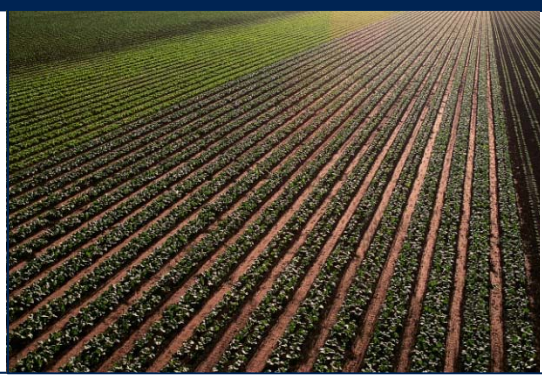
FDA Foods Program Review of Chemical Safety Capacity and Management:

Results of Chemical Safety Assessment Personnel Interviews





FINAL
June 17, 2013

Contract No. HHSF223201210011B
BPA No. 2

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Table of Contents

ES. EXECUTIVE SUMMARY

FDA is in the process of conducting an internal review to take stock of the Foods and Veterinary Medicine Program's (FVMP's) current chemical safety capacity, to evaluate how that capacity is deployed and applied across the program, and to evaluate management practices that affect how well staff and other resources are used to oversee chemical safety. The review also examines how the chemical safety program within FDA interacts with other U.S. government agencies, international organizations, the external scientific community, and other external stakeholders. The intended outcome of the review will be to improve the program in these areas as necessary so FVMP can better meet chemical safety challenges.

As part of this review, FDA organized interviews of chemical safety assessment personnel working in CFSAN and CVM. For the interview process, interviewees were asked a series of 22 questions: 10 addressing science issues; 7 addressing communication and collaboration within the Office of Foods and Veterinary Medicine (OFVM) and with other programs, agencies, and the public; and 5 addressing expertise and training. The complete list of review questions is presented in Appendix A.

The following report summarizes the responses of 82 OFVM employees who shared their thoughts and opinions on working within the Program, as well as their recommendations for improvements.

ES.1. General Observations

Most interviewees entered the interview process with a positive attitude, and clearly felt that their thoughts and opinions could make a difference. Based on responses to the 22 questions as a whole, the majority of interviewees (~54%) felt positive about the FVMP and felt that their Center was a good place to work, that their work made a difference, and/or that improvements to the Program were worthwhile and achievable. About 29% of interviewees were neutral about the Program, their job, and/or the potential for change, and 17% of interviewees were overall negative. In addition, many interviewees felt that, although there was need for improvement in their center, office, or other divisions, their division was doing many things well. There was much disparity in the level of job satisfaction across divisions, and this often appeared to be affected by mid-level management (supervisors).

There were clear trends for different offices and groups with respect to satisfaction and dissatisfaction. For example:

- Within OFAS, job satisfaction seemed to be generally higher among chemists than toxicologists, mostly due to more communication across groups and offices.
- OARSA personnel and OFAS chemists felt they worked well together.
- There was a division, and particularly among OFAS toxicologists, between staff members who were content with their role as regulatory scientists and those who it appeared might be happier with a job in a more research-oriented environment.
- Newer staff members appeared to place much more importance on increasing communication with the public than established personnel.

In terms of the two Centers, there was a noticeable difference in the responses received from CVM vs. those from CFSAN that seemed to be attributable mainly to CVM's being a much smaller and therefore more cohesive Center. In addition, CVM personnel appeared to be happier because of more workplace flexibility.

OARSA appeared to be interested and eager to have more collaboration and provide more support to scientists across the board, and they reported that the FVMP Strategic Plan has been an asset to this. They also felt that their being included in the decision-making process early on would enable valuable input to study design and protocol development and even decisions as to whether certain studies are needed.

There was a higher level of dissatisfaction among employees from two of the smaller groups represented in the interviews, CHAT and OCAC, that was attributed to a combination of issues including insufficient manpower and scope of expertise, lack of teamwork and peer review, lack of SOPs and guidance, and/or lack of regulatory authority.

Resources, in terms of manpower, funding, and time, were cited in conjunction with weaknesses, shortcomings, and impediments in response to many questions; however, nearly all interviewees acknowledged that resources were beyond the control of the Centers.

Recurring concerns, that crossed all questions and topics included:

- The need for increased communication across offices and groups and within and between the Centers (via the website, newsletters or reports or meetings, especially informal meetings).
- The need for a means of identifying subject matter experts within the Centers who are available for consultation.
- The need for a means of identifying when a substance is being worked on or has been worked on by more than one group or office.
- The need to address/fill the experience gap that is coming due to the retirement of large numbers of seasoned reviewers.
- The need for training on the job as "regulatory" scientists (as opposed to "research scientists").
- The need for more cross-training/details across groups and office.
- The need to address the increasing allocation of review efforts to post-market review, its impact on resources, and the concern that it is not adequately provided for in the mandate for the Centers.
- The impact of the Delaney Clause on the Centers' mandates, particularly those of CVM.

ES.2. Science Issues

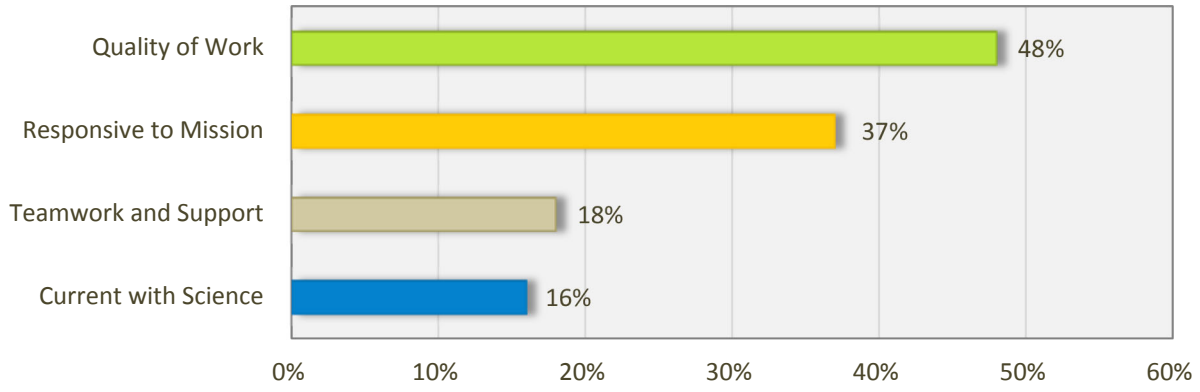
Overall Evaluation of the Chemical Safety Regulatory and Research Programs:

CFSAN/CVM personnel tended to feel that their programs were well qualified to address the requirements of the work in terms of scientific expertise, and that weaknesses tended to be the result of the conditions and restrictions of the regulatory environment and personnel shortages. Although none of these factors is completely under management control, additional areas

addressed under this topic, including program strengths of teamwork and support, timeliness, and use of resources, and weaknesses having to do with communication issues, lack of peer review, lack of SOPs/procedures, and insufficient feedback/support, suggest areas that could be addressed by management.

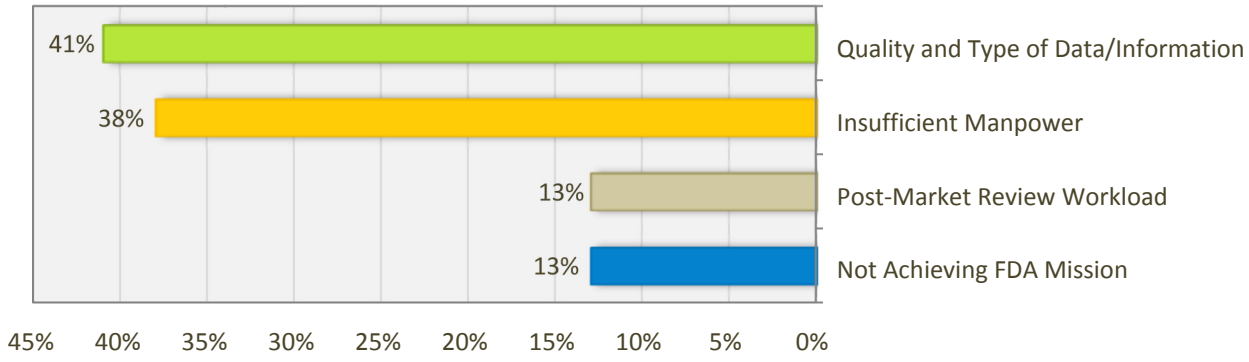
The four top responses for program strengths were quality of work, being responsive to the mission, teamwork and support, and being current with the science. Timeliness of completing review/research products and effective use of resources in terms of hiring and efficiently deploying personnel were cited to a lesser extent as program strengths.

Program Strengths



For program weaknesses, the two key factors cited across both centers and all offices were the quality and type of data/information available for conducting reviews and insufficient manpower. Another common area of concern was the impact of post-market review on workload, personnel resources, and funds. In addition, the concern was voiced that the Centers, and primarily CFSAN, are not achieving the mission of protecting food safety due to factors including: reliance on and obligation to the sponsors; questions concerning the Centers' approach to safety review; and a lack of ability to confirm the results of safety decisions.

Program Weaknesses



Chemical Safety Risk Assessment and Safety Evaluation Methods and Data, Research, and Guidance:

The majority of interviewees (~70%) felt that there were justifiable differences in chemical safety methods and data requirements between offices and centers attributable to differences in policies/regulations, different target compounds or products, and/or different guidances. Differences in methods were not felt to be justified where consistency was not attempted, due to lack of cross-talk, and/or lack of willingness to consider other approaches (i.e., territoriality).

The majority of personnel felt that methods were generally in keeping with the current and emerging state of the art (~78%) and were recognized as such by the external and scientific stakeholder communities (73-77%). Some maintained that being state of the art is not the role of the Agency as a regulatory entity, noting that the Agency must be conservative in adopting new methods to protect both the public health and the interests of sponsors. Those who felt methods were not current generally felt the Agency was behind the science because of unwillingness to change, reliance on outdated guidance, and an outdated approach to implementing new technology/science into safety assessment.

Chemical safety research was generally felt (~60-66%) to be adequate in scope, scale, and alignment. Alignment was felt to have been improved with the FVMP Strategic Plan 2012-2016 (dated April 2012). Limiting factors included: limited resources (personnel and time); difficulty in aligning priorities (topics, time, and scheduling) for accomplishing specific projects; conflicts between developing long-term research projects and focusing on specific regulatory questions; and inadequate communication between researchers and regulators.

