Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites — A Pilot Risk Ranking Model

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EXECUTIVE SUMMARY

The Federal Food, Drug, and Cosmetic Act states that FDA is to inspect domestic drug manufacturing establishments at least once every 2 years. Data show, however, that the number of registered human drug establishments has increased in the last 25 years while the number of FDA human drug inspections has decreased over the same period. The Agency no longer has the resources to meet this statutory requirement. Beginning in fiscal year 2005, as part of the Agency's CGMPs[1] for the 21st Century Initiative, the FDA will pilot a risk-based inspection model for prioritizing drug manufacturing establishments for routine inspection. The model is based on a risk-ranking and filtering method that is well-recognized, objective, and rigorously systematic. This approach should help the Agency make the best use of its limited surveillance and enforcement resources while maximizing the impact of those resources on the public health. Lessons learned from the results of the 2005 pilot will be incorporated into future iterations of the risk-based inspection model.

BACKGROUND

On August 21, 2002, FDA announced a major new initiative pertaining to drug quality regulation, *Pharmaceutical CGMPs for the 21st Century: A Risk Based Approach* (http://www.fda.gov/oc/guidance/gmp.html). In the initial concept paper issued on the initiative, FDA identified "a risk-based orientation" as one of the guiding principles that would drive the initiative. The concept paper stated that "resource limitations prevent uniformly intensive coverage of all pharmaceutical products and production" and that "to provide the most effective public health protection, FDA must match its level of effort against the magnitude of the risk." The concept paper noted that in the short term, FDA intends to place more emphasis on risk-based allocation of resources for the oversight of drug quality. However, the concept paper also acknowledged that developing more systematic and risk-based approaches would be a long-term effort and that an intermediate step is to "use emerging science and data analysis to enhance compliance programs to target the highest risk areas."

On August 20, 2003, FDA released its Strategic Action Plan, *Protecting and Advancing America's Health*. (http://www.fda.gov/oc/mcclellan/FDAStrategicPlan.pdf). This strategic plan reflects the Agency's continuing support and priority for the risk management goals of the *Pharmaceutical CGMPs for the 21st Century* initiative. The first core goal identified in the plan

[1] Current Good Manufacturing Practices (CGMP) Initiative.

is Efficient Risk Management, directed toward "ensuring that the Agency's limited resources can provide the most health promotion and protection at the least cost for the public." The discussion of this goal specifically highlights the efforts of the *Pharmaceutical CGMPs for the 21st Century* initiative as central to the Agency's risk management program. One of the objectives under this goal is to "provide high quality, cost-effective oversight of industry manufacturing, processing and distribution to reduce risk." Specifically identified under this objective is developing "new inspection approaches to more effectively utilize … resources." Also highlighted is the need to "use emerging science and data analysis to *target the highest risk* areas."

The Federal Food, Drug, and Cosmetic Act states that registered domestic drug establishments shall be inspected by FDA at least once every two years.[2] Although the Agency's resources used to be sufficient to meet this goal, data from human drug inspections (not including biological products) demonstrate that the Agency is no longer able to inspect at this level. FDA data indicate that the number of registered human drug establishments has increased by more than 400 percent in the last 25 years. Over the same time period, the number of human drug CGMP inspections conducted has decreased by more than 60 percent. As a result, it is impossible for FDA to achieve uniformly intensive CGMP inspectional coverage for all registered drug facilities. These resource challenges have required FDA to choose more carefully those sites it intends to inspect.

Prioritizing sites for inspection has been a long-standing challenge for Agency managers. In the past, FDA district offices have identified specific sites in their geographical areas for inspection each year. These decisions were made based on a variety of informally applied factors, including, for example, a district manager's knowledge of the inspectional history and corporate culture of the district as well as the perceived risk to the public health of manufacturing errors. Even before the CGMP Initiative, the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) prioritized the use of inspectional resources. Three categories of facilities were identified as high priority for inspections, those that produce sterile drug products, those that produce other (non-gas) prescription drugs, and new registrants that had not been inspected previously.

This prioritization was an important first step toward developing a risk-based approach for manufacturing inspections. However, FDA recognized that much more needed to be done to ensure a systematic approach to prioritize manufacturing sites and ensure that FDA inspectional resources and oversight achieve the maximum public health impact. Recognizing that FDA could not inspect every manufacturing site at equal frequency and depth with the present inspectional resources, an Agency working group was created to develop a more rigorous risk-based approach to resource allocation for CGMP inspectional oversight. This paper describes the results of that effort so far.

