (including seeing deviations, change control and analytical data, and trending thereof, and the measure of timeliness to close events) [14]
- allowing FDA inspector training at the site

Most importantly, FDA should add a further element to its compliance inspections. Inspectors should determine the existence and maturity of the quality culture in the inspected site. Simple cross-examination of operators and candid conversations with management at various levels will quickly tell what tone is set at the top, what costs of non-quality are accepted, and how much power the quality assurance department has over budgets, over purchasing or finance departments decisions. An assessment of quality culture should be central to any quality metric assessment—this has to be done by FDA on-site during an inspection.

In lieu of the complex metrics that are being discussed, Industry and FDA could agree on what is the roadmap to reach the Dean's List standard, what are the desired minimum attributes that would allow a site to apply to be invited into the program. It would be up to the site to check whether it meets the criteria, and application would be voluntary. To be accepted as an applicant would require a successful inspection that would assess the maturity of the quality system and the vibrancy of the quality culture.

The accepted applicant status itself will be a great motivator to improve quality performance and inspection readiness, while also having a marketing value. It does not require much additional financial cost to the agency and allows any plant to set its sights on an ambitious goal.

Finally, for those that make it to the Dean's List, FDA needs to go public and be able to say, "Well done!" and publish the names of those sites that made it onto the list. FDA has to decide how it will do this and also how it removes sites form the list (just as the Michelin or Zagat guides give and remove stars to restaurants… and neither justifies it).

Being on this public list of role models does not need to trigger any special treatment as in the case of OSHA's VPP star program. Being listed will be in itself a worthwhile reward. Being listed

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may not be gathered at all. Product/process understanding is an important factor in QbD, but in terms of generics / low profit manufacture, we are looking for is less onerous than the full QbD requirement for design space etc. as in ICH Q8.

Great care needs to be exercised in the use of the term QbD. It is unreasonable to expect the majority of generics manufacturers to 'go back to the drawing board' and implement full QbD design space determination for legacy products of low profit margin. There is a risk that by inferring the need / benefits from QbD we could divert significant company resources away from value-adding activities in the pursuit of a 'pseudo-QbD' approach which ultimately fails. We are also aware of some companies and consultants referring to QbD in terms of 'designing a quality system that works'. This is probably not helpful"

[14] See Hovione's Navstream as an example of IT tool for remote inspecting/auditing

will be a relevant element in FDA's risk-assessment and many NDAs or ANDAs are likely to be approved without PAIs (pre-approval inspections) if their product is produced in a listed site.

FDA needs its best manufacturers to be profitable and to grow. A transparent and public three level stratification of quality performance will enable a better site to charge a price that rewards enhanced quality.

It is disappointing to hear that still many in the pharmaceutical industry believe that a site's quality metrics and ranking should remain confidential. When Deborah Autor of Mylan argued for a site's ranking to be made public at a recent public meeting, other representatives of large multinational companies said that they were completely opposed. This is wrong; transparency underpins the 21st century. Our industry needs to change.

Of course none of what is being proposed is in FDA's comfort zone but as the breakthrough therapy designation and other examples illustrate FDA's greatest accomplishments happen when it innovates.

Guy Villax
6th September 2014

This paper is a long version of the article *A case for an FDA's Dean's List* that was published in the September CPhI supplement of Pharmaceutical Technology North America and includes new insights and more detailed arguments about the importance of quality culture.

The OSHA VPP Star Program:

Starting in 1982, VPP sets performance-based criteria for a managed safety and health system, invites sites to apply, and then assesses applicants against these criteria. OSHA's verification includes an application review and a rigorous onsite evaluation by a team of OSHA safety and health experts.

OSHA approves qualified sites to one of three programs:

Star: Recognition for employers and employees who demonstrate exemplary achievement in the prevention and control of occupational safety and health hazards the development, implementation and continuous improvement of their safety and health management system. Merit: Recognition for employers and employees who have developed and implemented good safety and health management systems but who must take additional steps to reach Star quality. Demonstration: Recognition for employers and employees who operate effective safety and health management systems that differ from current VPP requirements. This program enables OSHA to test the efficacy of different approaches.

Exhibit 1 - Quality Super Analytic straw-man prepared at Hovione by Luisa Paulo, Nuno Matos and Filipe Gaspar in June 2014.

Components of a Quality Metric						
	Rating (0-100%)		Applicable to Product or Site?	Information readily available to FDA?	Difficulty in impementation across industry	Objective/Subjective metric
Lagging (past up-to-present performance) (40%)	· Number of recalls (per batch released)	10%	both	No	easy	Objective
	· Rate of batch failure (per batch produced)	5%	both	No	easy	Objective
	· Rate of confirmed OOS (per batch produced)	5%	both	No	easy	Objective
	· Rate of unconfirmed OOS (per batch produced)	5%	both	No	medium	Objective
	· Rate of complaints (per batch released/per shipment)	5%	both	No	easy	Objective
	· Track Record with FDA (Index), *(see a)*)	10%	site	Yes	N/AP	Objective
Leading (future performance) (30%)	· Staff rotation (% of total staff in a year)	4%	site	No	easy	Objective
	· Number of external audits (per year)	2%	site	No	easy	Objective
	· Unplanned downtime of equipment (% of total time)	5%	site	No	medium	Gammable
	· GMP training (hours per employee)	2%	site	No	medium	Objective
	· Process capabilities (Cpk,min; Cpk.avg)	5%	product	No	difficult	Objective
	· Changes in industrial activity (batches per year, YoY basis)	2%	site	No	easy	Objective
	. Rate of deviations due to 'human error'	5%	site	No	easy	Objective
	· Supply chain index (see *b)*)	5%	product	No	difficult	Objective
Cultural metrics – drivers of quality behavior (30%)	· Quality Culture Index, (see *c)*)	30%	site	No	difficult	Subjective
TOTAL		**100%**				
a) includes among others: number of inspections in last 5 years, number of warning letters in last 5 years and average number of observations (per # of inspections)						
b) includes among others: rate of failure of critical raw materials, on-time delivery of critical raw materials, freuency of suppliers audits, redundancy of suppliers of critical raw materials and inventory levels						
c) includes among others: client satisfaction levels, adherence levels to preventive maintenance, training levels/education levels, participation in standards setting process, adoption of best practices and technologies (risk assessment, PAT, QbD), safety performance and continuous improvement programs, evidence of c suite involvement / close oversight in quality matters, a CEO that "walks the talk" - part of this data needs to be obtained by on-site inspections by a trained expert, this should become part of the FDA inspection.						