In addressing chemical safety guidance, the Redbook had both supporters, who felt that it represented sound, substantial, and validated methodologies and should only be updated with caution using adequately validated methods, and detractors, who felt that it was out of date and should be updated, significantly expanded, or completely revised. Areas in needing of updating/addition included: immunotoxicity, neurotoxicity, carcinogenicity, developmental and reproductive toxicity, use/applications of translational biomarkers, and Tox21 methodologies. To keep Redbook and other guidance up to date employees suggested assigning dedicated staff and establishing periodic updates or a combination of the two, as well as seeking external expertise. Where new guidance has been adopted (including OFAS Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations, and CVM Guidance for Industry), the process of keeping it up to date via periodic review was felt to be less arduous.

Emerging Issues and Questions in Chemical Safety Review:

The emerging chemical safety issues most often identified were new methods; nanotechnology; botanicals, supplements, and non-traditional entities; endocrine disruptors; and effects of mixtures and groups of chemicals. Other identified areas included: post-market review; low-dose/long-term exposure effects; effects on sensitive populations; genetically engineered organisms; and allergen thresholds. Under new methods, the majority of interviewees were concerned with the move toward Tox21 methods (*in vitro* testing, high throughput screening, *in*

silico methods). Suggestions for ways the Agency could be more proactive in identifying emerging issues included maintaining/increasing attendance at meetings and conferences, monitoring the literature, assigning dedicated staff, improving internal communication, increasing outreach to industry, increasing post-market surveillance, and maintaining a watch or alert list.

The Centers were generally felt to be improving or doing well in facilitating the needed developments in the science, despite stumbling blocks to the process including insufficient funding and staffing and insufficient time to work on emerging issues. Suggestions for improving facilitation of the science included: increasing coordination between chemists and toxicologists within OFAS; establishing designated staff or "super groups" to work on special topics/side projects; increasing involvement across CFSAN in emerging issues such as Tox21; increasing collaboration with outside scientists; increasing policy-focused research in OARSA and OR; and improving identification of "point people" within other offices, centers, agencies, to collaborate on emerging issues.

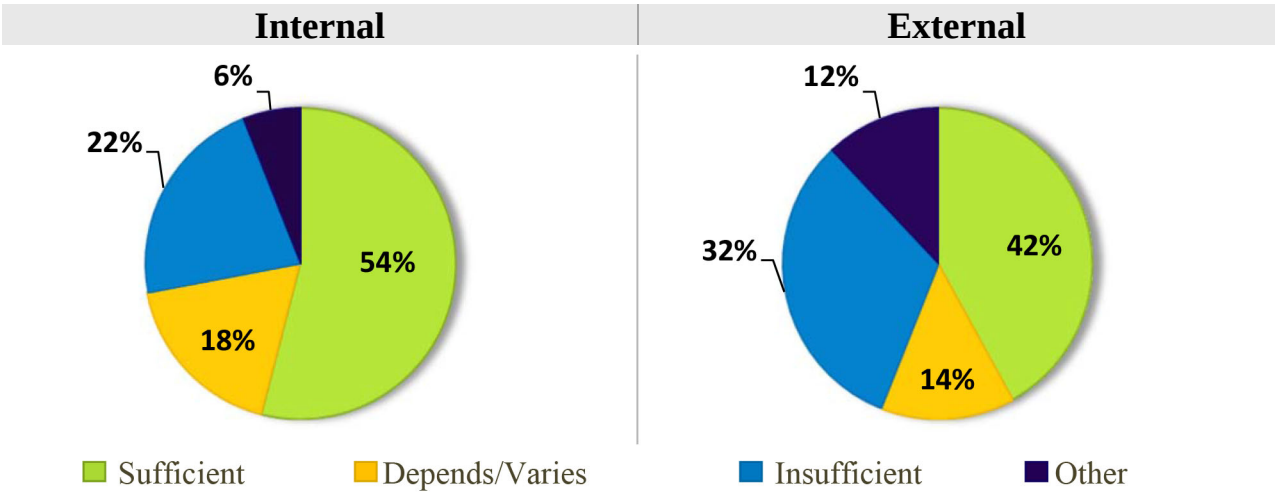
Internal Processes to Ensure Quality Assurance and Peer Review on Chemical Safety Matters:

The majority of personnel (~92%) indicated that there were generally established processes in place for quality assurance and peer review, and ~71% felt that the processes were implemented adequately to very well. The areas in which improvements were felt to be needed included dispute resolution between reviewers or offices, coordination of efforts between offices, coordination on issues between different disciplines, and maintaining a consistent historical approach for regulatory decision-making. Recommendations for additional quality assurance and peer review processes mostly fell under the areas of improving peer review, improving access to outside or subject area experts, establishing more formal processes or SOPs, and improving internal communication.

ES.3. Communication and Collaboration

Interviewees were nearly evenly divided between those who felt that coordination and collaboration across offices and centers were improving to very good (~48%) and those who felt it was poor or needed to improve (~46%). While the majority of interviewees felt there were sufficient opportunities for internal and external collaboration (~54% and 42%, respectively); significant numbers felt that opportunities were insufficient or varied. The issues of communication and collaboration highlighted two of the key concerns identified by interviewees under nearly every topic area of the interview process: insufficient communication across groups, divisions, offices, and centers, and the need for a means of identifying subject matter expertise within the Centers.

Opportunities for Collaboration



Effectiveness of Coordination and Collaboration within OFVM:

Interviewees on both sides of the issue of effectiveness of coordination and collaboration commented that success tended to depend on the personnel involved and often was the result of individual initiative, with few formal processes and/or too much red tape involved. Interviewees reported that there have been improvements in communication between CFSAN and CVM to solve regulatory issues and good interactions between CFSAN, CVM, and NCTR, and that there are clearly identified points of contact within other centers for when cross-cutting issues arise. The establishment of the OFVM was felt to have improved coordination between the Centers.

Where coordination/collaboration across offices was felt to be poor or in need of improvement, interviewees noted that there were few opportunities/occurrences at the staff level and that it was difficult to achieve due to: little outreach across offices; differences in office structures, opinions, and policy decisions; problems with identifying partners; and difficulties in navigating the office hierarchy. Limited resources, primarily in terms of staff availability and time, were acknowledged as the most serious and least fixable impediments to coordination/collaboration. Additional impediments included poor communication, time constraints, lack of support or mandate, physical separation, and nature of the work. Improving communication in general and increasing inter-group meetings and talks were the top suggestion for improvements to the process, followed by more support from the top, and exchange of staff.

Opportunities for Collaboration Internally and Externally:

Collaborations were generally felt to be neither discouraged nor specifically supported, and, aside from formal details and shadowing, not easy to participate in. Factors affecting opportunities for collaboration included identification and access to partners, lack of formal procedures, management approval/encouragement, time available, how well the different factions worked together, and whether the outcome of previous collaborations had been positive. Good opportunities for internal collaboration were felt to exist for big issues and projects and on internal details at other centers/offices, as well as between members of review teams and

between certain offices, the Centers, and NCTR. In terms of expanding collaboration between the Centers and NCTR via additional toxicology research, suggestions included having NCTR conduct additional research on compounds, chemicals, and components, and conducting methods development and validation. External opportunities were felt to be more difficult to achieve due to: restrictions in FDA's relationship with industry; travel and time restrictions; the rules and regulations governing the clearance/approval process; and the perception that such collaborations might be outside the scope of the Centers' mission and resources.

Recommendations for internal collaborations that would improve/benefit the programs tended to be general rather than specific and included increasing detail opportunities, increasing work with the labs, increasing collaboration between certain groups and offices, increasing involvement of management in identifying opportunities, increasing topic-based collaboration, and reducing bureaucracy in arranging collaborations. In terms of external collaborations, recommendations included expanding opportunities for personnel to give talks/presentations in their specific areas of expertise, increasing contracting by improving the contracting process; and increasing collaboration with academia, other regulatory science agencies, and organizations such as International Life Sciences Institute (ILSI).

ES.4. Interactions with Other Programs, Agencies, and the Public

Obtaining Exposure Data from FDA Laboratories and Access to Information from Databases:

The majority of interviewees (~67%) felt that those conducting chemical safety risk assessments and reviews were generally obtaining the type and quality of data they need from FDA laboratories, especially in terms of traditional toxicology studies, exposure data, and post-market data (e.g., Health Hazards Assessments). This was felt to be true, even though regulatory personnel might not always get all of the data they wanted and there are sometimes delays in getting the research approved and started.

Most personnel (~88%) felt that they had sufficient access to information from databases. The importance of having continued access to databases was emphasized. There appeared to be knowledge gaps concerning which databases were and were not currently available within FDA, and a recommendation was made to organize databases so that reviewers would know what was available. The major identified barriers to getting needed information were lack of knowledge of what is available, funding issues, confidentiality issues, access to primary vs. summary data, data sharing issues, confirming data quality, and obtaining data in a useful timeframe.

Differences in Safety Assessment Approaches/Methodology Between Regulatory Agencies and Potential for Harmonization:

Over ~90% of CFSAN/CVM personnel felt there were good reasons for different safety assessment approaches/methodology between regulatory agencies, and ~79% felt it would be possible, at least in part, to harmonize methodology with other agencies.

Differences in safety assessment approaches and methodology were attributed to differences in regulatory mandates, timelines, types of products regulated, types of data or studies submitted,

routes of exposure, assumptions, and paradigms, and to whether exposure is intentional or incidental. The Delaney Clause was cited as a specific differentiating factor which affects FDA but not EPA.

Not all employees felt that harmonization of methodology was necessary. Those who felt it was not necessary believed that the emphasis on harmonizing was the result primarily of consumer pressure and a lack of understanding, rather than a scientific need. They offered alternatives to harmonization including educating the public and making the processes more transparent to clarify why different agencies do things differently.

Those who did believe that harmonization of methodology is possible cited areas where harmonization has already been achieved between FDA and other U.S. government agencies and/or international bodies. They agreed that, in broad terms, safety and risk assessment methodologies are the same, and that, in some cases, outcomes are the same or similar (e.g., toxic endpoints, ADIs). Harmonization of new methods and technology (e.g., nanotechnology and Tox21) were felt to be easier to achieve because they do not fall under outdated guidances. There was also felt to be good potential for harmonization of the data analysis efforts between agencies. However, employees noted that even given the adoption of similar methodologies to collect similar data sets, different statutory directives, goals, and objectives, and differences in how the data are interpreted and results applied, precluded complete harmonization within FDA and between FDA and other government bodies.

There were few specific ideas to reach the goal of harmonization. Interviewees indicated that more communication, collaboration, coordination, and interaction, with a willingness to compromise, was needed via: informal or formal discussions; meetings between affected groups or agencies; sharing information; cross-training or exchange of staff; joint working groups/committees (JECFA model); and attendance at scientific meetings.