[2] See 21 United States Code 360(h).

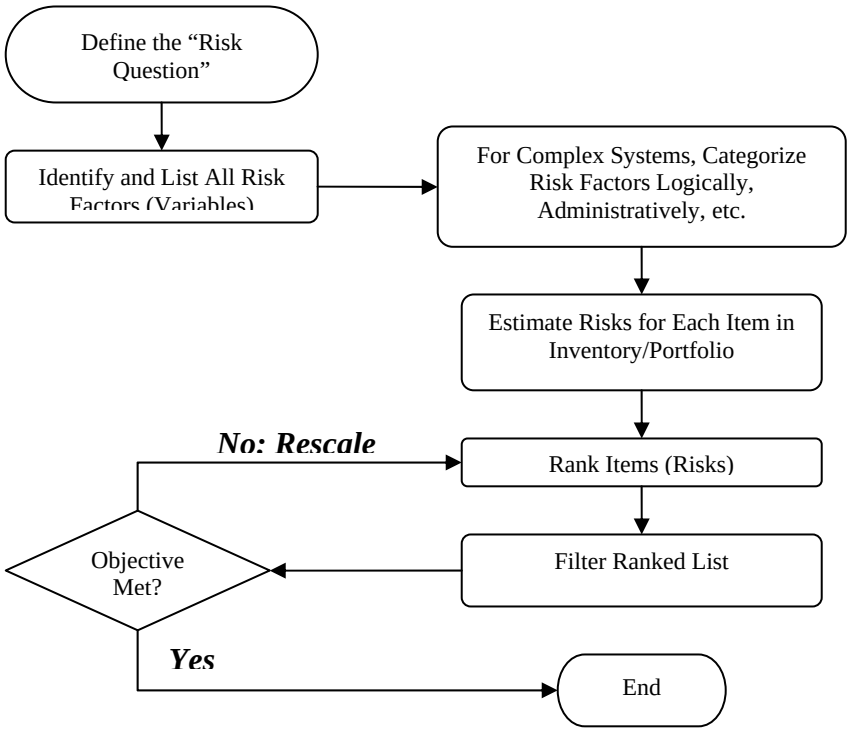
RISK RANKING

Risk ranking is a risk management tool for comparing and prioritizing risks. Risk ranking has a long track record among governmental agencies that prioritize work on portfolios of hazards that fall within their regulatory purview. Among the agencies that regularly use risk-ranking methods are the National Aeronautics and Space Administration, Department of Defense, Environmental Protection Agency, and Nuclear Regulatory Commission. Risk ranking, or similar approaches, have been described by Haimes (1998), Ayyub (2003), Finkel and Golding (1994), Davies (1996), Konisky (1999), and Health and Safety Executive (1999).

Often the need for risk ranking is driven by a disparity between obligations to manage, mitigate, or reduce an array of risks (or many sources of a given type of risk) and available resources. Formal risk ranking is based on well-defined analytical processes and enhances the quality, transparency, and, potentially, the performance of risk management programs. Formal risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool.

Formal risk ranking uses an analytical process to pose a risk question; identify potential hazards and risks; characterize factors that can be used as variables for quantifying risk; and mathematically combine the variables to yield an overall *risk score* for risk ranking. Described below are three typical elements of formal risk ranking: hazard identification, risk estimation, and risk filtering and ranking. The overall process is schematically outlined in Figure 1.

Figure 1. General Process for Risk Ranking



A high-level schematic is shown: the process includes numerous intermediate administrative activities, such as organizing teams of experts and determining data needs under each factor

Hazard Identification

Risk ranking of complex systems typically requires an identification of multiple quantitative and qualitative factors for each risk and/or hazard. These factors, in turn, often fall within a complex hierarchy of criteria under a stated risk question. For example, a simple risk question, such as "what factors might be related to the risk of poor drug product quality?" is likely to generate different lists of factors depending on the background, perspective, and expertise of the respondent. For example, one group might focus on physico-chemical parameters of the drug product. Another group might focus on the processes used in manufacture, or on the factors related to the facility's regulatory history with the FDA.

