

This article describes the development, implementation, and results of an expert elicitation survey about risks associated with pharmaceutical manufacturing processes, and discusses potential application of this data collection methodology to a broader range of experts.

Reprinted from
PHARMACEUTICAL ENGINEERING®

The Official Journal of ISPE
July/August 2005, Vol. 25 No. 4

Elicitation of Expert Knowledge about Risks Associated with Pharmaceutical Manufacturing Processes

by Dr. Nga L. Tran, Brian Hasselbalch, Dr. Kara Morgan, and Dr. Gregg Claycamp

Introduction

Recently, the FDA-Center for Drug Evaluation and Research (CDER) conducted a survey to elicit expert knowledge about risks associated with the manufacturing processes of a number of pharmaceutical product types. This survey was carried out as part of the Center's ongoing effort to develop and implement a systematic approach to prioritize sites for routine cGMP inspection.

The International Conference on Harmonization (ICH) in the current draft of ICH document Q9, Quality of Risk Management, defines risk as a combination of the probability of the occurrence of harm and the severity of that harm. As an ICH participant, CDER recognizes this definition of risk.

Prioritizing sites for inspection has been a long-standing challenge for Agency managers. Historically, FDA district offices have identified sites for annual inspection 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. More recently, under the cGMP Initiative, FDA-CDER has implemented a systematic approach to prioritize sites for inspection

in order to ensure that FDA inspectional resources and oversight achieve the maximum public health impact. This effort thus far has led to a risk ranking framework that is based on three principal components: *Product*, *Process*, and *Facility-Table A*. A more detailed description of the CDER-risk-ranking model has been described in a white paper published by the Agency.¹

To implement this risk-ranking framework, a risk estimate, rank, or weight must be assigned to the factor associated with each top-level component (Product, Process, and Facility). Such weight assignments ultimately determined the final site score, which would be used to rank and select site for inspection. As such, whenever possible, the weight assignment would be objectively based on empirical data. In order to estimate the relative contribution to risk for the product and facility scores, we used the available information on product recall, inspection, and compliance histories to operationalize these aspects of the risk-ranking framework. However, such data do not exist for factors relating to the process component.

The key issues in the implementation of the process factor of the risk-ranking model involve questions concerning the relevant inherent process risk factors, the relevant process control