<u>Interactions with NIEHS, CDC, EPA, USDA, Other Federal Agencies, and International Bodies:</u>

Employee perceptions of the levels and manner of interactions between FDA and other entities on significant chemical safety and risk assessment issues varied widely. Interactions with other agencies and international bodies were variously described as: close relationships; effective but affected by priorities; occurring when necessary and when regulations and law demand; occurring at all levels for significant issues; more effective when initiated at higher levels; limited to designated people selected by management; effective when occurring as informal interactions between reviewers; limited by the confines of each Agency's rules and regulations; limited in general, but with established points of contact for cross-cutting issues; more likely to occur after FDA decisions have been made; occurring as regular meetings with team leaders and management; occurring as telephone conversations on specific issues; not occurring as frequently as they should; and virtually nonexistent at the staff level.

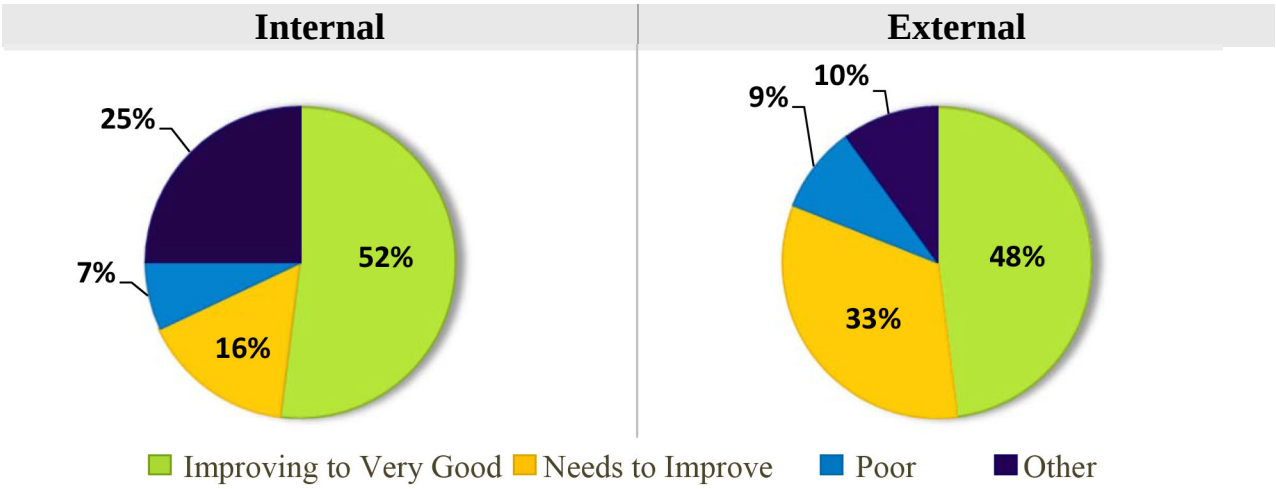
The following were identified as examples of what has worked well: addressing special issues (primarily with other Federal agencies); harmonizing standards and policy; and methods development and validation under the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Recommended improvements for such interactions included

improved communication, more support from the top, improved data sharing, better identification of relevant staff, and resolving differences in decisions.

Current State of Scientific Transparency and Engagement:

Regarding the state of scientific transparency internally between FDA's chemical safety scientists and programs and externally between FDA's chemical safety scientists and programs and the external scientific community and the public, most interviewees felt that both internal and external transparency were improving to very good (~52% and 48%, respectively), and most were satisfied with the current state of transparency (~55%).

Current State of Transparency



Those who felt internal scientific transparency was good/improving attributed this primarily to ease of access to and tracking of information and data and good communication/consultation across offices and divisions. Those who felt internal scientific transparency was poor or needed to improve cited the opposite: lack of access to reviews by other groups, and inadequate communication across centers concerning what people are doing and how and why decisions are made. The lack of a resource list of expertise was also cited as an impediment to transparency.

In addressing external scientific transparency, interviewees felt, in general, that the Centers were not as successful as they could be in communicating information to the public. Opinions were mixed concerning interactions with the scientific community as to how much of the problem should be attributed to the Agency. Those who felt external transparency was improving noted that: information can be obtained via FOIA; the Centers are trying to post as much information as possible on the website in addition to FOIA; most of the environmental decisions and supporting memoranda are already available; and decisions and final regulations are published in the Federal Register (FR). Several interviewees noted that transparency is much better when FDA has completed its assessments. Those who felt external scientific transparency was poor or needed to improve cited a lack of awareness/understanding among non-scientists concerning FDA's science-based policies and how the regulatory side of science works; lack of communication within the Agency that can lead to contradictory findings; and improper handling

of sensitive issues. Additionally, employees noted that the Centers' overly cautious position on sharing information via publishing, poster presentations, and/or asking questions or making statements at scientific meetings make it difficult to improve engagement and transparency with the scientific community.

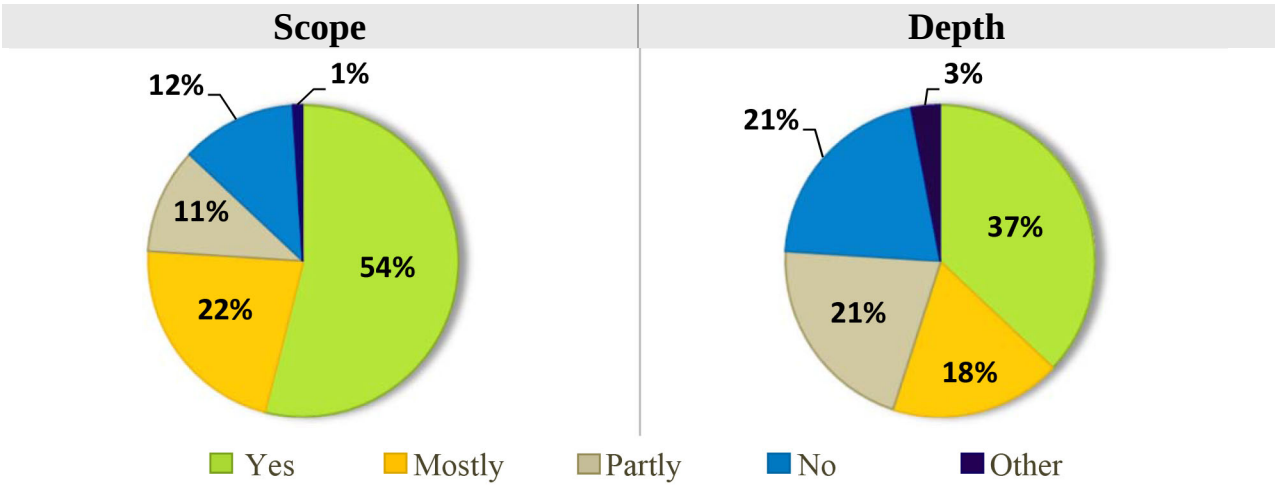
The main suggestions for improving transparency and engagement included improving interactions with the public, improving the FDA website, improving internal communication, increasing publishing and attendance at scientific meetings, and having more involvement from the top management at FDA. Two other suggestions for improving transparency were to increase external peer review of Agency decisions (by other government agencies or the NAS) and to increase engagement with industry (e.g., via more attempts to provide the regulatory perspective on a prospective submission before action is taken or by establishing regulatory liaisons within industry).

ES.5. Expertise/Training

Scope and Depth of Expertise:

The majority of CFSAN/CVM interviewees (~54%) felt that the Centers have adequate scope to fulfill regulatory obligations and meet today's and future challenges. There was more concern over depth of expertise, where only ~37% of interviewees felt depth was adequate. Within CFSAN, smaller offices/teams (e.g., CHAT and OCAC) tended to be less likely to feel that scope of expertise was adequate, while interviewees in all offices expressed concern about depth of expertise. Within CVM, all interviewees felt both the scope and depth of expertise were partly adequate or better; this seems to tie in with the relatively recent expansion of hiring within that Center.

Scope and Depth of Expertise



Concerning scope of expertise, many interviewees commented that the Centers have a good range of expertise across different technical areas and fields, represented by qualified scientists (mostly Ph.Ds.) who are able to move into or understand new areas as needed. The ability to access additional expertise, either across offices or centers or externally, was also considered to be a contributor to the scope of expertise. Inadequate scope of expertise was attributed to difficulties in hiring new expertise and retaining and utilizing available expertise. Suggestions for improving the scope of expertise included: improving internal communication/collaboration; developing a system for identifying and locating expertise within the Centers; allowing staff to maintain their expertise (and credentials) by participation in professional meetings; developing a more coordinated approach to hiring that encompasses program needs as well as individual group needs; expanding flexibility in management to increase utilization of expertise; increasing the use of integrated teams to address specific issues; and increasing the level of scientific expertise in management.

Concerning depth of expertise, the primary concerns were the loss of expertise due to retirement without sufficient "back-filling" and the changing perception of what constitutes depth of expertise, particularly within CFSAN. Interviewees felt there was a major gap in age and expertise within the Centers, that there was little or no depth in expertise for certain positions, and that insufficient training was being conducted to enable more junior employees to replace senior employees who were retiring.

General vs. Specialized Expertise:

Approximately 43% of interviewees felt the Centers should focus on acquiring a mixture of general and specialized expertise, with the remainder fairly evenly divided between general and specialized expertise. Many interviewees commented on the merits of training available staff to expand their expertise as an alternative to hiring.

External Expertise:

The majority of interviewees (~77%) felt that CFSAN/CVM were generally able to get adequate external expertise when needed, despite a number of impediments, including: availability of funding for contracting/consulting; time constraints; difficulties in identifying contacts/experts; conflicts of interest; complicated clearance procedures; and public perception.

Deployment and Efficient Use of Staff and Resources Across the Program:

The majority of interviewees (62%) felt that the staff and resources devoted to chemical safety were reasonably deployed and efficiently used across the Program. Most felt that their office, division, or the Centers were doing the best they could to maximize the efficiency of the available staff, and that regulatory obligations were being adequately addressed, despite obstacles including staff shortages, budget constraints, fluctuations in the workloads within the Centers, and the need to address emerging issues. The following issues were identified as more serious impediments to the efficient deployment and use of staff: the shift across the Centers to an integrated review team/interdisciplinary approach by work product vs. the "pool" approach which grouped reviewers by discipline; the lack of sufficient means of identifying expertise

within the Centers; insufficient communication and integration across offices and centers; the allocation of effort between "moving the freight" and addressing special projects; improper utilization of expertise; lack of flexibility in deployment and use of staff; and too much focus on building programs vs. doing the work.

Ideas for improving the allocation of staff and resources fell under the following general areas: revisiting the current integrated team approach; increasing details and/or cross-training; increasing communication and integration across centers; improving means of identifying expertise; addressing post-market obligations; establishing "strike teams" to address special issues; adjusting workloads; improving hiring practices; and finding help elsewhere.