The conceptual understanding and perception of risk is expected to differ depending on an individual's pertinent training, prior beliefs about the risk, and other psychosocial factors (e.g., Morgan et al., 2002). For the first phase of risk ranking, the job of risk analysts is to elicit from a diverse group of experts a broad range of factors, system concepts, and any other information that might inform the risk analysis.

This initial brainstorming serves as a qualitative *hazard identification* phase of the overall risk assessment. In hazard identification, sources of harm, or *hazards*, are identified as *possibilities* independently from the *probabilities* or likelihoods that the hazards cause harm in the defined system.

An open-ended, brainstorming approach to identify hazards will generate an abundance of factors believed by individuals or groups of individuals to contribute to risk. In a complex system, such as FDA's drug manufacturing inspection system, some factors are likely to be objective and quantitatively supported while others are likely to be subjective and value-based. Furthermore, the initial list of factors is likely to include competing, overlapping, and, perhaps, multi-dimensional attributes. The second phase of risk ranking typically includes organization and refinement of the original list hierarchically as a predecessor for model building. The need for logical organization (or classification) of factors into categories is apparent; however, other considerations are often useful in categorizing factors in the early phases of risk ranking (see Table 1, Morgan et al., 2000).

Table 1. Desirable Attributes of an Idealized Risk-Categorization System for Risk Ranking

Categories for Risk Ranking should be…
Logically consistent • Exhaustive so that no relevant risks are overlooked. • Mutually exclusive so that risks are not double counted. • Homogeneous so that all risk categories can be evaluated on the same set of attributes.
Administratively Compatible • Compatible with existing organizational structures and legislative mandates so that lines of authority are clear and management actions at cross purposes are avoided. • Relevant to management so that risk priorities can be mapped into risk-management actions. • Large enough in number so that regulatory attention can be finely targeted, with a minimum of interpretation by agency staff. • Compatible with existing databases, to make best use of available information in any analysis leading to ranking.
Equitable • Fairly drawn so that the interests of various stakeholders are balanced.
Compatible with cognitive constraints and biases • Chosen with an awareness of inevitable framing biases. • Simple and compatible with people's existing mental models so that risk categories are easy to communicate. • Few enough in number so that the ranking task is tractable. • Free of the "lamp-post" effect, in which better understood risks are categorized more finely than less understood risks.

Source: Morgan, M.G., et al., *Risk Analysis* 20:49-58 (2000).

Risk Estimation

Risk ranking requires estimates of risk for each identified hazard in a list of hazards. One approach is to use a single tool for estimating risks. For example, a risk matrix is often used for risk ranking in systems for which quantitative risk information is scarce. Risk matrices use the probability of occurrence of the defined risk as one dimension and the severity of the risk as the second dimension (see Figure 2).

A variety of risk tools for the estimation of risks are available to use in conjunction with, or in place of, risk matrices. Examples include fault tree analysis (FTA), probabilistic risk analysis (PRA), event trees (ET), failure mode and effects analysis (FMEA), and expert elicitation. In general, any method that can estimate the probability of occurrence of an adverse event of given severity, given an exposure or existence of the hazard, might suffice for risk estimation.

Figure 2. Example of a risk matrix for human health risks

Severity Scale	Probability of Occurrence				
	Very Low	Low	Medium	High	Very High
Death	*Medium*	*Medium*	*High*	*High*	*High*
Hospitalization	*Low*	*Medium*	*Medium*	*High*	*High*
Acute Illness	*Low*	*Medium*	*Medium*	*High*	*High*
Worry	*Low*	*Low*	*Low*	*Medium*	*Medium*

As shown in Figure 2, the matrix approach qualitatively assigns a level of risk: high, medium, or low. For example, the risk in question might be *botulism poisoning from canned food?* Contemporary food packaging standards reduce the probability of occurrence to *Low-Very Low*; however, the consequence of a poisoning event is sometimes death. Thus, the overall risk might be scored as *Medium*.

Ranking and Filtering Risks

Once risks — referred to as risk *scores*, *weights*, *ranks*, or *numbers* — have been estimated for each item in the risk management system, ranking (the risks) can occur. This phase of risk ranking has been referred to as "filtering" (Haimes, 1998), which seeks to scale or filter the list commensurately with the resources available to expend on risk management (e.g., mitigation or risk reduction). For some organizations, resources might be available for managing all items in the risk ranking; and for others, resources might be limited to accomplishing only the top N percent of the list. Risk ranking for the former is done to ensure that the worst risks are addressed first. In the latter situation, the ranking is done to prioritize resources with prior knowledge that not all items on the list can be allocated resources.