Table A. Top-level components for the site selection model.¹

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

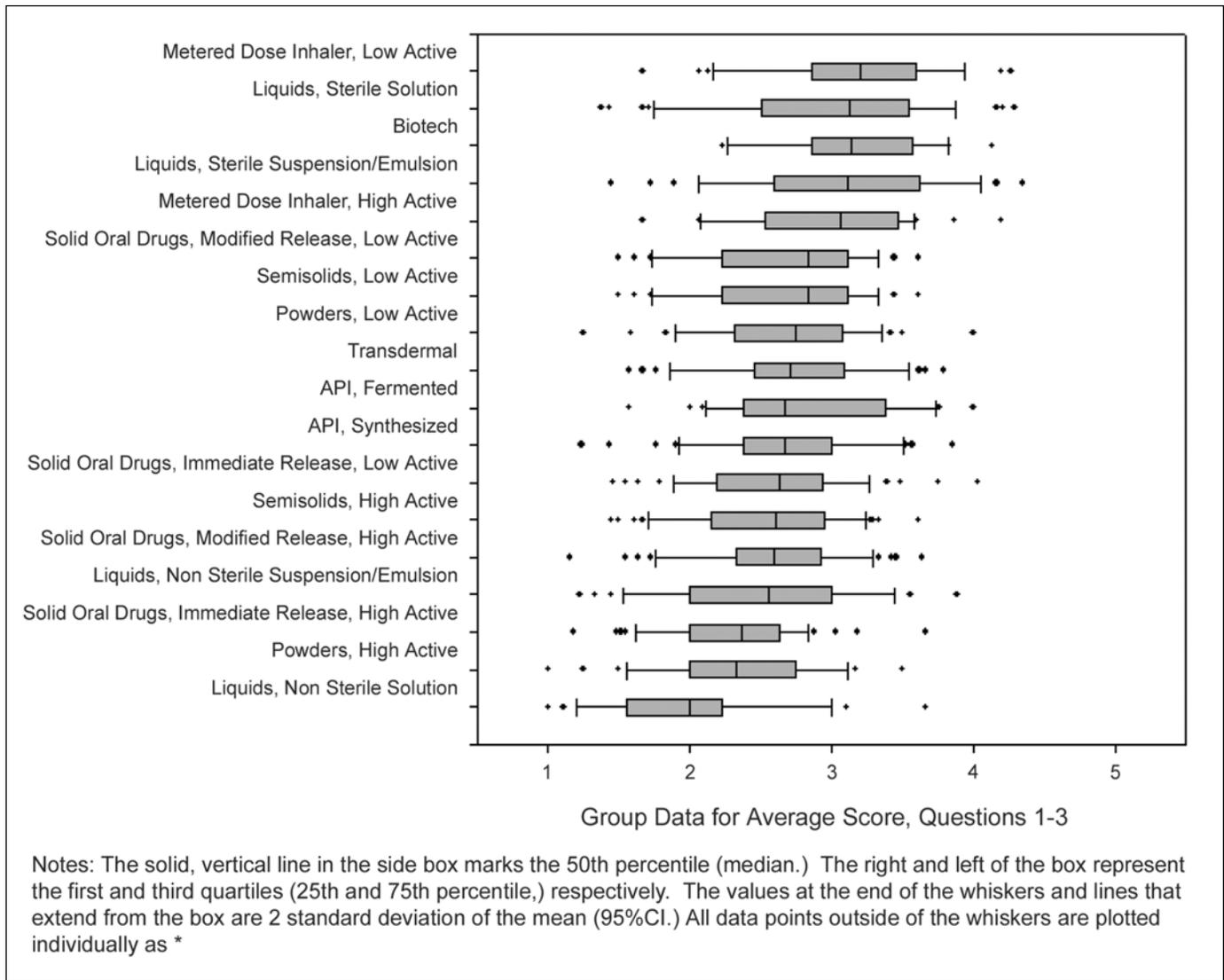


Figure 1. Box plots of product rankings based on potential for a loss of state of control.

and risk mitigation factors, and how to weight the importance or rank them. Although the Agency does not have the information needed to answer these questions, the Agency does have a large number of staff with expertise in this area. An expert elicitation survey was developed by an Agency-wide working group to systematically capture this body of knowledge, and formulate the key process-related factors and weights for inclusion in the current risk-ranking model.

Although it is preferred that data used in decision-making are empirically derived, it is widely recognized that the needed data are sometimes not available or, if available, are incomplete, unreliable, or only indirectly applicable. In such cases, expert judgment is the only way to complete the required knowledge. Expert data obtained under rigorous methodological rules are increasingly being recognized as a valuable asset in numerous scientific fields, including chemistry, nuclear sciences, seismic, and civil applications.

Methods

Expert Elicitation Survey Development

An FDA working group that included expertise in pharma-

ceutical manufacturing sciences, chemistry, risk analyses, and expert elicitation was established to develop the expert elicitation survey. The working group was initially confronted with several broad questions including:

- What are the relevant process-related risk factors?
- What are the sources of variability and poor quality?
- What, if any, units of operation and/or products are more liable to a loss of control or at risk to contamination?

Working group members agreed that answers to these challenging questions would depend on the type of products involved. However, it also was acknowledged that given the large number of potential products, it would not be feasible to conduct a survey that would elicit answers for every possible combination of product and manufacturing step (or unit of operation). To facilitate the survey, we recognized the need to identify “mutually exclusive” categories of products and units of operation and were encouraged by ISPE’s approach published in its Baseline® Guide on Oral Solid Dosage Forms.⁴ In this Guide, ISPE characterizes levels of effort and difficulty