Training Needs:

The majority of interviewees (~85%) felt that, in general, their training needs were being met. While several obstacles to meeting training needs were mentioned, including funding, time constraints, and communicating available opportunities to the staff, the main problems were seen to be budget constraints and allocation of funds for training and travel: maintaining a training budget was seen to be essential for the Centers to remain current with the science.

Suggested training types/topics included: analytical methods training; training in safety and risk assessment and management technologies; training in emerging technologies; training in data management; training in quality assurance, quality control, GLPs, and GCPs (Good Clinical Practices); toxicology training; training in translational science; training on industrial practices; and training in communications. Another area that was addressed by a number of interviewees, especially within CFSAN, was training on how to do the job of regulatory review. Suggestions for outside entities that the Centers could partner with for more training opportunities included other centers and programs under HHS, other agencies, academia, scientific societies and associations, industry groups, and non-profit organizations. A number of interviewees also recommended expanding in-house training rather than going outside.

Professional Development Needs and Development and Retention of Qualified Scientists:

To address professional development needs and retention of qualified scientists, interviewees recommended increasing emphasis on training, increasing opportunities for advancement, increasing recognition of contributions, increasing attendance at meetings and conferences, increasing incentives or money, and conducting regular surveys of employees or exit interviews. Other suggestions for ensuring development and retention of qualified scientists included: supporting virtual meetings, work from home, work from distance, and flexible hours; increasing opportunities for collaboration; allowing personnel time to do their own research or participate in collaborations in addition to work; including collaborative efforts, attending training, or publishing or reporting on new findings as a performance element in evaluations; reducing administrative duties by hiring editors for preparation of public documents; and increasing management's commitment to and support for science-based decision making.

1.0 INTRODUCTION

1.1. Purpose

The purpose of the Chemical Safety Assessment Personnel Interviews was to seek answers from those actually doing the work concerning what does and does not work within the program, where inconsistencies may lie, and what gaps need to be filled. The desired outcome was a true picture from within the program itself of where fixes might be made from the inside and where outside help might be needed to address issues.

1.2. Interview Process

FDA provided a list of 95 names of personnel involved in the chemical safety program at CFSAN (74 employees) and CVM (21 employees). This candidate list included all FDA scientists that worked in the chemical safety program as of August 2012. All candidate interviewees were contacted by Versar via email to schedule appointments for interviews on a wholly voluntary basis. From the original list of names, seven CFSAN and one CVM employee did not respond to requests to schedule an interview, and five CFSAN employees responded but did not participate in the interview process because they were unavailable during the interview period, were retiring during the interview period, or were no longer involved in the chemical safety review process. Interviews were conducted with 82 employees from five offices within CFSAN (62 interviewees) and three offices/groups within CVM (20 interviewees). The CFSAN offices included were ONLDS, OARSA, OFAS, OCAC, and OAO/CHAT. The CVM offices/groups included were ONADE, OSC, and ABIG. Employee areas of expertise included biology, chemistry, epidemiology, food chemistry, mathematics, medicine, pathology, pharmacology, residue chemistry, risk assessment, and toxicology.

Interviews were conducted under conditions of anonymity by Versar, Inc. during the months of August and September 2012 at the Harvey Wiley Building (College Park, MD), and Metro Park North Building (Rockville, MD). During the interviews, employees' responses were written down by hand. In addition, if permission was granted by the interviewee, the interview was digitally recorded to improve accuracy of transcription. A written summary of each interview was prepared by Versar, and the results of the interviews were used in writing this report, as follows: (1) direct quotes and paraphrases (with no attribution to source) were selected where they were felt to be the most accurate means of expressing employee thoughts or sentiment (these are presented either in quotation marks or in italics herein); (2) representative ideas and thoughts (with no attribution to source) were extracted and are presented herein with no particular designation; (3) employee responses were extracted into a spreadsheet designed by Versar to capture main ideas and thoughts to produce quantitative results.

The following measures were taken to preserve anonymity:

- Individual interviews were conducted in private rooms separate from staff offices;
- Appointments were scheduled on the basis of availability only and were not grouped by program office;

- Appointments were generally separated by sufficient time that an interviewee exiting an interview was unlikely to encounter an interviewee arriving for the next interview;
- Each interviewee was assigned a number, and the interviews were stored by number only;
- Relevant comments, thoughts, and quotes were extracted from the individual interviews with no attribution other than office, center, or area of expertise where it was felt to be relevant.

Written summaries and recordings of individual interviews will be maintained by Versar, and the recordings have been deleted upon delivery of this final report.

Responses to questions ranged from global/overview approaches (how can we fix the Center or how can we improve food safety) to personal (discussion of relative pay rates for employees). Some questions were also answered differently depending on the interviewee. For example, Science Issues Question No. 10, concerning peer review and QA, was addressed on two distinctly different levels: either with respect to the product produced within a given group or division, or with respect to the safety decision being made as a whole. Responses were affected by the interviewee's center, office, or division, job title (e.g., toxicologist, chemistry, research scientist), area of expertise, and/or years of experience, often resulting in trends which are identified throughout the report.

2.0 INTERVIEWEE RESPONSES BY QUESTION

The interview results are addressed by individual question below. Where applicable, quantitative results are summarized first, followed by an overview of the question responses, and then a detailed discussion of the responses.

2.1. Science Issues

2.1.1. Question 1: What do you see your program doing particularly well with respect to chemical safety review or research?

In identifying program strengths, the areas cited most often by interviewees were quality of work and being responsive to the mission. The distribution of responses to this question is summarized below.

Program Strengths	Responses (% of 82 interviewees)[1]
Quality of work	~48%
Responsive to the mission	~37%
Teamwork and support	~18%
Current with the science	~16%
Timeliness	~11%
Use of resources	~6%
Other	~9%
None	~6%

[1] Up to 3 responses/ideas captured per interviewee as follows: 6 interviewees had ≥3 responses; 31 had 2 responses, 40 had 1 response, and 5 had no response.

In terms of **quality of work**, those who conducted reviews felt that they conducted thorough reviews that were scientifically sound, well documented, and transparent, resulting in good technical documents. The review process was felt to be well defined and streamlined, with established systems and procedures in place, as well as flexibility when needed. CVM reviewers, more so than CFSAN reviewers, seemed to feel that there was a thorough guidance base for reviewers, although CFSAN reviewers also described themselves as well trained and equipped for safety reviews. The Centers were commended for obtaining and retaining appropriate scientific expertise, and the diverse expertise of team members was cited as a major contributing factor to resolving issues, conducting thorough reviews, and producing high quality reports. A newer hire noted that experienced staff were impressive in squeezing the most value out of the available data. Those involved in research within ONLDS and OARSA felt that they did a good job with safety and exposure assessment (in conjunction with NTP and NCTR), and in conducting *in vivo* studies and investigating initiatives identified under the Toxicology in the 21st Century program (Tox21). OARSA felt they were responsive to program office needs.

In terms of being **responsive to the mission**, interviewees stated that they were successful in focusing on the job that they are mandated to do (i.e., protecting the public health, investigating the safety of chemicals in dietary ingredients), while working within the parameters and regulations they have. For OFAS, established industry guidance (Redbook 2000) and a standardized systemic review process for food additive petitions was cited as a strength, while the GRAS and Food Contact Substance (FCS) Notification programs were commended by interviewees within the programs as well as those from other groups for having developed innovative notification programs responsive to the mission (including use of conservative methodology in evaluating exposure), with timely completion of tasks and reviews. OARSA interviewees stated that the research conducted was mission-oriented, consistent with the objectives of the FVMP Strategic Plan 2012-2016 (including Tox21 methodologies), and that they were responsive to the needs of other offices within CFSAN. Within CVM, interviewees felt that they were effective in achieving consistent procedures and scientific approaches to the standard regulations, and were improving in stepping outside the guidelines to make decisions. CVM interviewees also mentioned good support from their research office, OR.

Teamwork and support were cited as program strengths primarily by chemists within OFAS and by CVM personnel. Many chemists referred to a collegial work atmosphere and/or good working relationships between staff members and between review staff and research personnel. Weekly chemist meetings, which cross divisions within OFAS, were mentioned as a means of promoting cohesiveness, maintaining cross-support, monitoring the status of work in-house, identifying/resolving issues, and obtaining help and advice from other experts. The successful collaboration between chemists was felt by some to extend to better collaboration with the rest of the review teams. Under this category, interviewees (including toxicologists) also cited the inter-disciplinary approach to the review process as a program strength. Teamwork, within groups and across divisions, and an overall willingness to collaborate and help out with problems and issues was also cited as a program strength by CVM interviewees.

Being **current with the science** was most often identified as a program strength by OARSA personnel. These interviewees felt that, while their Office is strong in established methodologies pertaining to reproductive and developmental toxicology, they are also successfully expanding

their research to include nanotechnology (developing methods to detect and evaluate toxicity) and *in vitro* screening safety assessment assays to assess anything from cytotoxicity to the functional assays that might be affected by an individual organ system: hepatotoxicity, neurotoxicity, kidney toxicity. Additional research areas that were identified included new ways to detect toxins (e.g., bacterial cell wall exacerbation), biologic and molecular research, and emergency response methods for extracting toxins. In response to this question, interviewees within OFAS also cited state of the art chemistry knowledge, increased focus on emerging issues to incorporate new methodology or consider whether it should be adopted, and participation in the Toxicology Study Selection and Review Committee (TSSRC) process to nominate compounds/chemicals.

Timeliness of completing review/research products and effective **use of resources** in terms of hiring and efficiently deploying personnel were cited to a lesser extent as program strengths, at ~11% and ~6% of responses. Additional identified areas included **working well with industry** in terms of providing guidance and consultation pre- or post-submission, and **adequacy of the data/information available** for the review process as program strengths. Five interviewees listed no program strengths.

2.1.2. Question 2: What do you see as the most obvious weakness in your program with respect to chemical safety review or research?

When asked about program weaknesses, the two factors cited by interviewees from both centers and all offices were the quality and type of data/information available for conducting reviews and insufficient manpower. The distribution of responses to this question is summarized below.

Program Weaknesses	Responses (% of 82 interviewees)[1]
Quality and type of data/information available for conducting reviews	~41%
Insufficient manpower	~38%
Impact of post-market review on workload, personnel resources, funds	~13%
Not achieving the mission of protecting food safety	~13%
Communication issues	~9%
Lack of peer review	~7%
Lack of timeliness	~6%
Lack of SOPs/procedures	~5%
Insufficient feedback/support	~5%
Other	~22%
None	~1%

[1] Up to 3 responses/ideas captured per interviewee as follows: 13 interviewees had ≥3 responses; 20 had 2 responses, and 49 had 1 response.