DEVELOPMENT OF RISK RANKING MODEL

The term *model* has different meanings and degrees of formality depending on the scientific discipline and the intended application. In this discussion, *model* refers to risk analytical processes that are used to systematically categorize risk factors for conceptual modeling and convert raw data and expert judgment into quantifiable information. The mathematical formalism in the final risk ranking tool is also considered part of the model. It is important to note that models are ultimately abstract representations of reality and that there is no right model, but only ones that are useful in answering the risk management question at hand.

To develop the risk ranking model for site selection, FDA followed a multi-step analytical process similar to those described above: hazard identification and conceptual modeling, risk estimation, and risk filtering.

Hazard Identification and Conceptual Modeling

A two-step process was conducted: First, a wide range of factors that could be incorporated in the model (henceforth *potential risk factors*) was identified. Second, these factors were organized into principal, or top-level, components of the risk-ranking model.

A diverse group of FDA experts with experience in (drug) review, manufacturing controls, and inspectional oversight from CDER, CBER, CVM, the Office of Commissioner, and ORA (Headquarters and Field Offices) participated in a number of brainstorming sessions and a survey to identify potential risk factors. The initial brainstorming served as a qualitative hazard identification phase for the overall risk assessment. In hazard identification, sources of harm (i.e., hazards) are identified as *possibilities* — not *probabilities* with stated likelihoods of occurrence. The conceptual-level modeling exercise sought the universe of hazards as a baseline from which to begin focusing on those hazards for which the likelihood of occurrence may be significant.

The general question posed of these experts was "in your experience, what are the principal factors important in predicting adverse impacts to drug quality?" Specific questions that the expert group considered, directly or indirectly, in identifying candidate risk factors included:

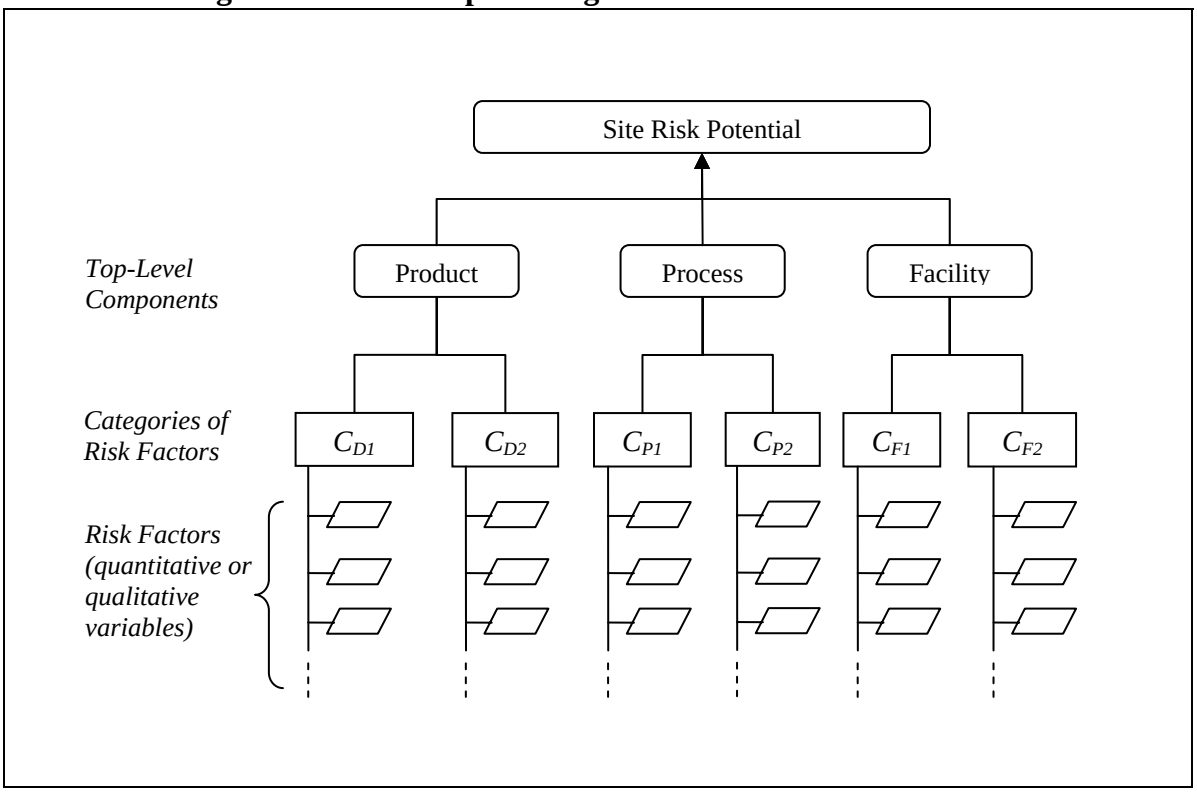
- What hazards (sources of harm) related to manufacturing can adversely impact drug quality attributes?
- What variables are associated with, or predictive of, those hazards?
- What processes and process parameters are critical for quality attributes?
- What factors may affect the identified hazards and critical parameters and processes?
- What factors are predictive of high or low quality manufacturing?