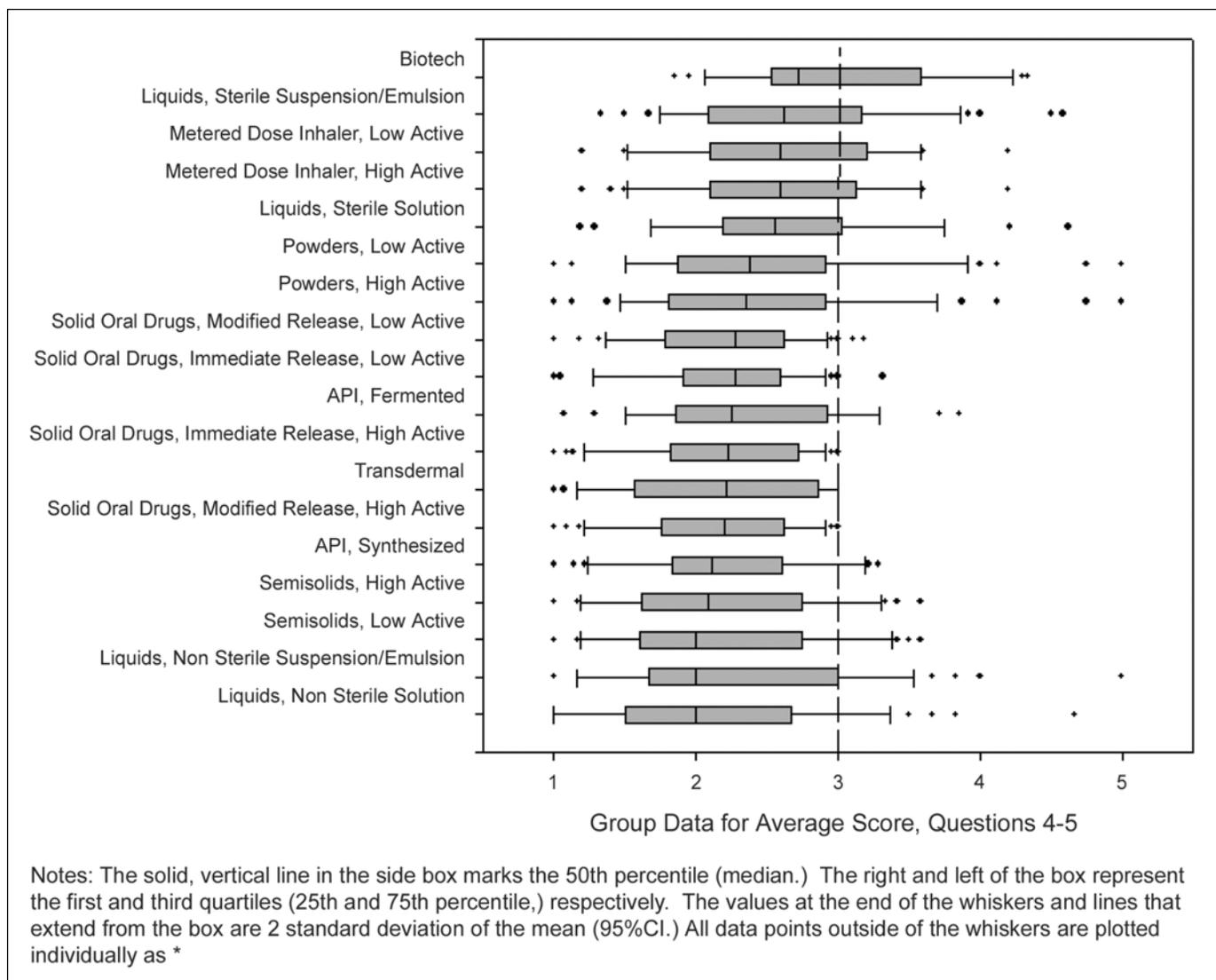


Figure 2. Box plots of product rankings based on potential for contamination.

across a variety of areas of consideration in constructing a new production facility broadly by unit operation and equipment level.

In general, the survey we used was designed to elicit from respondent a relative ranking of the likelihood of a loss of a state of control and of the vulnerability of the process to contamination for a product category and for each individual processing operation associated with that product category. Experts were asked to rate the manufacturing steps according to the 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).

Subsequent to the initial discussion, the Working Group met on several occasions to discuss and identify variables that would be used to evaluate the risk to product failure and variability, “mutually exclusive” categories of products and key units of operation typically associated with these product groups. The following sections describe these steps.

Step 1: Identifying Variables of Interest and Developing Survey Questions

A list of potential variables that could be used to evaluate risk of product failures and variability were first generated by the Working Group members. Among the initial list were: contamination (product to product and environment to product), protecting operators (if operators could be harmed by exposure to material under process, it could result in less control or attentiveness to quality), yield, changeover, cleanability, validation/qualification (validation to be defined as inclusive of qualification), and maintenance. From this initial list of variables, the Working Group identified two broad types of process-related factors:

- factors associated with maintaining process control, i.e. process control variables
- factors associated with potential vulnerability to product or environmental contamination, i.e., contamination variables

1. API Fermentation
2. API Synthesized
3. Biotech
4. Liquids, Non-Sterile, Solution
5. Liquids, Non-Sterile, Suspension/Emulsion
6. Liquids, Sterile, Solution
7. Liquids, Sterile, Suspension/Emulsion
8. Metered Dose Inhaler (MDI), High Active
9. Metered Dose Inhaler (MDI), Low Active
10. Powders, High Active
11. Powders, Low Active
12. Semisolid (Ointment/Cream), High Active
13. Semisolid (Ointment/Cream), Low Active
14. Solid Oral Drugs, Immediate Release, High Active
15. Solid Oral Drugs, Immediate Release, Low Active
16. Solid Oral Drugs, Modified Release, High Active
17. Solid Oral Drugs, Modified Release, Low Active
18. Transdermal

Table B. Product categories in process elicitation survey.

As these two main factors were crystallized as the central focus of the expert elicitation survey, questions were developed to capture the important concepts underlying each of these factors. The following three questions were constructed to capture the experts' input on the three mutually exclusive elements of risk to loss of control deemed to be critical by the Working Group. Response options are shown after each question.