With respect to the quality and type of **data/information available**, interviewees expressed concerns with the data/information provided by industry, that which might be obtainable from other sources, and that which could/should be generated within the Centers. Many interviewees stated that it is difficult to get the data needed from industry to do a thorough assessment of chemical safety. Although most acknowledged that the amount of data available was limited by the law and the regulatory environment under which the Centers operate, some felt that industry

was not forthcoming with data/information when not required to produce it. Another area of concern for CFSAN interviewees was the Center's apparent reluctance to accept data generated by new methodology (e.g., *in vitro* testing, pharmacokinetic data). Interviewees acknowledged that some of these methods have not been fully validated and probably could not replace *in vivo* testing; however, they felt that considering data generated by newer methodology could help to advance the science, avoid controversies, and provide additional insights. In terms of data that might be obtained from other sources, interviewees mentioned the limitations of data available in the literature and the absence of adequate market survey databases addressing foods, food additives, and food packaging, as well as those addressing cumulative exposure and chemical safety in general. The shortages or lack of availability of adequate data/information were felt to result in: worst-case assumptions for decisions that might not reflect the actual situation or necessarily be to the sponsors' advantage; exposure calculations and decisions weakened by limited information; and/or a canting of decisions in industry's favor. In discussing data which might be generated within the Centers, interviewees noted that, although research is not funded at FDA as it is at NIH or DOE, there are questions that could be answered more expeditiously in-house, and there are new methodologies and safety investigations that could be explored in-house.

In terms of **insufficient manpower**, interviewees expressed concern over being short-handed, losing senior expertise or institutional memory due to attrition through loss or retirement, and poor distribution of available staff to handle the workload. Short-handedness was believed to impact negatively on: timeliness; the ability to conduct extra projects; the ability to maintain personal areas of expertise/stay current with the science; the ability to assign appropriate staff to a given task; and regulatory outcomes (e.g., an application with a problem may be rejected to meet the statutory deadline, when additional staff might have been able to resolve the problem). Loss of senior expertise was felt to be a current and looming problem, with many interviewees feeling the Agency has insufficient planning and/or ability to hire qualified personnel to replace experienced staff. In addition to the loss of specific areas of expertise, interviewees felt that the loss of senior staff could result in a reduction in quality of product and a general erosion of the scientific base. The need for a plan to redistribute the staff and/or workload to accommodate day-to-day operations was cited. Toxicologists within OFAS, CHAT, and OARSA commented specifically on the dwindling numbers of toxicologists within their offices, although it appeared that OARSA is addressing this issue. A shortage of personnel with mathematics/engineering backgrounds (mathematics, statistics, programming skills) to aid in performing safety assessment calculations and data interpretation was also identified. Unique to CVM was the concern that a shortage of manpower for inspection of overseas facilities could result in the Agency being taken advantage of by producers.

A major concern expressed by a number of interviewees is that the Centers, and primarily CFSAN, are **not achieving the mission of protecting food safety** due to factors including: reliance on and obligation to the sponsors; questions concerning the Centers' approach to safety review; and a lack of ability to confirm the results of safety decisions. Regarding the role of the sponsors, interviewees expressed concern that because programs like the GRAS Notification process are voluntary, the Agency is trusting the system to take care of itself: trusting the developers to come to the Center with their products, to provide sufficient and appropriate data/information, and to follow the appropriate regulatory path for a given product. For new

compounds, one interviewee commented: "Once they give us all the information [for a product] we have to let them use it." Another side of this issue was the obligation felt to work with the sponsors in getting products to market. In fulfilling this obligation, interviewees felt there might be compromises made in safety screening, addressing science issues, and achieving a consensus of safety. Within CVM, there was concern that as a result of the Animal Drug User Fee Act (ADUFA) "now that we are dealing with a paying customer", the Center might be losing sight of the safety objective in favor of getting a product approved. One interviewee noted that it appeared that submission quality was going down under ADUFA, even though the Center was giving sponsors more recommendations. Regarding the Centers' approach to evaluating safety, interviewees raised questions about: the problems of adjusting the standard review approach for products that don't fit into the standard paradigm of safety review; an overall decrease in emphasis on review in general (e.g., less evaluation of raw data and of the quality of the research); the representativeness of exposure calculations in consideration of susceptible populations (children, the elderly, those self-selecting diets); the failure to consider mixtures in safety assessments; the failure to establish clear differentiation between risk assessment and risk management; the inability to resolve the issue of dose-response characteristics for toxicology and to integrate dietary exposure assessment with the dose-response assessment; the reliance on outdated safety factors; and the existence of different safety standards for different products (e.g., contaminants vs. food additives). Finally, interviewees were concerned about the inability to confirm the effectiveness of safety decisions due to lack of follow up (e.g., market testing, periodic re-evaluation of approved products) once a product has been approved. One OFAS interviewee also noted that the industry has found ways of circumventing FDA review via various "legal" routes, making new food additives more difficult to track.

Four additional areas of concern were identified by interviewees across offices and/or centers as program weaknesses:

- **Impact of post-market review** (~13% of responses) on workload, personnel resources, and funds;
- **Communication issues** (~9%) between: other groups/offices (sharing professional expertise and/or familiarity with similar compounds/situations, coordination between divisions on a common product); reviewers and researchers; centers (integrating exposure estimates for cumulative intake); agencies (better data sharing); and the public (more publishing, more sharing available data); and
- **Lack of timeliness** (~6%) due to cumbersome regulatory procedures.
- **Lack of SOPs/procedures** (~5%) for conducting reviews (guidance on how to transition from research to regulatory science, specific guidelines for chemical safety review, comprehensive approach to maintaining historical records and tracking decisions to improve consistency).

Insufficient **feedback/support** (~5% of responses) was cited as a weakness primarily by OARSA personnel who felt that, despite some improvements, there was a lack of support in terms of: feedback from program offices; funding; recognition of potential contributions to the review process; and consideration of public health issues that might fall under a broader category (e.g., translational or risk assessment research, impact of toxins on susceptible populations, health impacts other than cancer, allergens research). Researchers felt that frequent, regular,

issue-specific discussions between program office personnel and researchers would provide benefits, including better alignment of research with the program offices and better risk assessment decisions overall. Toxicologists within OFAS and CHAT tended to be concerned with the lack of **peer review** in the review process, suggesting the need for more internal expert committees and/or additional levels of QA (specifically review of their work by other toxicologists) to achieve consensus in interpreting toxic endpoints.

Other identified weaknesses included: insufficient funding; lack of emphasis on training or expanding areas of expertise; being resistant to change; being reactive instead of proactive; lack of emphasis on emerging technologies; lack of science expertise in management; asking staff to follow up on activities "outside" the mission; hesitance to make final decisions ("even given the scrutiny under which the Agency operates"); and being pressured to make decisions in support of another division, group, or organization.

2.1.3. Question 3: Are you aware if chemical safety risk assessment and safety evaluation methods are consistent across offices and centers? For example, are there consistent requirements for submission of raw data and data tables and if not what is the rationale for the inconsistency or inconsistencies?

When asked whether chemical safety risk assessment and evaluation methods were consistent across offices and centers, ~20% of interviewees felt that methods were consistent, ~32% felt methods varied between offices and/or centers, depending on various factors, ~39% felt that methods were inconsistent. The primary rationales for inconsistencies were differences in policies/regulations for different centers and offices and different target compounds or products (together ~78% of responses), while ~10% of interviewees felt that consistency was not attempted.

Interviewees who responded that **safety assessment and evaluation methods were consistent** across the Centers, tended to speak in broad terms about the overall principles of safety and risk assessment. These interviewees generally felt that methods were consistent both within and between CFSAN and CVM and tended to feel that differences in data submission and interpretation and in specific endpoints, as influenced by regulatory mandates, the safety standard, and/or types of product, were insignificant. These interviewees often made a distinction between CFSAN/CVM and CDER due to differences in regulatory authority and requirements, the risk/benefit paradigm for drugs vs. the safety paradigm for foods, and the review of human data. Those who responded that methods were consistent within offices, tended to speak more often in terms of individual divisions. In these cases, interviewees felt that methods were consistent because the type of data required was consistent (e.g., primary data vs. published research), and essentially the same concepts, programs, and procedures could be applied. Most who felt that methods were consistent also felt that the regulatory structure was reasonable and that a reasonable safety standard was maintained.

Those who felt that **methods varied or were inconsistent** were more focused on the differences between CFSAN and CVM and the differences in the data requirements for each center or office. These interviewees tended to be divided between those who felt the rationale for inconsistencies was valid and those who felt it was not. A CVM interviewee noted, "There are different

regulatory mandates, and therefore the programs and assessments have to differ to meet those mandates. There are clear differences and there should be for what we can/should require for a GRAS application vs. a new animal drug application vs. a food additive petition." Several interviewees felt that the lack of consistency between the Centers was the result of differences in actual risk assessment practices resulting from CVM's adoption of harmonized guidelines under the VICH and CFSAN's continued reliance on the Redbook. One interviewee commented specifically on a gap in guidance for immunotoxicology data between the two Centers. Others felt that there was no consistency in methods across offices and centers because it was not attempted, due to: the need to protect proprietary information; different regulations; lack of cross-talk; and/or lack of willingness to consider other approaches (i.e., territoriality). Some of these interviewees were less confident that the safety standard was being maintained. One interviewee stated, "The Food Contact Notification Program has many different options for a product to get to market without a thorough safety evaluation."

For most of these interviewees, the lack of communication or knowledge of what each Center does within the OFVM was the larger issue. Several interviewees stated that, due to lack of communication between centers and/or offices, they were not sure whether there were differences in safety assessment methods across centers and offices or not. One interviewee stated: "It would be advantageous if: (a) the offices and centers were aware of how everybody does their reviews and there was a knowledge of it; and (b) there would be an attempt to streamline it as much as possible [via SOPs]."

Interviewees from both CHAT and OCAC felt that their offices were too different to be included in this discussion. One CHAT interviewee commented "There are some cases where we could discuss the underlying science and get to some consistent resolution, but we don't. We generally don't talk to each other." OCAC interviewees commented on the lack of authority under the cosmetics mandates and the difference in risk profile for cosmetics as a reason for lack of consistency in methodology: "the approaches need to be tailored to each product."

Regarding **consistent requirements for submission of raw data or data tables**, nearly all interviewees recognized that there were different requirements for submission of raw or primary data as opposed to available data or information (usually published in peer reviewed journals), depending on the type of compound or product being regulated and the laws and regulations governing review. Premarket review of direct food additives and new animal drugs was generally felt to be the most rigorous process because primary data (generally collected under GLPs) are required; whereas, regulation under GRAS and FCS notification programs was considered to be somewhat less rigorous because the submitted data/information are generally publically available and may or may not have been generated under GLPs and/or undergone external review. Most interviewees felt that the correlation between the type of data required and the relative impact of a given product on human health was appropriate in terms of safety assessment. The cosmetics program and the dietary supplements programs were felt to be the least reliable in terms of safety due to lack of regulatory authority to require data: "There are some assumptions that somehow the manufacturers are ensuring that cosmetics are safe."

