PDA
Parenteral Drug Association

Connecting People, Science and Regulation®

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

Reference: FDA Drug Shortages Strategic Plan Docket No. FDA-2013-N-0124)

Dear Sir/Madam,

PDA appreciates FDA initiating this important dialog with industry regarding the drug shortage issue. PDA recognizes the seriousness of the current situation and supports efforts on the agency's part to address it. New and innovative concepts should be discussed with the goal of establishing mechanisms which will promote an industry wide sustainable quality culture that can guarantee high-quality products are consistently manufactured with no disruption to the patient.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical manufacturing including members representing our Board of Directors and our Regulatory Affairs and Quality Advisory Board.

The development of consistent and transparent quality metrics across the pharmaceutical industry is a concept that requires further exploration and discourse between the various stakeholders. Multiple factors should be taken into account when determining the risk of potential shortage and appropriate contingency preparations. For example, some biological products that require long product disposition cycle times, may necessitate more stringent contingency planning with additional agency scrutiny of inventory levels to prevent and mitigate potential shortages. Other products available from multiple suppliers may require the creation and tracking of an overall market inventory.

PDA would be willing to facilitate a meeting between FDA and manufacturers with the purpose of encouraging open discussion on the questions posed in the notice. PDA thanks the FDA for initiating this dialog and looks forward to discussing our thoughts in greater detail as the strategy and implementation of this initiative is developed and implemented.

Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,

Richard Johnson
President, PDA

CC: Denyse Baker, PDA
Rich Levy, PhD, PDA

1. In an effort to address the major underlying causes of drug and biological product shortages, FDA is seeking new ideas to encourage high-quality manufacturing and to facilitate expansion of manufacturing capacity.

a. To assist in the evaluation of product manufacturing quality, FDA is exploring the broader use of manufacturing quality metrics. With that in mind, FDA would like input on the following issues:

What metrics do manufacturers currently use to monitor production quality?

Manufacturers use a variety of internal metrics to monitor production quality. PDA has listed below various types of metrics currently used in the industry and added information on how these metrics are widely used in no particular order or ranking.

- Organizational Health: metrics such as safety (EHS), employee satisfaction, employee engagement, employee talent retention/turn-over, effective people management, employee suggestions and the % implemented, and training effectiveness.
- Risk Management: a change in risk profile, effectiveness of risk management plan, and number of self-identified risks. The comparative metric may also provide transparency to measuring performance across multiple sites.
- Predictive or "Forecast" Metrics: This metric should measure a company's performance against plan, their adherence to meeting the plan, predictive maintenance backlogs and creation or reduction of backlogs related to compliance events.
- Availability of Multiple approved manufacturing sites: Percent of products with dual or back-up manufacturing sites and suppliers for raw materials and primary packaging materials.
- Supplier Metrics: Pharmaceutical and biotech companies often ask the following from their suppliers: Supply assurance of up to 10 years (i.e.: No changes to the item); Redundant facilities for supply; Quality systems, which reach into the raw material supplies and assure the supplies from raw material suppliers; Contingency plans for Act-of-God situations (pandemic, etc.); Safety stock level for critical raw materials of two years minimum and for assembled goods of minimum 3 months.
- Process Capability (CpK): CpK values are indicative of the effectiveness of the control strategy for manufacturing processes and are supported by an in-depth understanding of the causes of variability for both products and process (see PDA's Technical Report TR 59). This is a key metric to ensure predictable performance and reliable supply of pharmaceuticals thereby avoiding drug shortages.
- Trends for in-process and final product test results: Trending metrics may indicate a process that is slowly biasing to the high or low end of validated, normal manufacturing variability and ranges.
- Yield Analysis: Analysis of trends or abnormalities of product yield per batch over time can be a leading indicator of other process or raw materials problems that could have potential to impact quality of product.

- Batches Right First Time: The percent of lots that meet specification and are released with no major investigations indicate if processes and products are robust and can be consistently made in a state of control. The metric could be success rate calculated as (number of lots released) / (number of lots initiated).
- Product Disposition Cycle Times: This metric serves as an indicator of the level of control for the manufacturing process. Longer than planned cycle times might be evidence that there are numerous errors during manufacturing and/or numerous product or supply chain failures that must be identified, documented, investigated, remediated and closed before the product can be released. Cycle time can vary from facility to facility and product to product. It is often longer for biologics.
- Error rates and trend analysis: This metric is used when evaluating non-conformances, discrepancies, deviations, near misses, or investigations. Elements associated with this metric are 1) time to initiate, 2) lack of repeat occurrence (effectiveness), 3) adherence to planned closure time, 4) percentage of 'no root cause found'. Some companies employ a tiered scale for these events that utilize resources based on the criticality of the non-conformance being investigated. A higher error rate or an increasing trend signal could be an indication of inadequate process control, insufficient training of operators and oversight by supervisors, poorly maintained equipment and facilities or a lack of product and process characterization and/or knowledge.
- CAPAs: The metrics are lack of repeat deviations (effectiveness), number of extensions of timelines, adherence to planned closure time which could be an indication of adequacy of resources and prioritization to fix and prevent issues.
- Inspection Outcomes: This metric accounts for critical and major observations and the number of repeat and/or similar observations and the timeliness in meeting corrective actions, including CAPA effectiveness, that are intended to eliminate the repeated citation.
- Complaint rates (complaints per units sold): Trends in complaint rates may indicate deficiencies in the robustness of the manufacturing process and control strategy in addition to product and process design controls and performance. This metric should consider the seriousness of the complaint.
- Recalls: Types of Recalls (Class I, II, and III), BPDRs and FARs submitted to the FDA. This data is already transparent to FDA.