1. To what degree does this unit of operation contribute to variability in quality of the final product?
 1. minimal; 2. minimal to moderate; 3. moderate to high; 4. high to very high; 5. very high
2. How difficult is it to maintain this unit of operation in a state of control?
 1. slightly; 2. slightly to moderately; 3. moderately; 4. moderately to very; 5. very
3. If a problem does occur, how reliable are the current detection methods?
 1. very; 2. very to moderately; 3. moderately; 4. moderately to slightly; 5. slightly

And the next two questions were developed to capture the expert judgment on the two mutually exclusive elements deemed critical by the Working Group regarding contamination:

4. Is this unit of operation more or less vulnerable to contamination from previous product?
 1. slightly; 2. slightly to moderately; 3. moderately; 4. moderately to very; 5. very
5. Is this unit of operation more or less vulnerable to contamination from the environment?
 1. slightly vulnerable; 2. slightly to moderately vulnerable; 3. moderately vulnerable; 4. moderately to very vulnerable; 5. very vulnerable

Step 2: Identifying Product Categories and Units of Operation

Because the manufacturing of pharmaceutical products closely track product dosage form, products were categorized by dosage form, i.e., tablets, liquids, and metered dose inhalers. For each dosage form, additional distinction would be made if it was determined by the Working Group that such distinction would lead to a different answer to the questions listed in Step 1. For example, higher and lower active weight content was used to further categorize similar dosage forms since the Working Group members believed that the responders would need to make these distinctions in order to be able to accurately answer the posed questions. Using this approach, the Working Group identified 18 mutually exclusive product categories to be included in the expert elicitation survey. Table B lists these product categories.

To identify the manufacturing steps that are typically associated with the majority of the above product categories, the Working Group relied on its own expertise as well as the following references:

- Remington: Pharmaceutical Sciences, 18th edition⁵
- Modern Pharmaceutics, 3rd edition⁶
- Pharmaceutical Process Validation, 3rd edition⁷
- ISPE Baseline® Pharmaceutical Engineering Guide, Vol. 2, Oral Solid Dosage Forms, 1st edition⁴

Expert Selection and Survey Delivery

Prior to the full implementation of the survey, a pilot survey was conducted in December 2003 through in-person interviews with five FDA experts. Feedback on the clarity of the survey instructions, questions, options for answering the questions, product categories, and units of operation were obtained from the pilot survey. In general, the pilot survey showed that the survey was clear and questions were answerable. Based on comments received from the pilot survey, minor refinements were made and the survey was finalized prior to final delivery to a full panel of experts.

The panel of FDA experts to whom the survey was delivered was selected from the following groups: 1) reviewers from CDER, 2) senior CDER staff in the Office of Compliance, and 3) senior Office of Regulatory Affairs (ORA) field staff. Fifty experts were selected for the survey, based on the expertise needed and the level of experience of the individuals. The overall response rate was 100%. The survey was conducted in May 2004. The survey was sent to the experts via email, and the experts were instructed to print and complete the survey by hand. Data from the completed and returned surveys were entered by the Office of Compliance staff. Data quality assurance was conducted by the staff of the Office of Compliance.

Analyses and Results

Average Summary of Responses

Ranking responses on a 5-point scale (from 1 as the lowest to 5 as the highest rank) as elicited from the survey for questions

Product Category	Potential for a Loss of Control		Potential for Contamination		Percent Response
	Average Ranking (Questions 1, 2, & 3)	Standard Deviation	Average Ranking (Questions 4 & 5)	Standard Deviation	
Biotech	3.1	0.5	3.0	0.7	48%
Liquids, Sterile, Solution	3.0	0.8	2.7	0.8	92%
Liquids, Sterile, Suspension/Emulsion	3.1	0.7	2.7	0.8	100%
Metered Dose Inhaler, High Active	3.0	0.6	2.6	0.7	62%
Metered Dose Inhaler, Low Active	3.2	0.6	2.6	0.7	62%
Liquids, Non-Sterile, solution	2.0	0.6	2.1	0.9	94%
Powders, High Active	2.3	0.6	2.4	0.9	92%
Solid Oral Drugs, Immediate Release, High Active	2.3	0.5	2.1	0.6	94%
Liquids, Non-Sterile, Suspension/Emulsion	2.5	0.7	2.3	0.9	100%
Semisolid (Ointment/Cream), High Active	2.5	0.5	2.2	0.7	84%
API, Synthesized	2.6	0.6	2.2	0.6	100%
Solid Oral Dose, Immediate Release, Low Active	2.6	0.5	2.2	0.6	94%
Solid Oral Drugs, Modified Release, High Active	2.6	0.5	2.1	0.6	92%
Powders, Low Active	2.7	0.6	2.5	0.9	92%
Semisolid (Ointment/Cream), Low Active	2.7	0.6	2.2	0.7	82%
API, Fermentation	2.8	0.6	2.3	0.7	100%
Solid Oral Drugs, Modified Release, Low Active	2.8	0.5	2.2	0.6	92%
Transdermal	2.8	0.6	2.2	0.7	66%

Table C. Average ranking and response rate for each product category.