Interviewees felt consistency of requirements for submission of data was improving for those programs involved in premarket review. Specifically, interviewees within ONADE at CVM and

chemists within OFAS Division of Petition Review (DPR) at CFSAN felt that the adoption of updated guidelines (primarily VICH Guidances for ONADE and Chemistry Recommendations for Industry for DPR) had resulted in improved consistency in data submissions. Both groups indicated that they were taking further steps to improve data consistency via pre-submission meetings with producers and/or via development of additional materials (e.g., electronic formats for data submissions). We note that consistency of raw data requirements was not specifically addressed by most toxicologists within OFAS DPR. One CVM interviewee stressed the importance of maintaining requirements for raw data in the regulatory process as a means of expanding data interpretation, especially for non-traditional applications. CVM interviewees also noted that certain steps were being taken, in terms of increased flexibility in data requirements, to accommodate smaller companies manufacturing veterinary drugs.
A general lack of consistency in data submissions was reported for the notification programs and for post-market reviews, where reviewers needed to rely on what was provided by industry or what was available in the literature for data/information. An interviewee in the GRAS Notification program noted that because most of the data reviewed are available in peer-reviewed journals, it is assumed that they are acceptable and any questions would have been addressed in the peer review process or in a rebuttal in an alternate publication. However, many interviewees within these programs also asserted that they do not simply accept what is provided by industry, but do additional investigation themselves. Data requirements were also felt to be less clearly defined for animal feed petitions reviewed under OSC at CVM. Within OARSA, there was disagreement as to data consistency, depending on whether the research involved was conducted under GLPs or not. An interviewee from OCAC noted that improving consistencies in data format and submissions would contribute significantly to conserving resources with the Agency.

2.1.4. Question 4: If you are aware of differences, do you understand what the rationale is for these differences?

Question No. 4 was addressed under Question No. 3.

2.1.5. Question 5: Is chemical safety research at CFSAN and CVM adequate in scope and scale and well aligned with the Centers' regulatory mission and priorities? If not, what are some examples? What suggestions do you have for changing the scope, scale and alignment?

The majority of interviewees felt that chemical safety research at CFSAN and CVM was adequate or mostly adequate in scope and scale (~60%) and adequate to excellent or improving in alignment (~66%) with the Centers' regulatory mission and priorities. Only ~20% of interviewees felt research was not adequate or only partly adequate in scope and scale, and ~15% of interviewees felt that alignment was poor or needed to improve; ~20-21% of interviewees had no opinion on this issue. Many of the interviewees who felt they could not comment on the adequacy of the research program were those involved in notification programs, where most or all of the data reviewed were received from industry. Because they did not need to ask in-house researchers for much data or information, they were unaware of their capabilities.

The following general trends were observed among personnel within different offices and centers: responses from CVM personnel and chemists within OFAS were overwhelmingly positive concerning scope, scale, and alignment. For toxicologists within OFAS the majority of responses were positive (~60%); however, ~30% felt improvement was needed. For OARSA, the responses were nearly evenly divided between positive and negative.

Those who felt the **research programs were adequate to support** the Centers' regulatory mission and priorities listed the following factors: well-qualified personnel; good communication, collaboration, and working relationships (including regular meetings) between regulators and research personnel; improvements in setting priorities; capability to address difficult questions; and appropriate focus for establishing safety. Along with the installment of a new Director within OARSA who has made an effort to improve outreach, the FVMP Strategic Plan was cited as a major factor in improving the alignment of the research programs with the Centers: "At CFSAN [this] aspect has improved dramatically. Previously, the two groups that we rely on for our research, NCTR and OARSA, would follow whatever research they felt was important. Now there is increased focus on supporting the regulatory science." Interviewees within OARSA stated that there is now consensus between research and upper management at CFSAN, so that the needs of the Center are outlined and the research is being adapted to meet these needs.

Interviewees who felt the **research programs could provide better support** to the regulatory reviewers cited the following issues: limited resources in terms of personnel and time (the Toxicology Division of OARSA in particular was widely felt to be under-staffed); difficulty in aligning priorities in terms of topics, time, and scheduling for accomplishing specific projects; the conflict between developing long-term research projects and focusing on answering specific regulatory questions; and loss of proximity and resulting reduced communication between researchers and regulators due to re-organization of the Center. One OARSA interviewee stated, "We are the only office within CFSAN that is not tied to a product or program. We are depending on the program offices for feedback as to what the key safety issues are. Unfortunately, many times this is not straightforward." Several interviewees noted the conflict between developing long-term research projects vs. focusing on answering specific regulatory questions. One interviewee stated, "People that are planning research like to plan for years ahead, but if you are a regulatory reviewer, you might have a question that you need answered quickly that doesn't fit into their long-term research project." There were also interviewees who felt that the research conducted within OARSA and OR was not necessarily supportive of the Centers' overall safety mission. One noted that research does a good job of dealing with detection and measurement of chemicals, but does not do as well in determining whether a chemical is safe. Another stated, "Very little chemical safety research has been done in CFSAN, and most of it has avoided subjects of major significance and fails to address current regulatory data gaps."

Although there was general agreement among OARSA interviewees that the FVMP Strategic Plan had improved alignment with the regulatory mission and priorities, several maintained that the boundaries of research could/should be expanded with comments such as:

There is a lot of research that would fall under the definition of public health that is not being done: you can't always see the contribution of a project at the outset.

Even though we are not a basic research institution, there should be some time for exploratory research.

Sometimes . . . the lab misses opportunities to do research that they are capable of doing but that is not strictly part of the mission (e.g., research on tobacco byproducts).

When asked for examples of where and how the research program might improve its support of and alignment with Center priorities, interviewees provided examples of accomplishments, as well as areas where additional work is needed.

Research program accomplishments	Research program work needed
• Various special projects for DPR • Post-market work on melamine and BPA • Method transfer trials for CVM • Fish research for CVM • Antimicrobial research for minor use/minor species drug manufacturers	• Methods development and validation for OFAS • Cumulative exposure calculations • Clinical studies on food safety • Broad-scope chemical safety and human health research

Suggestions for changing the scope, scale, and alignment of the research programs fell into several broad categories, including improving communication (between groups, offices, and centers; ~24% of responses), modifying/expanding the in-house research program (~13%), and increasing details/training between the research and regulatory sides (~4%). About 49% of interviewees made no suggestions. Specific suggestions for changing the scope, scale, and alignment of the research programs are summarized below.

Suggestions for Changing the Scope, Scale, and Alignment of the Research Programs.	
Improve Communication	**Modify/Expand In-House Research Program**
• Improve communication of regulatory office needs. • Improve communication of research capacity and capabilities. • Provide more input from upper management to define/establish research priorities. • Improve planning/forecasting on research needs. • Improve follow-through on requests and assignments from both sides. • Increase information exchange venues (e.g., Traction at CVM). • Increase opportunities for informal exchanges (e.g., poster sessions, workshops). • Increase communication of key Center-wide evaluation efforts. • Increase communication/coordination between OARSA and OR (note: monthly meetings have been initiated). • Improve communication between OARSA and toxicologists within OFAS DPR.	• Increase capabilities for post-market research/analysis. • Increase research on long-term and/or low-dose impacts. • Increase safety research on products with limited premarket requirements (e.g., supplements). • Increase work on evaluation and validation of emerging methods (especially with respect to Tox21). • Establish a clinical research function within CFSAN. • Clarify the time division between follow-through on regulatory issues and conducting exploratory research (allowing for both). • Expand personnel resources here rather than at remote sites. • Establish "strike teams" for special projects. • Increase expertise in *in vivo* animal research and endocrine disruption.
Training/Details	**Other**
• Establish working groups comprised of both regulatory and research staff with similar expertise (e.g., genetic toxicology). • Increase details and/or staff exchange between research and regulatory personnel (preferably longer-term assignments). • Establish mechanism for providing coverage for the regulatory review process to accomplish critical review tasks when employees go on details.	• Streamline process/improve turn-around time for scheduling special projects. • Increase opportunities for peer review of research proposals. • Establish a competitive funding process for research based on mission relevance. • Establish a mechanism for challenging decisions/resolving disputes. • Consider safety testing for children. • Make clear to new hires that mission-oriented research supersedes their individual research. • Establish a research committee within each office that develops a research plan for the next 2, 3, and/or 5 years.

2.1.6. Question 6: Are the program's risk assessment and safety evaluation methods (a) in keeping with the current and emerging state of the art and, (b) recognized as such by the external scientific and stakeholder communities? If not, what are the shortcomings?

The majority of interviewees (~78%) felt that program's risk assessment and safety evaluation methods were **in keeping with or mostly in keeping with the current and emerging state of the art**. Only ~16% of interviewees felt the program's methods were not current/state of the art. In this area, as well, OCAC interviewees felt the question did not apply due to lack of authority: "there is no premarket approval and therefore no established safety evaluation methods."

Those who felt confident that program methods were current cited supporting factors including the following: staying current with and working with international agencies, including EFSA, JECFA, and Codex Alimentarius to keep up with new methodology and to harmonize data requirements and testing methods; staying current with industry; possessing a high level of staff expertise (world-wide expertise in exposure estimates/risk assessments, access to professional

training); having access to up-to-date analytical equipment; combining core safety assessment guidance (i.e., the Redbook) with advances in confirmatory and screening methodology (e.g., quantitative structure-activity relationship (QSAR) modeling); and continuing exploration of new methodologies (e.g., *in vitro* methods).

Those who felt the program's **methods were mostly current** tended to maintain that being state of the art is not the role of the Agency as a regulatory entity. These interviewees felt the Agency must be conservative ("stay a half-step back") in adopting new methods to protect both the public health and the interests of sponsors ("we can't require industry to take that risk"). Interviewees cited the necessity for risk assessments and safety determinations issued by the Agency to be based on guidance, data requirements, and/or methods that are/have been: within the scope of established regulations; thoroughly validated; widely accepted by the scientific community; found to be effective and applicable to the program's mission; and/or incorporated into the established safety paradigm. Nearly all of these interviewees felt that, despite limited resources, sufficient efforts were being made to stay current with new and emerging methodologies in terms of training, re-evaluating regulatory assumptions, membership in societies, attendance at meetings, and examination of the literature. Interviewees stated the following:

To be fair, while there is ferment and widespread feeling that the current state of the art is badly outdated and in need of reform, it would be hard to argue that there is as yet a new state of the art behind which CFSAN lags. There are many exciting proposals for new methodology and paradigms but as yet none have taken hold.

