

**PQRI / FDA Workshop
Manufacturing Science
Workshop Report
6/16/03**

- 1. Desired State of Manufacturing Science and the Related Regulatory Processes**
- 2. Achieving the Desired State**
 - a. Culture Change Required**
 - b. Moving from Current Relationship Between Manufacturing Science and Regulatory Processes to Desired State**
- 3. Next Steps**

Desired State of Manufacturing Science and the Related Regulatory Processes

Manufacturing Science encompasses knowledge about products and processes, technology used to manufacture and control these processes, and the underlying foundation of a robust quality system at the manufacturing site.

The Desired State:

- The application of manufacturing science to facilitate the manufacture of pharmaceutical active ingredients and drug products in a reproducible manner, and to mitigate the risk of an event impacting fitness for use.**
- The sharing of knowledge between pharmaceutical firms and FDA to define risk in a culture of trust.**
- The application of regulatory processes proportional to the level of risk and applied manufacturing science demonstrated by the firm.**
- Consistent application and predictability of the regulatory processes .**

Achieving the Desired State

- Culture Change is required by both industry and FDA to move to the desired state.**
 - Trust is the first element required to facilitate the sharing of knowledge that is fundamental to the FDA and industry reaching a common understanding of the state of manufacturing science and risk. Firms must be willing to share the right knowledge with FDA (this does not necessarily mean more data) and FDA must utilize this knowledge in a manner appropriate to achieve the common goals of industry and FDA.**
 - Communications must be open and based on scientific principles.**
 - Firms must evolve from the perspective that “change is bad” to “change is good”. FDA must move from a focus on assessing change**

- through standardized documentation to that of assessing change through the acquisition of appropriate knowledge.
- FDA and Industry have a common objective to ensure that high quality pharmaceutical products continue to be available to the public. Firms must understand that FDA's mission cannot be compromised. FDA must understand that activities that do not contribute to the supply of high quality products inhibit continuous improvement.
 - Firms must continue to move from a compliance mindset to quality by design. FDA must understand that one size does not fit all for regulatory processes and quality by design will only be facilitated by increased flexibility.
 - Fitness for use must be the ultimate driver for FDA and industry.

Moving from Current State of Relationship Between Manufacturing Science and Regulatory Processes to Desired State

The desired state is based on a sharing of knowledge. The knowledge base begins in research and development and continues through technology transfer and commercial manufacturing. Information related to the active pharmaceutical ingredient and drug product formulation, manufacturing processes and analytical methods, critical to quality parameters/attributes, and product specifications are all key elements of the knowledge base.

Currently, firms have a substantial knowledge base on products, however, due to traditional regulatory expectations, only the knowledge requested by FDA is shared. This knowledge base varies from product to product and from firm to firm, but is constantly increasing. FDA may not currently understand what knowledge is available or what the Agency needs to understand the capability of pharmaceutical processes and the key fitness for use indicators.

Firms use the knowledge to understand process capability and the risk of an event impacting fitness for use. Continuous improvement efforts are employed to increase process capability and reduce risk. Risk mitigation strategies using innovative technologies are limited due to real and perceived barriers to implementation.

One of the barriers is the existing regulatory process that does not facilitate the sharing of knowledge and hinders the ability of industry to fully leverage improvements in manufacturing science. Since the knowledge base and potential risk mitigation strategies are not shared, regulatory processes remain inflexible and disproportional to risk in some cases. One area where certain FDA District Offices currently demonstrate limited flexibility is in exercising the option to waive PAI inspections for facilities with good compliance records.

Manufacturing science is dynamic. To achieve the desired state, the regulatory processes have to be similarly dynamic. Four key elements are needed to move from the current state to the desired state.

- 1. Knowledge sharing – what, how and how much?**
- 2. Risk classification using appropriate methodology.**
- 3. Risk mitigation where feasible using technology.**
- 4. Regulatory processes proportional to risk.**

The knowledge sharing process (action item #1) by the firm should be sufficient to provide FDA with an understanding of the following:

- Formulation is appropriately justified .**
- Critical to quality parameters and attributes are known.**
- Preliminary process capability data is available.**
- Rationale for specifications and analytical methods.**

With this knowledge the firm and FDA can determine the potential for events to impact fitness for use (i.e. risk). Using a mutually developed risk classification system (action item #2) a product can be classified.

A firm may choose to mitigate risk using advanced technologies (action item #3). By sharing risk mitigation strategies with FDA the product may be reclassified to a lower risk class. *This is one of the key benefits of a science and risk based approach to GMPs.*

PAT is an example of an advanced technology that can both facilitate building the knowledge base and mitigate risk. PAT will allow a better understanding of changes that impact fitness for use thereby reducing the risk implementing process change. PAT is not a panacea, cannot be applied everywhere, and should not be considered mandatory. PAT will change the traditional concepts of process validation and lead to continuous quality verification strategies.

The preceding items are prerequisites to establishing science and risk-based regulatory processes. Such processes will ensure FDA resources are focused on the highest risk areas and firms are encouraged to use innovative technology to mitigate risk. However, it is incumbent upon the firms to ensure that low and medium risk areas remain in appropriate state of control, since these risk classes will receive less regulatory attention. The regulatory processes will remain unchanged from today when a firm chooses not to use technology to mitigate risk.

Examples of science and risk based regulatory processes follow:

- 1. Specification life-cycle**
 - a. Specifications set at the time of initial filing represent only limited experience with full scale commercial processes**
 - b. Agreements reached at the time of approval would give flexibility for refocusing specifications (e.g. targets, ranges) to provide better control of the process and better product quality**

- c. Not all specifications would lend themselves to a life-cycle approach
- 2. Inspections
 - a. Partnering to ensure a trained FDA inspectional cadre
 - i. Use industry/association personnel to provide training
 - ii. Bring training in-house to FDA to reach more people
 - iii. Leverage FDA's internal experts
 - iv. Provide learning sabbaticals in industry
 - b. Options for the PAIs
 - i. Desired alternative is to have quality systems inspections determine if a facility is acceptable from a cGMP perspective and only selectively use PAIs for inspecting new technology, previously non-compliant firms, first-in-class products, high risk products etc.
- 3. Change management (flexibility): Ability for industry to make changes in a timely manner; to innovate and to reduce the non-value added burden on FDA (action item #4).
 - a. "Super Supplements"
 - i. Information is learned about a process during the first year of commercial production that could only come from manufacture in a routine environment. This information is critical to providing better control of the process and quality of the resulting product.
 - ii. There is a reluctance to submit multiple changes/improvements because the regulatory process does not provide this level of flexibility without significant studies or justification
 - iii. The result is that industry usually opts to forego many of the improvements
 - iv. The desired flexibility would be to allow multiple changes/improvements in a single supplement
 - b. SUPAC Revisions
 - i. Expansion of SUPAC guidance
 - ii. Consider development of a PAT SUPAC (developed similarly to the equipment SUPAC)
 - c. Interpretation of regulations pertaining to supplements
 - i. Evaluate and redefine, as needed, the use of prior approval supplements, changes being affected supplements and annual reports.

Next Steps and Action Items

1. Industry and FDA need to collaborate on what knowledge is to be shared, how best to share that knowledge and how much to share.
2. Industry and FDA need to collaborate on the development of a risk classification.

- 3. Industry and FDA need to agree on how technology can be used to mitigate risk.**
- 4. FDA needs to issue guidance to provide a broader interpretation of current regulations governing original filings, supplements, and regulatory inspections.**