1, 2, and 3 were averaged together to represent average rating of risk for the potential loss of control. Then, they were averaged across units of operation and respondents to determine the average risk ranking for potential loss of state of control for each product category. Similarly, responses to questions 4 and 5 were averaged across units of operation and respondents to determine the average rank of potential for contamination for each product category. Table C summarizes the average ranks and standard deviations for potential loss of state of control and potential for contamination for each product category. Biotech, MDI (both high and low active), and sterile liquid (both solution and suspension/emulsions) product categories have the highest average ranking for both potential for loss of a state of control and potential for contamination.

Experiences with product categories were not equal among the surveyed experts. As such, not all respondents provided answers to all product categories included in the survey. Biotech, MDI, and Transdermal product categories have the lowest response rates, 48%, 62%, and 66%, respectively. Response rate for each product category also is summarized in Table C.

Box-plots of the ranking responses for questions 1, 2, and 3, which were averaged together and across units of operations to represent average rating of potential for a loss of control for each product category are shown in Figure 1. Similarly, box plots of responses for questions 4 and 5 to represent potential risk of contamination for each product category are shown in Figure 2. Biotech, MDI (both high and low active), and sterile liquid (both solution and suspension/emulsions) product categories remain the top ranked product categories based on median scores.

Cluster Analyses of Responses on Combinations of Product Categories and Units of Operation

In addition to averaging the responses, multivariate K-Mean clustering analyses of responses to the combinations of product category and unit of operation also were carried out using S-Plus.⁸ Responses to questions 1, 2, and 3 for the product category and unit of operation combinations were clustered into five groups. Each cluster was assigned a ranking based on the rank-order of the clusters' centers, i.e., cluster with the highest center was given the highest rank of five and cluster with the lowest center is given the lowest rank of one. A product category and unit of operation combination belonging to a cluster would assume its cluster rank. A similar clustering approach also was applied to questions 4 and 5. As in previous averaging analysis, the cluster ranks based on questions 1, 2, and 3 provide ranking of potential risk of loss of state of control, and the cluster ranks based on questions 4 and 5 provide the ranking of potential risk of contamination.

Ranking of Potential for Loss of a State of Control

The cluster ranking of the combinations of product categories and units of operation resulted in the same top five ranked product categories (biotech, liquid sterile solution, liquid sterile suspension/emulsion, MDI low active, and MDI high active) as those ranked based on averaging responses. Within each product category, ranking varied between units of operation. While most of the processing steps associated with the top five ranked product categories also are ranked high, the measuring step is typically ranked lower. For product categories with overall low ranking, such as the solid oral

Risk Assessment

Product Categories	Product Category Ranking	Units of Operation	Unit of Operation Rankings
Biotech	5	Bioreaction, Seed; Bioreaction, Production; Cell Bank Maintenance; Isolation Recovery; Pasteurization; Purification; Viral Clearance Filling; Formulation Measuring	5 4 3
Liquid, Sterile, Suspension/Emulsion	5	Aseptic Filling, Form-Fill-Seal; Aseptic Filling, Isolator; Aseptic Filling-Traditional Method; Mixing Blending; Terminal Sterilization Measuring	5 3
Liquid, Sterile, Solution	5	Aseptic Filling, Form-Fill-Seal; Aseptic Filling, Isolator; Aseptic Filling-Traditional Method; Filtration; Lyophilization; Terminal Sterilization Measuring Mixing Blending	5 3 2
Metered Dose Inhaler (MDI), Low Active	5	Assembly; Filling; Micronization of components; Mixing Blending Measuring	5 4
Metered Dose Inhaler (MDI), High Active	5	Assembly; Filling; Micronization of components; Mixing Blending Measuring	5 3
API Fermentation	4	Fermentation; Inactivation; Isolation; Purification Processing Primary Packaging; Weighing	5 4 2
API Synthesized	4	Isolation; Purification; Reaction Processing; Workup Weighing Primary Packaging	5 4 3 2
Powders, Low Active	4	Mixing Blending Milling Measuring Primary Packaging	5 4 3 2
Semisolids (Ointment/ Cream), Low Active	4	Emulsification; Mixing Blending Deaeration; Heating Cooling Measuring Primary Packaging	5 4 3 2
Solid Oral, Modified Release, Low Active	4	Coating; Pelleting Compression (tablet); Drying; Encapsulation (hard gel); Granulation (dry and wet); Milling; Mixing Blending Measuring Primary Packaging	5 4 3 2
Transdermal	4	Active Deposition, Coating; Extrusion Cutting; Drying; Mixing Blending; Primary Packaging Measuring	5 4 3
Liquid, Non-Sterile, Suspension/ Emulsion	3	Emulsification; Mixing Blending Measuring Primary Packaging	5 3 1
Semisolids (Ointment/ Cream), High Active	3	Emulsification Deaeration; Heating Cooling; Mixing Blending Measuring Primary Packaging	5 4 3 2
Solid Oral, Immediate Release, Low Active	3	Mixing Blending; Granulation (dry and wet) Coating; Compression (tablet); Drying; Encapsulation (hard gel); Milling; Pelleting Measuring Primary Packaging	5 4 3 2
Solid Oral, Modified Release, High Active	3	Coating; Pelleting Compression (tablet); Drying; Encapsulation (hard gel); Granulation (dry and wet); Milling; Mixing Blending Measuring Primary Packaging	5 4 3 2
Solid Oral, Immediate Release, High Active	2	Compression (tablet); Granulation (dry and wet); Mixing Blending; Pelleting Measuring Coating; Drying; Encapsulation (hard gel); Milling; Primary Packaging	4 3 2
Powders, High Active	2	Milling; Mixing Blending Measuring Primary Packaging	4 3 2
Liquid, Non-Sterile, Solution	1	Measuring Mixing Blending Primary Packaging	3 2 2