As mentioned in our cover letter, PDA welcomes the initiation of a dialog on Quality Metrics between FDA and the pharmaceutical industry.

To what extent do purchasers and prescribers use information about manufacturing quality when deciding how to purchase or utilize products?

Purchasers may have limited knowledge about manufacturing quality based on press reports or their own personal experience but are generally unaware of potential variation in pharmaceutical product quality and assume products are manufactured to high standards and are closely regulated by the FDA. Product quality information may not be a factor in purchaser or prescriber decision-making because it is not readily available. Purchaser perception of quality is more likely associated with a brand name.

What kinds of manufacturing quality metrics might be valuable for purchasers and prescribers when determining which manufacturers to purchase from or which manufacturers' products to prescribe?

PDA suggests that the following possible quality metrics might be beneficial to purchasers and prescribers.

- The rate of customer complaints or adverse events associated with a particular product.
- Compliance status of the company and/or manufacturing site.
    - Would FDA open TURBO EIR database to manufacturers, buyers and payers?
- Level of service: percent of orders satisfied within agreed upon timeframes and maintaining agreed upon level of inventory with wholesalers.

What kind of manufacturing quality metrics might be valuable for manufacturers when choosing a contract manufacturer?

Metrics used in choosing a contract manufacturer would be similar to the metrics that companies use internally to monitor their own operations and include metrics specific to the quality agreement with the contract manufacturer. Examples are:

- Ability to meet the Contract Giver's Quality System requirements.
- Status of supplier qualification, evaluation of raw materials, supply chain quality management and control system. Availability of alternate suppliers, and contingency plans in case of a catastrophic event.
- Employee turnover rates, combination of skills, knowledge and experience of the employees (education, continuous training and qualification).
- Availability of state of the art/new technologies allowing for more robust manufacturing processes and faster product disposition cycle times.
- Facility maintenance and the on time performance of preventive maintenance and equipment calibration.
- Use of the Knowledge Management and Quality Risk Management concepts
- Process capability (CpK) for manufacturing processes
- Quality System metrics such as OOS data, number of deviations, discrepancies, batch rejection rate, issues/recall rate, complaint rate. In particular, repeat incidents, other CAPA items, with all data logged not just those that relate directly to the specific sponsor product but metrics showing all incidents.
- Environmental monitoring trends and media fill data for sterile product manufacturing
- Facility related inspectional findings and inspection history

How frequently would such metrics need to be updated to be meaningful?

It is important to evaluate data over a period of time, so common cause variation in the metrics can be understood. The frequency would depend on how the metrics are being used. For internal management review, quarterly would be sufficient. For process monitoring to prevent issues, monthly or as close to real time as possible, is suggested to prevent issues from developing unnoticed.

b. The use of a qualified manufacturing partner program similar to one used under the Biomedical Advanced Research and Development Authority (BARDA) has been suggested as a potentially useful approach to expanding manufacturing capacity and preventing shortages. FDA recognizes that there are important potential differences between the BARDA program and the use of a parallel program to address shortage. For example, the BARDA program covers a relatively stable and limited number of products, but drugs at risk of shortage are many, may change rapidly over time, and are difficult to predict in advance. In addition, FDA does not have funding to pay manufacturers to participate in a drug shortages qualified manufacturing partner program or to guarantee purchase of the end product.

With these differences in mind, is it possible to design a qualified manufacturing partner program that would have a positive impact on shortages?

Yes. It could be possible to develop and implement an emergency site ("hot site") that is used in the event of shortages, however there are complexities that must be considered. The preferred approach would be for companies to have backup manufacturing strategies in place for each of their products. This could be alternative internal manufacturing sites or use of CMOs.

c. Are there incentives that FDA can provide to encourage manufacturers to establish and maintain high-quality manufacturing practices, to develop redundancy in manufacturing operations, to expand capacity, and /or to create other conditions to prevent or mitigate shortages?

- Rapid review of new technology implementation and proposed manufacturing line upgrades.
- Faster and simpler approval of additional manufacturing lines as potential backups for single source products at companies.
- Expedited post-approval change process for changes that improve process capabilities or quality.
- Provide positive, feedback for manufacturing sites where a significant improvement was detected in a follow up inspection (e.g., no 483 or proven success of quality improvement programs).
- Reduced regulatory oversight/requirements for companies with a good compliance status and adequate risk mitigation plans to prevent drug shortages, including: downgrading filing categories for other filings such as site transfers, assay improvements as well as the increased use of an extended comparability protocol. Use of other agencies' inspection reports instead of only FDA compliance inspections.
- Waive PDUFA establishment fees for an additional, redundant production site, approved to serve as backup production capacity in the event of a supply shortage from the routine manufacturing site.

