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26th November 2015

Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville
MD 20852

Re: FDA Draft Guidance for Industry: Request for Quality Metrics – FDA-2015-D-2537

Dear Sirs,

Hovione thanks the FDA for the opportunity to present comments and suggestions on the draft guidance for industry "Request for Quality Metrics".

Hovione has been in business for 56 years supplying services as a CDMO to Innovators, and APIs to the generics industry to enable it to offer high quality affordable medicines. Our first FDA inspection was in 1982. We employ 1345 employees and supply to 50 countries. In each of the last 5 years we were the manufacturer behind 1 to 3 NDA approvals per year, in addition to being the referenced DMF holder for multiple ANDA approvals.

I have been CEO of Hovione for almost 20 years. For about 40 years I have been fortunate to have had a front row seat at watching the global pharmaceutical industry evolve. My first words on this guidance are of amazement and congratulations to FDA for giving a role to "quality culture" [109] in its compliance requirements. The USA is fortunate to have the World's gold standard regulator, the one that pushes innovation and is continuously raising the bar. Quality Metrics is another feather in its cap.

The Quality Metrics guidance amounts to a major innovation in FDA practice as it allows it to focus on quality and good performers rather than just on non-compliance and poor performers. We are very much used to an FDA that excels at using the stick, this guidance announces that FDA will learn to use the carrot. This is good because patients want capsules full of quality, not capsules full of compliance.

Hovione is in full support of the proposed guidance in terms of concept and its proposed mechanics. Implementing the proposed Quality Metrics will entail considerable work for tens of thousands of people but that is very little compared to the benefit to the patient, to the quality and reliable supply of medicines in the US and elsewhere. If you do not measure you cannot manage, having mandatory quality metrics should set the industry on a journey towards better quality medicines. We also hope it will also provide patients, clients, prescribers and payors with an objective measure of quality that enables them to differentiate between manufacturers of both APIs and FDFs.

Imperatives

Transparency
The public disclosure of aggregated Quality Metrics of every product and every site must be the end goal [310]. Transparency is one of the unstoppable driving forces of the 21st century. Our industry needs to have the courage to change and be more open to public scrutiny – whether these are patients, prescribers, insurers, payors, or clients. To date the quality of medicines has been taken for granted -all that was needed was for FDA to approve, after that all products had the same quality- those in the industry know this is not the case. Let the data speak.

FDFs v APIs
This guidance must apply equally to Finished Dosage Forms (FDFs) as to Active Pharmaceutical Ingredients (APIs). The quality of an FDF can never be greater than that of the API it is made of. FDA needs to consider that these are however two different industry segments – one mixes, the other transforms matter; one has patients as its customers, the other has companies as customers.
The guidance needs to clarify:

- For APIs the Quality Metrics must be calculated based on all the isolated GMP steps contained in the filing (DMF or CMC). If several different sites are involved in different GMP steps of one final API then all sites need to be covered and the one issuing the CofA for the final API should be the reporting establishment. The industry has far too many sites doing just a crystallization of the crude API. FDA must not allow this practice to obscure the true measure of quality.

- In APIs the sequence of chemistry steps are seldom one batch into one batch into one batch – sometimes batches get split, other times aggregated. Some companies have the genealogy of a batch fully computerized others don't, so this could be highly complex to compute. It's doable but the resulting Quality Metrics may be less comparable across the industry as in the case of FDFs: data interpretation needs care, so the written text explanation fields are appropriate.

- If Quality Metrics are to be remitted on a quarterly basis, FDA needs to consider that the number of produced API batches per year may vary enormously. As widely as 3 batches a week for a full year, to one batch every 18 months. So quarters may have many divisions by zero. Cut-off definitions are also important as the complete synthesis of one batch may require 3 quarters – so reporting time should be the date of the CofA of the API.

- Complaints from patients, pharmacists and doctors regarding a medicine are a very different class of complaint from that coming in from a manufacturer that buys an API. In this case Quality Metrics need to only take into account those complaints that are valid and belong to the API producer as per the spirit of what Quality Metrics is trying to achieve.

Generics v Innovators
The supply chain of an innovator tends to be simple and is the object of strong controls and oversight by a single entity. Sometimes licensing deals cause 2 or more sponsors to be involved. In which case the same CMO may be making the same product under different codes and with specifications evolving differently. The API CMO that serves an Innovator (or two) exclusively for one product should

be reporting to FDA as a "reporting establishment" for the API, it may well also share its Quality Metrics for that product with its client(s).

The CMO that serves an Innovator often has its hands tied. Much of the period of time allowed to generate documents that are time sensitive (eg deviations, investigation reports, product quality reviews…) are mostly consumed by the QA of the Sponsor bargaining with the QA of the CMO on the exact wording to be used. That said 30 days is fine; this will just cause everyone to dedicate staff to this process, and force Sponsors and CMOs to agree on Rules for Successful Collaboration.

In the case of a generic the complexity of the supply chain is infinitely greater. This may involve multiple API producers supplying multiple ANDA holders, sometimes with middlemen. The Quality Metrics of API X will be combined with the FDF Quality Metrics for submission to the FDA by the generic manufacturer of product X. The API quality metrics to be used would combine all the API Quality Metrics from all approved and used sources of API (combined on a pro-rata basis considering the relative quantities of API used from the several approved sources used). Not simple. One should also expect API producers to use the Quality Metrics of their individual APIs or the metrics of the site as marketing data. Definitions need to consider the marked complexity of generic supply chains.