Table D. Cluster ranking of product categories and units of operation for potential loss of a state of control.

immediate release high active category, most processing steps are ranked low; however, there are several processing steps that are ranked high, such as compression (tablet), wet and dry granulation, mixing-blending, and pelleting. Product and unit of operation rankings for potential loss of a state of control based on K-mean cluster analysis are summarized in Table D.

Potential for Contamination

Cluster ranking of contamination risks for the combinations of product categories and units of operation also resulted in biotech, liquid sterile solution, liquid sterile suspension/emulsion, MDI low active, and MDI high active as the top ranked product categories. Ranking also varied between units of operation within each product category. Product and unit of operation rankings of contamination risks based on K-mean cluster analysis are summarized in Table E.

Discussion and Recommendations

Survey Protocol

Formal methods for obtaining the judgments of experts have been evolving since their inception after World War II. Despite its long history of application, standardized protocols for the selection, preparation, and elicitation of experts do not and should not exist.⁹ Analysts in the field of expert elicitation have consistently argued that rather than standardized procedures, protocols should be crafted to suit the particular problem under investigation.^{3,10,11} In accordance with conventional practice, an FDA team developed a protocol, in a form of a survey and detailed instructions, to elicit expert judgments about the potential for a pharmaceutical manufacturing process to be subject to loss of process controls or contamination. As such, it should be noted that the scope of the elicitation is limited to obtaining expert judgments about the likelihood relating to the manufacturing processes such that if a product category is judged to involve more risky manufacturing steps it would then have a higher potential for poor quality. This protocol does not extend to judgments about risk to public health.

Experts

Expert judgment studies make use of a panel of experts who bring in different information, arising from different interpretations, different analytical methods, and/or different experiences.² Fifty-five experienced FDA officials were chosen to participate in this survey and 50 responses were received. Nearly half of the participants were senior drug program investigators from the Office of Regulatory Affairs with the remaining being senior review and drug cGMP compliance officials in the Centers for Drug Evaluation and Research and Veterinary Medicine. Review staff represented disciplines such as chemistry, engineering, biochemistry, microbiology, pharmacology, and pharmacy. Nearly all responders reported having 10 or more years combined experience in FDA and the drug industry.

Utility

Information obtained from the survey has been of great utility in the implementation of the risk ranking model to prioritize pharmaceutical sites for cGMP inspection. To implement this risk-ranking framework, a risk ranking (or weight) is first assigned to the factors associated with each top-level component (Product, Process, and Facility) and subsequently, the combination of these factor-ranks (weights) would determine the site overall potential risk scores, which would be used to rank and target inspection. As previously indicated, the Agency has systematically compiled product and facility related information such as product recall, inspection, and compliance histories that could be used to operationalize these aspects of the risk ranking framework. However, such data do not exist for factors relating to the process component. The expert elicitation survey provides a systematic means of gathering knowledge and an objective approach to assign ranks to the factors associated with the process component of the risk-ranking model. Ranking results also provide a basis for investigators to better focus their product quality inspection. For example, once a site has been chosen for inspection based on overall site risk score, variability in the ranking of units of operation within each product category (Tables D and E) could help the inspector to focus on units of operation that have been ranked as more vulnerable to potential loss of process controls or contamination.

The results from this formal and systematic approach of collating judgments from a broad range of experts also could provide the pharmaceutical industry with benchmark data, which can be used to examine a company's risk assessment practices. If a company's assessment leads to conclusions that are different from the experts' norm then additional evaluation can be carried out to determine reasons for differences.

Limitations

There are a number of limitations associated with this survey. First and foremost, since the expert elicitation survey was only delivered to FDA experts, the results reported in this article do not capture the broad range of expertise that exists outside of FDA. The response rate to the surveys for the Biotech Product Category was only 48% (only 24 responded out of 50 surveyed experts). While the expert elicitation was not a random survey and statistical validity is not at issue, the low response rate presents some concern with regard to the potential lack of expertise in the biotech area among the pool of experts included in this survey. An additional consideration is the fact that the survey was designed to elicit judgments about the manufacturing risks associated with very broad product categories (Table B) and not specific product. As such, experts were forced to average their answers across a broad range of products that fall into such product category. While broad aggregation of products helped to facilitate the delivering of the survey i.e., reduce respondent's time spent on the survey and fatigue, the consequence could be a loss of a significant amount of information.