2. In our work to prevent shortages of drugs and biological products, FDA regularly engages with other U.S. Government Agencies.

Are there incentives these Agencies can provide, separately or in partnership with FDA, to prevent shortages?

FDA or other government agencies could offer the additional incentives including:

- Financial incentives, such as tax credits and/or federal grants, could be provided to companies that develop a robust risk management program that includes establishing and maintaining redundant manufacturing capacity or extra manufacturing capacity that is dedicated to prevent and mitigate drug shortages.
- Work with DEA to identify potential manufacturers with appropriate licensing to produce controlled substances on shortage.
- Economic incentives to compensate the manufacturers who invest in facilities and quality systems to ensure supply of products for which Medicare reimbursement rates or hospital negotiated prices are lower than the cost to produce.
- Under terms of an agreement similar to BARDA agreements, the FDA could mandate inventory levels for critical drugs.

3. When notified of a potential or actual drug or biological product shortage, FDA may take certain actions to mitigate the impact of the shortage, including expediting review of regulatory submissions, expediting inspections, exercising enforcement discretion, identifying alternative manufacturing sources, extending expiration dates based on stability data, and working with the manufacturer to resolve the underlying cause of the shortage.

Are there changes to these existing tools that FDA can make to improve their utility in managing shortages?

FDA can:

- For drug product, require sole manufacturers to establish a contingency business continuity plan identifying back up manufacturing options that could be executed for an emergency transfer of the manufacturing process.
- Expedite approval for firms adopting new technology and/ or adding redundant manufacturing sites that would mitigate potential drug shortages. This would include both review of submissions and GMP inspections if necessary.
- Waive user fee requirements for post approval changes for approval of additional redundant manufacturing sites.
- Evaluate firms' product supply risk management programs and plans as part of the product approval and/or supplement application process and during GMP inspections, including review of the business continuity plans.

4. To manage communications to help alleviate potential or actual shortages, FDA uses a variety of tools, including posting information on our public shortages Web sites and sending targeted notifications to specialty groups.

Are there other communication tools that FDA should use or additional information the Agency should share to help health care professionals, manufacturers, distributors, patients, and others manage shortages more effectively?

As FDA understands the quality and necessity of products made by sole manufacturers and the impact should their product be at risk for a drug shortage, FDA should engage the manufacturer to identify alternative sources in a swift and timely manner.

Are there changes to our public shortage Web sites that would help enhance their utility for patients, prescribers, and others in managing shortages?

FDA's drug shortage web page and emails to interested stakeholders are excellent and timely. PDA encourages FDA to continue in this manner. The key is to provide rationale that would encourage the manufacturers to make quality products and ensure supply and capacity needs are met.

5. What impact do drug and biological product shortages have on research and clinical trials?

Drug shortages have directly delayed clinical trials. Patient concerns have created delays in program enrollment and in trial completion.

What actions can FDA take to mitigate any negative impact of shortages on research and clinical trials?

FDA could expand their allowance of non-US sourcing of comparator or companion drugs, especially in a shortage situation. There is often the same drug available in Europe or other major markets but not necessarily labeled for US use or sourced from the same facilities as the US product.

FDA may need to modify procedures so that trials conducted with these alternate sourced comparators or companions are considered equivalent to those conducted with US sourced material.

Allowing the use of these sources with appropriate documentation submitted in the IND in shortage situations can facilitate clinical trials.

6. What other actions or activities should FDA consider including in the strategic plan to help prevent or mitigate shortages?

FDA could take the following actions to mitigate or prevent drug shortages:

- Establish economic incentives for manufacturers to invest in new technology and capacity.
- Report compliance status of manufacturing sites and products made at the sites.
- Consider use of a qualified third party to expedite reviews for applications to produce drugs currently on shortage.
- Identify and publish a list of "critical drugs" and require an acceptable risk mitigation plan as a condition of approval. This would apply to all critical new drugs, biologics, and generic drugs.
- All NDA/ANDA and BLA holders must report to FDA on their inventory of "critical drugs" upon request. This information kept with the MA would give FDA transparency to the supply levels with an overall picture of drug supply capability across manufacturers. This would be particularly relevant for ANDA approved drugs where the drug is available from more than one manufacturer.
- In a supply crisis situation, allow and facilitate parallel trade from another country with equivalent approaches to quality system management.
- Improve the ability to of purchasers to cross reference similar or interchangeable products using current NDC codes. Current information based on NDC codes and packaging configurations does not allow prescribers and purchasers to easily find comparable replacements. For example purchasing five packs of 20 vials to satisfy a need for 100 vials when the product packaged in 25 vials is no longer available.