This process resulted in a list of over 70 potential risk factors, of which some are potentially predictive (e.g., batch sizes, dedicated lines) and others are directly relevant to quality and public health (e.g., sterility, intrinsic toxicity). To develop the conceptual framework for the risk ranking model, these factors needed to be hierarchically organized according to their level of generality and causal relationships. By direct observation, several FDA experts organized the list of risk factors into broad categories, or *top-level* components, of *Product, Process* and *Facility*, see Table 2 and Figure 3.

Table 2. Top-Level Components for the Site Selection Model

Factor Category	Description	Example(s)
Product	Factors pertaining to the intrinsic properties of drug products such that quality deficiencies could potentially and adversely impact public health.	Dosage form; intrinsic chemical properties
Facility	Factors relating to characteristics of a manufacturing site believed to be predictive of potential quality risks, such as the lack of effective quality systems.	Poor CGMP compliance history
Process	Factors pertaining to aspects of drug manufacturing operations that may predict potential difficulties with process control and/or vulnerability to various forms of contamination.	Measuring; mixing; compression; filling

Figure 3. Conceptual Organization of the Site Selection Model



The construct for a risk-based site selection model was developed based on the above hierarchical modeling framework. Under this construct, a Site Risk Potential (SRP) is a function of the weighted risk potentials for each of the categories, *Product*, *Facility* and *Process*.[3] The risk potential for each top-level component is, in turn, a function of select potential risk factors. Thus, a SRP score is derived by mathematical combination of weights or ranks assigned to select potential risk factors. The assignment of weights or ranks to select potential risk factors is based on either empirical evidence or expert judgment or combination of both. To calculate the SRP score, weights/rankings for individual potential risk factors are numerically discrete values (e.g., 0.1, 1, 2, 3, 6).

Implementation of the Model and Risk Estimation

The selection of potential risk factors within each top-level component (Product, Process and Facility) and their weight assignments have significant influence on the SPR score. In implementing the risk-ranking model, it is important that the assignment of a weight or rank to each potential risk factor is grounded in empirical evidence or based on systematic and transparent collection and analyses of expert judgment. Many potential risk factors that were initially identified by the FDA expert group were excluded from the current implementation of the model because of lack of data or other data limitations, including difficulties in linking data elements with specific manufacturing sites and differing data dictionaries among various existing databases. The current iteration of the Agency's pilot risk ranking model includes the following elements:

Product Component

Currently, there are two types of factors in the product component of the model, as depicted in Figure 4.

1. Intrinsic factors

Factors such as sterility, medical gas, and the determination of prescription (Rx) versus over the counter (OTC) currently in the model are crude surrogates to distinguish between products with higher and lower potential for public health consequence should there be a drug defect. For example, the current model assumes that if there is a quality defect, sterile drugs would have a higher public health consequence than nonsterile drugs; hence, sterile drugs are given a higher weight.