Drug Shortages

Unlike FDA, and unlike many others, Hovione believes that drug shortages are to a material extent caused by excessive price competition driven by irresponsible companies. In many instances such companies are also found to use non-compliance as a competitive advantage. Whatever the root cause, a good leading indicator of the reliability of a supply chain is OTIF (on-time-in-full). FDA should consider including this measure in the Quality Metrics.

Quality Metrics

Hovione supports the Quality Metrics FDA intends to calculate as set out in B. [407 to 437].

Quality Culture

Hovione supports 100% the intent of bringing Quality Culture into the overall assessment process of the quality performance level of covered establishments. Hovione feels that the "Optional Metrics Related to Quality Culture" should be selected very carefully and changed periodically otherwise they are likely to be gamed.

- **Hovione recommends against the Proposed Optional Metric 1 "who is reviewing and approving" [468].** This is easily gamed, workflows can be routed through added seniority, this will add workload to someone that may not have the knowledge of the detail relevant to assess the data, or the time to consider and discuss. More important than generating such APRs in a timely fashion or ensuring that a very senior person is signing them, is what you do with the APRs' findings. Are the right corrective actions taken? Are they introduced into a CAPA system, is the rate and speed of CAPA closing improving and reviewed by senior management, is there an in depth regular review of quality and is the site general manager specifically accountable? is his or her boss present at that review at least annually?

- **Hovione recommends for the Proposed Optional Metric 2 "% of CAPAS addressed with re-training" [481].** This is an excellent measure. Within a few years those that try hard will have realised this is not the root cause and will have evolved in the right direction. Those that don't try hard will have found work-arounds – and so the metric will either be gamed or won't be relevant any more. The recommendation is to revisit the selected metrics at least every 5 years.

- **Hovione recommends for the Proposed Optional Metric 3 in its entirety [506]** subject naturally to there being a sufficiently high number of batches to make such measures statistically significant. FDA should determine what is the minimum number required, if a site is short of that number the answer should be NA (not applicable].

Setting up metrics to measure a quality culture is difficult. The moment FDA singles them out all establishments will race to adjust their systems, behaviours and processes accordingly – this is a compliance attitude and not a driver to develop a quality culture.

Inspecting for Quality Culture

It has been said by many that one cannot define a culture of quality but one recognizes it the moment one sees it.

When this guidance is issued FDA will embark on a journey that requires to assess quality culture as a key driver for quality of medicines, this is highly innovative. To date the sense of Industry is that FDA inspectors are primarily focused on detecting non-compliance. This must naturally remain a key requirement but FDA's inspectors will now need to open their minds to indicators that give them a sense of the culture of quality existing at a site. To achieve this FDA inspectors would benefit from visiting automobile assembly plants. The car industry may have compliance issues but they are well ahead in promoting a quality culture. When you walk along a car assembly line you see a great deal of visual management. The management culture is highly developed to cut costs and the principles of Deming quality can be seen at work: elimination of waste, making things right first time, promoting ideas to re-design and engineer-out weaknesses. In these plants management goes to great lengths for teams to take pride in their work, for the end product to give meaning to the workers' life. If this can be achieved when one makes cars why can't the same thing be more visible in plants that make medicines that save lives?

The FDA inspection check list needs to be updated to assess the site's quality culture. What's the extent of visual management, do complaints filter down to the shop floor, what's the extent of staff turnover, does top management talk about quality, can one tell the team's ownership, is there a sense that the work done aims to make patients' lives better?

Our Macau site has developed a game that is a mix of "Jeopardy!" and "Who wants to be a Millionaire?": teams answer quiz questions on GMP for points that can be gained or lost. In a non-threatening yet competitive scenario individuals show what they know and find out what they don't know. What is a mark of a richer culture of quality – getting and ever-more senior person to sign the product quality review, or, getting all levels and all disciplines to participate in the quiz? Is it not healthy for plant management to volunteer to have their GMP knowledge tested alongside operators and analysts?

FDA Dean's List

The quality metrics guidance would be incomplete if it did not lead to an FDA Dean's List. FDA already publicises extensively what companies' sites lie at the other end of the bell shaped curve: who receives import alerts and warning letters, what plants are shot down, who is in a consent decree. FDA now needs to come up with a system that identifies the role-models.

The FDA Dean's list algorithm could combine the quality metrics ratings, compliance track record, rate of adoption of best practices, intensity of participation in the standard setting process, inspection performance and feedback on quality culture attributes.

The purpose of singling out those on the FDA Dean's list would be for Industry to know who makes APIs and FDFs really well. Who is ahead in adopting best practices and is innovating in the direction FDA is keen the industry to go to. These sites could be expected to be open for academics to study and report on, and be prepared to be training sites for FDA inspectors. Like in OSHA's VPP star programme, maybe the FDA Dean's List is nothing other than the sites that have been given a special flag: the FDA flag that identifies the sites where its inspectors train. Nothing would give more pride to any site to be part of this élite group, everyone working at such a site will do their very best to never lose that status.

Transformational Guidance

As this guidance defines standard measures of quality that are suitable to compare products, plants and companies across the industry many will start asking for this information. Expect financial analysts, purchasing departments, auditors, payors, prescribersand prospective employees to ask about them to enable decisions on which companies/products to invest in, buy from, prescribe, become employees of… or not. Expect this guidance to have global impact

We remain available should any further clarification be required.

Yours sincerely,

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