Question 3 in the survey (“If a problem does occur, how reliable are the current detection methods?”) would require experts to account for the average rate of firms implementing expected process controls. As such, the results from this survey do not reflect risk associated with firms that are performing below average expectation or standard industry practices, i.e. not implementing minimal in-process controls; nor do results reflect firms exceeding expectations, e.g., firms with Process Analytical Technologies (PATs). Nevertheless, for the purpose of selecting a site for cGMP inspection, such deviation from average/expected practices would be captured during the actual inspection. As such, using the results from this survey for the site-selection model does not preclude the inspector’s ability to differentiate between firms with enhanced controls from those performing below averages.

Recommendations

In light of the limitations described above, the following

recommendations are provided to improve the expert elicitation survey:

- Expand the expert panel to include expertise outside of FDA such as ISPE working members.

ISPE has a broad range of members who would have current working knowledge of the robustness and capabilities for a variety of products. They are likely to be familiar with units of operation that require frequent attention and in-process monitoring and maintenance. Hence, inclusion of expert judgments from this group would greatly enhance knowledge about risk associated with various pharmaceutical manufacturing processes.

- Future revision of the survey protocol should consider further differentiation of the existing product categories and units of operation.

Product Categories	Product Category Ranking	Units of Operation	Unit of Operation Rankings
Biotech	5	Bioreaction, Production; Bioreaction, Seed; Filling; Formulation; Isolation Recovery; Purification; Viral Clearance	4
		Cell Bank Maintenance; Measuring; Pasteurization	3
Liquid, Sterile, Solution	4	Aseptic Filling-Traditional Method	5
		Aseptic Filling, Form-Fill-Seal; Aseptic Filling, Isolator; Filtration; Lyophilization; Measuring; Mixing Blending	3
		Terminal Sterilization	1
Liquid, Sterile, Suspension/Emulsion	4	Aseptic Filling-Traditional Method	5
		Aseptic Filling, Form-Fill-Seal; Aseptic Filling, Isolator; Measuring; Mixing Blending	3
		Terminal Sterilization	1
Metered Dose Inhaler (MDI), High and Low Active	3	Micronization of components	4
		Filling; Measuring; Mixing Blending	3
		Assembly	1
Powders, High and Low Active	2	Milling; Mixing Blending	2
		Measuring; Primary Packaging	1
API Fermentation	2	Fermentation	3
		Inactivation; Isolation; Processing; Purification	2
		Primary Packaging; Weighing	1
API Synthesized	1	Processing; Purification	2
		Isolation; Primary Packaging; Reaction; Weighing; Workup	1
Liquid, Non-Sterile, Solution	1	Mixing Blending	2
		Measuring; Primary Packaging	1
Liquid, Non-Sterile, Suspension/Emulsion	1	Mixing Blending Emulsification	2
		Measuring; Primary Packaging	1
Semisolids (Ointment/ Cream), High and Low Active	1	Emulsification; Mixing Blending	2
		Deaeration; Heating Cooling; Measuring; Primary Packaging	1
Solid Oral, Immediate Release, High and Low Active	1	Granulation (dry and wet) Milling; Mixing Blending	2
		Coating; Compression (tablet); Drying; Encapsulation (hard gel); Measuring; Pelleting; Primary Packaging	1
Solid Oral, Modified Release, Low Active	1	Compression (tablet); Granulation (dry and wet); Milling; Measuring; Mixing Blending	2
		Coating; Drying; Encapsulation (hard gel); Pelleting; Primary Packaging	1
Solid Oral, Modified Release, High Active	1	Granulation (dry and wet); Milling; Mixing Blending	2
		Compression (tablet); Coating; Drying; Encapsulation (hard gel); Measuring; Pelleting; Primary Packaging	1
Transdermal	1	Active deposition, coating	3
		Extrusion; Mixing Blending	2
		Cutting; Drying; Measuring; Primary Packaging	1

Table E. Cluster ranking of product categories and units of operation for contamination risks.

In the current survey, products are categorized based on broad dosage forms. These broad dosage forms could be further differentiated. For example, the oral solid dosage form could be differentiated into several product groupings, including hard and soft capsules and tablets. Further, for products with additional processing steps that are not captured in the current survey, these additional steps should be identified and included in future revision of the survey. Differentiations should be made where experts believe there are true differences.

- Uncertainty

Expert knowledge is not a certainty, but it is entertained with an implicit level of confidence or degree of belief.² Survey methods that allow the experts to express their degree of confidence in their responses will also permit a determination of the level of confidence in models that use these data. As such, future surveys should allow experts to express uncertainties in their responses.