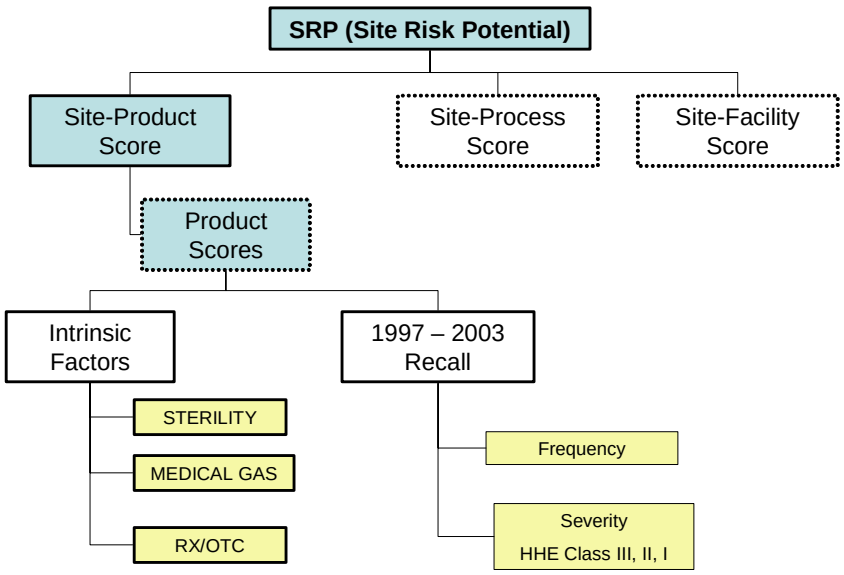
Existing FDA data describing types of products manufactured at each site have been accessed and sites have been assigned weights based on these intrinsic factors. In addition, the current model considers sites manufacturing specific products where there is a heightened risk of cross-contamination, such as sites manufacturing highly sensitizing agents (e.g., penicillin) and at least one other product using similar processing methods.

[3] The default approach is to estimate SRP from a linear combination of the *Product*, *Facility*, and *Process* estimated risk potentials. Issues concerning higher order terms, such as interactions (*Product* × *Facility*), and optimization of the coefficients (weights) for filtering, are presently under study.

2. Past recalls for quality defects

FDA human drug recall data provide information on past recalls for quality defects with potential for human health hazard. The data were analyzed based on product types (i.e., routes of administration and dosage forms). Using a likelihood and severity matrix, weights were assigned to product types based on frequency of recall and health hazard severity (i.e., HHE class I, II, and III). Product types with a high frequency of recall occurrence and high hazard severity have been given higher weights. Existing FDA data describing types of products manufactured at each site have been accessed, products manufactured at each site have been correlated with product types developed for the recall data, and sites were assigned weights based on recall classifications associated with the recalled product types.

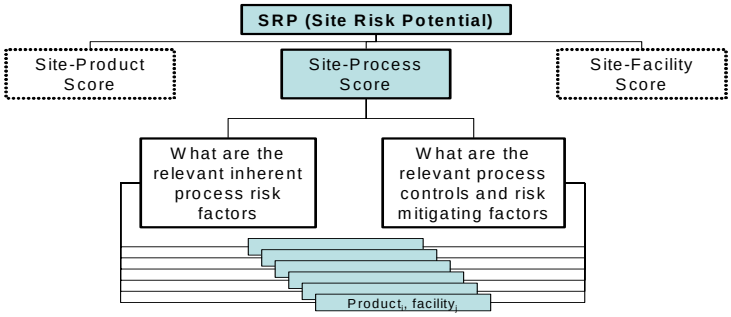
Figure 4. Product Component Factors



Process Component

It was agreed among FDA internal experts that some processes are more complex and more susceptible to problems than other processes. It was further recognized that one primary goal of the CGMP inspections is to ensure that processing operations are in a state of control. Thus, consensus among FDA experts was that it would be important to include process-related risk factors in the risk-ranking model. The key issues in the implementation of the risk-ranking model involves questions concerning the relevant inherent process risk factors, the relevant process control and risk mitigation factors, and how to weigh/rank them, as depicted in Figure 5, below:

Figure 5. Process Component Factors



Although the Agency lacks specific databases to answer these questions, the Agency has a large number of staff with expertise in this area. To systematically capture this body of knowledge and to formulate the key process-related factors and weights for inclusion in the current implementation of the risk-ranking model, an expert elicitation survey was developed by an Agency-wide working group. The working group included FDA expertise in pharmaceutical manufacturing sciences, chemistry, risk analyses, and expert elicitation.