To go beyond [validated methodologies] we are aware of and provide comments on [emerging methods], but until they have been validated and can be meshed with the information that we ask for, they can't be used at this point. This is not where our mandate is at this point.

Protocols and tests need to be validated to be adopted, but it takes more time to validate methods than to develop new methods, and the procedures are not great. We can't always use evolving science.

Interviewees within OARSA felt they were able to progress more rapidly toward state of the art methods because they are not driven by the petition/notification process: "We are moving off from Redbook guideline studies to Tox21 approaches (biomarkers, reducing/replacing animal models)." They noted the recent development of new analytical techniques and acquisition of sophisticated instruments/equipment as strengths but acknowledged that the "private sector will move faster."

Those who felt **methods were not current**, generally felt the Agency was behind the science because of unwillingness to change, reliance on outdated guidance, and an outdated approach to implementing new technology/science into safety assessment. One interviewee noted: "[Our methods are not] in keeping with state of the art and, in fact, we hardly consider it. Right now we just do the same things we have done for the past 30 years." Specific areas where the programs were felt to be lacking included: adoption and application of Tox21 methodology; expanding risk assessment to include non-mutagenic carcinogens; investigation/application of

the low-dose hypothesis; requiring screening for endocrine disruptors; and incorporating consideration of sensitive populations (e.g., infant safety) into risk/safety assessments.

The majority of interviewees (~73-77%) felt that the program's risk assessment and safety evaluation methods were **generally recognized by the external and scientific stakeholder communities** as being in keeping with the current and emerging state of the art, while ~15-18% felt this was not the case. There was general agreement that FDA's methods were recognized as being current by the international community, including EFSA, EMA (European Medicines Agency), JECFA, Codex, OECD, and the Canadian regulatory agencies. Otherwise, most interviewees agreed that external communities were mixed in their recognition of Agency methods and that this largely depended on their point of view and/or understanding of the Agency's role in food safety: "Those who understand what we do [e.g., industry and the scientific community] think we do a good job with the resources that are available to us; those who do not understand [e.g., consumer groups, Pew Research Center, possibly academia] do not." Most agreed that there was respect for the scientists (education and background) who work in the Centers. Those who felt the Agency's methods were not recognized by the external communities generally cited a lack of transparency and communication concerning why the Agency uses the methods that it does and why cutting edge or new and emerging methods cannot be adopted into the regulatory process except in a supporting role.

When identifying real or perceived (by the external communities) **shortcomings** in the Centers' risk assessment and safety evaluation methods, the majority of responses fell under the categories of adoption of new methodology (~28%), communication (~20%), and insufficient funds, staff, and/or time (~9%). About 27% of interviewees felt there were no shortcomings, and ~10% did not identify any specific shortcomings.

In discussing **adoption of new methodology**, most interviewees were divided between those who felt that new methods were not appropriate for use in the regulatory environment and those who felt that the Agency had made insufficient attempts to incorporate new methodology into the safety paradigm; specific points for these arguments are listed below. A few interviewees felt that there was a general lack of knowledge of what was "out there" in terms of new methodology and food production, processing, and packaging procedures, or that there was a lack of expertise within the Centers to generate the data necessary to put new methodology to use. One interviewee stated, "If government sector research can push how quickly [new methodology] is catching up, it will help align scientific developments in the regulatory requirements.

Adoption of new methodology	
Incorporation Inappropriate for the Regulatory Environment • The Agency must be conservative in its approach. • New and emerging sciences have not been properly evaluated and validated. • Many new methodologies are directed toward a specific tissue or time and cannot give an adequate picture of what happens in intact animal. • Application of some methods is restricted by the impact of the Delaney Clause. • The Agency cannot bypass the scientific community in addressing new methods. • More can be done, but we don't necessarily need to keep up. Industry can push the bounds. We are result-oriented because we need to establish safety. • Sometimes we would like to do . . . collaboration but there are limitations in how we deal with the private sector [which] has the state of the art technology.	**Insufficient Attempts Made by the Centers** • Lack of involvement by CFSAN/CVM in the shift in the toxicology and safety paradigm initiated by Tox21 • Management unwilling to improve safety and risk assessment evaluation methods as has been done in other centers (CDER, CDRH) • Lack of willingness to explore "accepted" alternatives that have not been used here before • Lack of training in new methodology so that it can be evaluated for usefulness • Lack of incorporation of acceptable tests outside of gross animal pathology models • Other than the computational toxicology group in OFAS, little attempt to keep up

In terms of **communication**, many interviewees felt that inadequate information concerning the Agency's processes was relayed to the external scientific community and stakeholders, noting that: "the best spokesperson is not always put forward to speak for the Centers." This was not perceived to be as big a problem for stakeholders in industry because they "understand [what we do and] what they need to do." Some interviewees felt there was a lack of understanding of the regulatory assessment process by both the consumer and the external scientific community, noting that scientists in academia could also benefit from more education in the regulatory process. One interviewee stated: "We have our priorities right, but communication needs to be improved. We will never completely satisfy the external scientific and stakeholder communities, but we could do better at communicating so at least we are a little bit closer." Although publishing, going to meetings, serving on panels, and presenting papers or posters, were all seen as valuable means of communicating with the external communities, interviewees saw the need for more interaction. The need for a "good PR campaign" was seen for consumers, while for the stakeholders, one interviewee stated: "When we are right, we need to explain that we are right, and when we are wrong, we need to admit it." Increased internal and external peer review was seen as another means of engaging stakeholders, by expanding methods evaluation outside the regulatory scientific community, and increasing transparency, improving decisions via further scrutiny, and identifying new data sources, data gaps, and additional data to be considered.

Resources including **funding, staffing, and time** were also identified as deterrents to improving the risk and safety evaluation methods, with all three required to stay current with, identify, validate, and eventually adopt new methodology. Other methods shortcomings included: lack of exploration of new areas and databases (e.g., label and market survey data), especially for post-market work; lack of sharing between groups and centers; lack of sufficient research effort in major chemical assessments; lack of centralized research activity [e.g. research under one umbrella, separate from review); and too much input from legal/policy (causing science to "take a back seat").

2.1.7. Question 7: What do you see as some of the emerging issues and questions in chemical safety review? How well do we facilitate the needed developments in the science to address and answer these issues and questions?

When asked to identify emerging issues and questions in chemical safety review, the five issues most often identified were **new methods** (~39%); **nanotechnology** (~22%); **botanicals, supplements, and non-traditional entities** (~17%); **endocrine disruptors** (~15%); and **effects of mixtures and groups of chemicals** (~13%). Other identified areas included: post-market review; low-dose/long-term exposure effects; effects on sensitive populations; genetically engineered organisms; and allergen thresholds. Under new methods, the majority of interviewees were concerned with the move toward Tox21 methods (*in vitro* testing, high throughput screening, *in silico* methods), and when discussing **nanotechnology**, several interviewees noted that the agency has done a good job of recognizing this emerging issue and working across centers, yet concerns and questions were still identified. The emerging issues and associated questions and concerns are listed below.

New methods
• How do we handle and use the new methods and data and where do they fit in our guidance? • What do we do with results of quick-screening assays? Can/will they be integrated into safety review? • Should data generated by these methods be relegated to case-by-case, weight of evidence use? • What does *in vitro* testing mean in terms of human health? • Can these tests be used without some intervening physiological assessment? • Is animal-based testing insufficient due to gaps in the area of human effects (e.g., Alzheimer's, diabetes)? • How do we adopt new methodology without losing our conservatism and time-tested processes? • Additional methods issues included use of QSAR modeling, validating analytical methods used across other agencies/countries, and the need to re-assess dietary exposure methodologies.

Nanotechnology
• How do we detect and qualify these compounds? Do existing methods apply? • What are the regulatory impacts for use in foods vs. drugs and cosmetics? • How do nanoparticles react with other chemicals? • How will nanotechnology figure in risk assessment?

Botanicals, supplements and non-traditional entities (including biologics, protein-based, large molecules, organisms, anti-virals)
• These entities represent much more complex and variable substances that don't fit the typical flow chart. • With no premarket safety testing requirements, can we do enough to establish safety? • Botanicals are automatically assumed to be safe, but not enough safety studies have been done. • For functional-type food ingredients, we need to be clear to the public that FDA does not assess benefits. • How do we deal with excessive nutrient access via supplements (sodium, phosphates) and how do we address the increasingly widespread use of supplements? • How do we handle pathogens (e.g., dose-response curves)? • What do we do with byproducts from agriculture intended for animal feeds (e.g., algae for biofuels)?

Endocrine disruptors

- Do we need to re-evaluate the review process for these chemicals?
- Should we require screening for them?
- How do we recognize them and prevent them from entering the food supply?
- How can we incorporate other affected fields such as microbiology, physiology, and pharmacology in dealing with them?

Effects of mixture and groups of chemicals

- Because NIEHS included mixture toxicology in its strategic plan, it will certainly be a big issue in the years to come. We need to be part of this.
- We need to expand the safety assessment to include biological as well as toxicological effects so that we can better evaluate additive/synergistic effects.
- We need to begin addressing low molecular weight oligomers (LMWOs) in conjunction with target compounds.
- How do we expand our risk assessments to account for real-life exposure to mixtures of components and microbes (chemicals, nanoparticles, bacteria, drugs) at the same time?
- What are our options for evaluating groups with the same mode of action and all current uses of a compound vs. one food additive?
- What adjustments are needed to perform aggregate/cumulative risk assessments?

Post-market review

- We need to change our approach to post-market review from the old model (chemists do exposure assessments, toxicologists do safety assessments) to a new model where there is a chance to comment on each other's reviews or ask questions.
- With problems like BPA and thiates/phthalates, we need to find safe alternatives with adequate supporting data to replace them if they can't be used.
- We need additional funding to monitor levels of approved chemicals in the food supply (e.g., testing from the shelf).
- We don't have a mechanism to routinely go back and re-evaluate our previous analyses and to see if new data will change them (e.g., new consumption/usage estimates). Should we institute some sort of cyclic review process?
- How do we conduct premarket and post-market reviews in a timely fashion with limited resources?
- How do we address industry's reluctance to provide information for post-market review?
- How do we deal with old materials that were previously replaced by something like BPA, but are now being put back into use?

Effects of low-dose/long-term exposure

- Too many chemicals have been approved for use without characterization of their ability to interact with biological systems.
- We have only focused on toxic effect at high doses, which are not usually encountered.
- We have good understanding of short-term benefits but not of long-term effects.
- We do not consider the complex mechanisms of toxic effect such as induction of enzymes producing increased metabolism and alteration of metabolic paths for hormones and drugs.
- We have a decent understanding of acute carcinogenic effects, but it is hard for us to see the long-term effects.
- Should we incorporate the low-dose hypothesis into our approach?
- How do you handle long-term chronic exposures versus short-term acute exposures?