References

1. FDA-Center for Drug Evaluation and Research (FDA-CDER), Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model. Department of Health and Human Services U.S. Food and Drug Administration. Rockville, M.D., September 2004, <http://www.fda.gov>.
2. Van Der Fels-Klerx, I. H. J., L.H.J. Goossens, H.W. Saatkamp and S.H.S. Horst, “Elicitation of Quantitative Data from a Heterogeneous Expert Panel: Formal Process and Application in Animal Health,” *Risk Analysis*, Vol. 22, No. 1, 2002, pp. 67- 81.
3. Morgan, M.G. and M. Herion, *Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis*. N.Y., Cambridge University Press, 1990.
4. International Society for Pharmaceutical Engineering Inc. (ISPE), *Baseline® Pharmaceutical Engineering Guide*, Vol. 2, Oral Solid Dosage Forms, 1st edition, 1998.
5. Remington’s *Pharmaceutical Sciences*, 18th edition, P.A., Mack Publishing Company, 1990, p. 2000.
6. *Modern Pharmaceutics*, 3rd edition, Revised and Expanded, N.Y., Marcel Dekker, Inc., 1996, p. 943.
7. *Pharmaceutical Process Validation*, 3rd edition, Revised and Expanded. N.Y., Marcel and Dekker, Inc., 2003, p. 860.
8. *S-Plus for Windows Professional Version 4.5 Release 1*. MathSoft, Inc. 1998.
9. Walker, K, J.S. Evans, and D. MacIntosh, “Use of Expert Judgment in Exposure Assessment Part I. Characterization of Personal Exposure to Benzene,” *Journal of Exposure Analysis and Environmental Epidemiology*, Vol. 11, 2001, p. 308-322.
10. Hora, S.C. 1992. Acquisition of Expert Judgment: Examples from Risk Assessment. *J. Energy Eng.* 188(2):136-148.
11. Otway, H. and D. von Winterfeldt, “Expert Judgment in Risk Analysis and Management Process, Context, and Pitfalls,” *Risk Analysis*, Vol. 12, No. 1, 1992, p. 83-93.

Disclaimer

The views expressed herein do not represent official FDA or US government policy. No official support or endorsement by the FDA is intended or should be inferred.

Acknowledgement

We would like to thank the many FDA staff who helped design and develop this survey, especially Charles Gray of the Center for Veterinary Medicine, Diane Kelley and Thomas Arista from the Office of Regulatory Affairs, Elaine Cole from the Center for Biologics Evaluation and Research, and Nicholas Buhay, Jon Clark, Lindsay Cobbs, Stephen Mahoney, Vilayat Sayeed, Rajendra Uppoor, and Christopher Watts from the Center for Drug Evaluation and Research. We greatly appreciate the participation of our 50 FDA expert respondents who will remain anonymous. Last but not least, we would like to thank CDER-Director of the Office of Compliance, David Horowitz, without whose support and forward thinking this project could not have happened.

About the Authors



Dr. Nga Tran is a Senior Managing Scientist at Exponent’s Food and Chemicals practice in Washington, DC. She earned her Dr.P.H. in environmental health sciences at Johns Hopkins University, Bloomberg School of Public Health in 1994, and her Masters in public health at Yale University, Department of Epidemiology and Public Health in 1985. Dr. Tran has more than 15 years of experience in environmental and occupational health risk assessment from the private and public sectors. Prior to joining Exponent, Dr. Tran was a faculty member at the Johns Hopkins University, Bloomberg School of Public Health where she conducted research and taught exposure and risk assessment, risk prioritization, and risk harmonization. Dr. Tran remains an Adjunct Assistant Professor at the University.

Exponent, 1730 Rhode Island Ave. NW, Suite 1100, Washington, DC 20036.



Brian Hasselbalch is a Senior Officer with the U.S. Food and Drug Administration’s Center for Drug Evaluation and Research, where he works on cGMP related guidance and policy matters, and reviews recommendations for regulatory action. He is a former FDA drug process investigator. Hasselbalch received his BS from University of California

at Riverside. He has been with FDA for 15 years.



Dr. Kara Morgan is the Senior Advisor for Risk Analysis in the Office of Policy and Planning in the Office of the Commissioner at the U.S. Food and Drug Administration. She earned her PhD in engineering and public policy at Carnegie Mellon University in 1999, and her Masters in environmental science from the School of Public and Environ-

mental Affairs at Indiana University in 1995. She has 13 years of experience in risk and decision analysis. Dr. Morgan's research interest focuses on developing tools to support effective risk management decisions in the face of uncertainty.



Dr. Gregg Claycamp is Director of Scientific Support Staff at the U.S. Food and Drug Administration's Center for Veterinary Medicine, Office of New Animal Drug Evaluation. He received his MS and PhD in radiological health engineering from Northwestern University in 1977 and 1982, respectively. Dr.

Claycamp has more than 25 years of experience in risk assessment and decision analysis. Prior to FDA, he was Professor and Associate Chairman at the University of Pittsburg, Department of Environmental and Occupational Health. 