Based on the working group deliberation, two types of process-related factors were identified for inclusion in the survey and subsequently the risk-ranking model:

1. Factors associated with maintaining process control
2. Factors associated with potential vulnerability to product or environmental contamination

The survey was designed to elicit from appropriate Agency experts a risk-ranking (i.e., from high to low) of the probability of a loss of a state of control and, independently, the vulnerability of the process to contamination for a product category and processing operations associated with that product category. Experts were surveyed on risks associated with commonly employed manufacturing operations (e.g., measuring, mixing, compression, and filling) and for a variety of product categories (e.g., immediate and modified release solid-oral drugs, sterile liquids, metered dose inhalers, and active ingredients by chemical and fermentation processes).

Survey results were statistically analyzed and process control and contamination weights were assigned to each product category identified in the expert elicitation survey. Existing FDA data describing types of products manufactured at each site were accessed, products manufactured at each site were correlated with product categories developed for the expert elicitation, and sites

were assigned weights based on process and contamination weights associated with the expert elicitation product categories.

Facility Component

Currently, the facility component of the risk ranking model includes 4 factors:

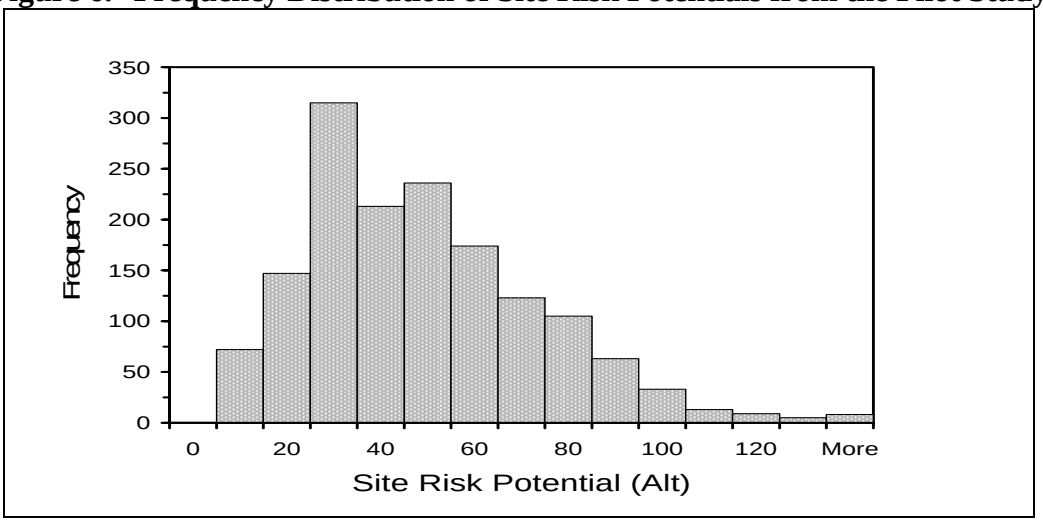
1. History of violation (e.g., CGMP deficiencies have higher weights)
2. History of inspection (e.g., no prior inspection, newly registered/licensed or no CGMP inspection in the past 2 years have higher weights than those with recent CGMP inspection)
3. Estimated volume of production output (surrogate for exposure, e.g., higher volume and production output, higher weights)
4. Type of establishment (e.g., manufacturer, repacker, contract lab)

These factors were identified from existing FDA databases. These factors were assigned weights using an ordinal scale similar to the Product and Process factors. Most of the factors are self-explanatory.

Risk Filtering and Model Summary

To test the robustness of the risk ranking model, a pilot analysis of an inventory of over 1,500 facilities was conducted. The pilot ranking, based on the historical data as described above, showed that model could adequately *spread* the site risk potential (SRP) score for filtering and that the distribution of the SRP scores is only slightly right-skewed (see Figure 6).

Figure 6. Frequency Distribution of Site Risk Potentials from the Pilot Study



The distribution of scores, shown for illustration only, shows that the first-pass modeling yields a reasonably normal distribution of scores. The magnitude of the SRP scale is arbitrary.

In the current iteration, the risk ranking model will lead to a ranked list of sites for routine CGMP inspection coverage such that a site's chance of being selected for inspection would increase if it:

- has not been inspected recently (or ever)
- has a higher production volume
- has a history of significant violations
- makes products associated with a high frequency of recalls and for serious defects
- uses processes expected to have a greater potential for cross-contamination and/or loss of a state of control
- makes sterile and/or prescription drugs[4]

This model does not exclude any site or product type from being potentially selected as a high priority site. It is expected that sites with effective quality systems and superior process understanding will be less likely to have a history of significant violations or have multiple product recalls, and such sites would, generally, be expected to have less frequent or intense inspectional coverage than would otherwise be the case. Similarly, sites that have successfully implemented risk-mitigation techniques would likely have a better inspectional history and fewer recalls.

Individual risk-factor weights and final scoring information, as well as specific information used to generate the weights and scores, are intentionally not provided in this paper. FDA does not intend to publish or disclose such details of a site's individual score or ranking, in order to be able to effectively enforce the law.

[4] Medical gas trans-filling operations are outside the scope of prescription drug manufacturing sites described herein.

FISCAL YEAR 2005 PILOT

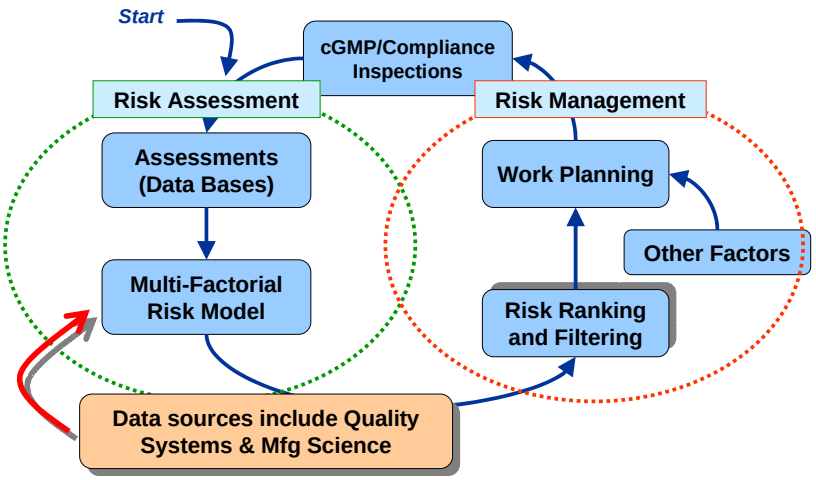
CDER will use this risk-based model to assign a SRP score to each site in accordance with the identified factors and will report this information to each district office as per normal planning cycles. The report will include a description of the basis for each site's score, so that the district will be aware of factors influencing the site score. It is anticipated that the model will be used to select approximately half of all sites inspected under CDER's routine CGMP inspection program (CP7356.002, Drug Manufacturing Inspections), and in fulfillment of the established performance plan for inspecting high-priority manufacturing sites. Each FDA district office will decide which remaining sites to inspect. Feedback from each district office will be solicited on their local assessment of the risks associated with the selected sites and their use of the model SRP scoring elements.

FUTURE REVISIONS

A first principle of risk management is that risk management is an iterative process. In essence, risk management is a performance-based activity because risk managers assess the effectiveness and efficiency of their risk management programs with an eye toward modifications in program or model parameters that might improve future performance.

The selection of risk factors in this version of the model was largely driven by the readily available data. As data quality improves and new data are gathered, the Agency will adjust and redesign the model using a similar process involving Agency expert assessment and peer-review. Additionally, FDA intends to seek opportunities for source data outside the Agency, including, for example, a survey of existing practices or elicitations of industry experts. FDA envisions that this risk management effort will follow a cycle of improvement, which may be depicted as follows in Figure 7:

Figure 7. Risk Ranking and Filtering in the Risk Analysis Cycle



In the figure above, risk assessment and risk analysis activities intersect when the risk assessment model is applied to predictions of risk (e.g., site risk potentials). In the iterative process of risk analysis, the risk assessors learn from the performance of the model (here, in *CGMP Compliance Inspections*), and use that knowledge to question, test and possibly modify the model for improvement.

An important consideration for the future will be to explore the feasibility of benchmarking public health outcomes from poor drug quality to better align resources and programs to maximize public health benefit in this area. Other changes under consideration include incorporating more active mitigating risk factors, such as process capability metrics for each site's product line and other indicators of process understanding and control.

FDA understands that this inspectional model may help create additional incentives to develop enhanced process understanding and controls (for example, see the PAT Guidance), and successfully implement risk-mitigation techniques including effective quality systems and use of modern manufacturing technologies and analyses. FDA intends to continue to adjust the model to capture the benefits of various risk-mitigation strategies that are adopted as FDA and the industry come to better understand the variables associated with high quality pharmaceutical manufacturing.

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