Additional emerging issues and questions

Effects on sensitive populations:

- Is the current safety assessment process capturing the risk to groups including the elderly, infants, those on special diets (gluten-free), those self-selecting their diets, and adults undergoing chemotherapy?

Allergen thresholds:

- We need to do a better job of understanding the threshold response vs. the safe response; these are not necessarily linked.
- Our methods for determining allergen thresholds are not current.

Genetically engineered organisms:

- Are these organisms the same as the wild species?
- Will they react to drugs in the same way as wild species?

Other emerging issues:

- Re-evaluating the risk assessment process and incorporating/integrating more procedures from risk assessment into the safety review process
- The precautionary principle vs. dose response (especially as it relates to the Delaney clause)
- The increase in consumer awareness of what goes into food products
- The need for consistency/harmonization across agencies and countries in terms of safety
- Active food packaging
- Immunology and ingredients intended to bolster the immune system
- Developmental neurotoxicity adverse effect, neurobehavioral effects, and epigenetic issues

When asked how well the Centers **facilitate the needed developments in the science** to address and answer emerging issues and questions, ~28% of interviewees felt efforts were adequate to excellent and ~28% felt the Centers were trying or improving, while ~21% felt they needed to improve; only ~8% of interviewees felt efforts in this area were poor or inadequate.

Those within CFSAN who felt the Centers were **doing well in facilitating developments** in the science cited the following: interactions with industry (communication, outreach, and collaboration on new issues and methods; keeping current with new technology); improving interaction/communication with the research group; addressing emerging issues quickly, thoroughly, and conservatively; hiring and training staff as needed to address new issues; providing access to databases; and organizing and/or encouraging attendance at workshops. In addition to improved communication with the research office, interviewees within CVM reported a "great push" by the Center to begin addressing these issues via technology teams and working groups, and initiatives to address areas such as innovation, novel products, and nanotechnology. Specific examples of successful interactions included: investigations related to BPA (collaboration between CFSAN, NCTR, TSSRC, and academia to initiate a study on low-dose effects); nanotechnology (collaboration between centers); and melamine ("CVM was recognized as having reacted with lightning speed and transparency"). Implementation of the FVMP Strategic Plan was seen as an advance for some emerging issues, such as allergens; however, one interviewee noted that, in prioritizing mission-critical projects, the Strategic Plan could move emerging issues research "down the ladder."

Interviewees who felt the Centers were **improving** in this area cited funding and staffing issues, as well as insufficient time to work on emerging issues, as stumbling blocks. One CVM interviewee stated: "We do a reasonably good job as an organization. There is support to look

outside the box, but this is difficult to do if you're working under a deadline; the will and the tools are there, but the opportunity to access and use them is not." Another interviewee noted, "We do a pretty good job of [addressing issues] as the needs arise [e.g., arsenic in apple juice], but it is difficult to anticipate, and we don't always have the money or manpower." Suggestions to improve facilitation of the science included:

- Minimizing the regulatory barrier between chemists and toxicologists within OFAS to enable interdisciplinary assessment of all accessible useful information from all sources, to embrace emerging issues and look at them on a practical level (e.g., impact on different populations);
- Establishing a separate half of the group to work on special topics/side projects;
- Increasing involvement across the entire Center in emerging issues such as Tox21: "This is the problem with each and every issue in the Center; there are just a few people who deal with a few things . . . the majority of the people don't know";
- Expanding the use of inter-center "super groups" (such as that established for nanotechnology) to address new areas, including toxicology and Tox21;
- Increasing collaboration with outside scientists via seminars, workshops, symposiums;
- Increasing policy-focused research in OARSA and OR; and
- Improving identification of "point people" within other offices, centers, agencies, to collaborate on emerging issues.

A lack of cooperation from industry in providing new information/data was also cited by several interviewees as an impediment to FDA's efforts to facilitate the science.

Those who felt the Centers **did not facilitate developments in the science or needed to improve**, provided a variety of reasons, including:

We rely on the old safety paradigm.

It is not FDA's role to advance the frontier of science; this is for the research community. We adapt.

The most we can do as regulatory scientists is to participate in the review of developing science and figure out how to incorporate it.

We address issues as they come up and don't contribute to the development of [science];

This is not our job on a day-to-day basis--it's an academic, scientific field, big picture question.

There is an outreach issue [inefficient administrative process] with industry, trade associations, and the scientific community to get expertise and data in a timely manner.

Until we have a more liberal approach to using current technology and science, we are not going to be able to address some of these issues . . . . The groups from the other centers seem to be much more active and more willing to take a chance on new technologies than we are.

2.1.8. Question 8: How can we keep the Redbook and other guidance up to date with the pace of new science? Is there an alternative to the lengthy guidance procedure that you could suggest?

The question of how to keep the Redbook and other guidance up to date led to much discussion concerning the relative merits of Redbook and other guidances (including Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations and CVM Guidance for Industry) as well as discussion of the guidance approval process within FDA.

Regarding the **Redbook**, there were mixed feelings among reviewers concerning whether Redbook needed to be kept up to date and how much it should be updated. Most of those who felt Redbook did not need to be updated or that it should be updated only with caution were toxicologists within OFAS who believe that guidance issued by the Agency must be conservative to maintain the scientific consensus needed for a regulatory standard, and therefore, will always be "behind." These interviewees felt that the Redbook already contains the traditional studies that are needed, that the testing methods in the Redbook are sound, substantial, and validated, and that new methodologies cannot be incorporated until they have been adequately validated and their value in terms of establishing food safety has been established:

> *Until new science has been validated and accepted and we're sure the methodology can be utilized correctly within a day-to-day science review for risk assessment, there's no point in trying to force it into the Redbook. Somebody needs to make a case for the new information being equivalent to or better than what we have been using/receiving in terms of risk assessment.*
>
> *We can keep [the Redbook] up to date when new technologies/safety research has been accepted by the scientific community at large, thoroughly tested, and established that it reflects the correct endpoints.*
>
> *Manufacturers want recommendations [for methods] that they can rely on, perform, and [from which] they can count on FDA accepting the resulting data.*
>
> *Animal studies cannot be totally replaced. New methods might be included as additional tools, but we must indicate that they are corroborative and do not replace the traditional studies.*
>
> *[The Redbook] needs to be updated, but there can be a problem with updating. Attempts to simplify or eliminate the requirement for animal testing may result in allowing less toxicology data to be submitted in support of a new compound.*

Among those who felt that the Redbook should be updated, responses varied from those who felt efforts should be made to update individual chapters (immunotoxicity was specifically identified as being out of date by several interviewees) to those who felt it should be significantly expanded to include additional methodology and topics. A CFSAN interviewee noted that the failure to keep the Redbook up to date has resulted in its relevance being minimized, causing reviewers to turn to other guidance (e.g., OECD, EPA, JECFA guidelines). Interviewees cited a need for more willingness to consider new information and ideas, including new methodology and new

review approaches; to consider international harmonization; and to perhaps focus less on validation. Areas identified as needing to be updated/added included: immunotoxicity, neurotoxicity, carcinogenicity, developmental and reproductive toxicity; use/applications of translational biomarkers (gene alternatives, protein expression) and high throughput assays; and investigation of hormonal changes and other endpoints (glucose, insulin, and kidney function). One interviewee stated, "We may get data produced from testing that is not/cannot be required in the Redbook, but we need to evaluate these data as well, so Redbook should be updated to include this type of test." Another noted, "As long as people continue to use the Redbook as a check-list of tests that need to be done, it will never keep up with the pace of new science."

A few interviewees felt that the Redbook should be replaced or should essentially be replaced. A CFSAN interviewee recommended: "Update it to be current with Tox21, then update accordingly. The classic methods are no longer effective. We need to get to the mechanism of toxicity." A CVM interviewee felt that the Redbook should be replaced (as was done by CVM) to reflect harmonization with international guidelines, noting that "[they] should not be keeping it up to date. . . . The Redbook should not be reinventing the wheel. The difficulty in maintaining it emphasizes the problems."

Several interviewees also pointed out that CFSAN does consider data generated by methods that are not included in Redbook: Industry is encouraged to submit the information, and the data are typically used as supporting data. It was noted, "[We need to] find ways to encourage submission of new/novel data, but not hold results of review against the submitter (for example, having inadequately validated methodology holds up the petition or penalizes the submitter), so the data could be evaluated over time."

Where **new guidance** has been adopted (within OFAS and CVM), the process of keeping it up to date via periodic review seems to be less arduous. This was attributed by interviewees to: more flexibility in accepting different approaches and incorporating new methodology and databases; more focus on method outcomes/endpoints and performance as opposed to specific methodology; and/or more reliance on previously validated methodology via international harmonization with other organizations/countries. A CVM interviewee noted: "We have inter-agency groups like ICCVAM to discuss *in vitro* and other methods that can be used. That probably moves faster than Redbook."

Finally, there were numerous comments concerning the difficulties of getting guidance updated and approved. In addition to the time and effort required to reach scientific consensus on a new topic, interviewees noted that, even for Level 2 guidance, the approval process may take so long that by the time the guidance is issued, it is no longer relevant.

Ideas for **how to keep the Redbook and other guidance up to date** primarily included assigning **dedicated staff** and establishing **periodic updates** or a combination of the two. As in other areas, interviewees acknowledged the lack of sufficient resources to do the job efficiently. When discussing dedicated staff, several interviewees stated that updating the Redbook needed to be assigned as a primary responsibility to a person or standing committee (e.g., 75% time commitment); others added that the assigned staff needed to have some executive power to establish regular meetings, allocate manpower, and set firm deadlines. The identified staff

members would be tasked with soliciting input, reviewing the literature, evaluating new scientific methodologies and tests, and validating new study types. Recommendations concerning the ideal composition of the review staff generally included a mixture of senior and junior toxicologists ("new hires fresh out of the labs"), drawn from different offices, to give the perspective of history and familiarity with new methods. Related ideas included: having groups tasked with updating specific subject areas with the emerging science as appropriate tests/methodology are developed/validated, with an editor assigned to each section; establishing standing committees at the division or team level to develop guidance on a smaller scale and streamline the update process; and having regulatory personnel, rather than scientists, write the guidance. The recommended update cycle ranged from "continually" as needed to quarterly, biannually, and up to 6 years.

A few additional recommendations were also made. Several interviewees felt that external expertise should be sought in updating the Redbook. Thoughts included: identification of a diverse group of external experts (physiologists, endocrinologists, true toxicologists, pharmacokineticists, food scientists, nutrition scientists) guided by in-house personnel; establishment of a working committee consisting of personnel from NTP, FDA, and non-DHHS food scientists and clinicians; inclusion of experts from the international regulatory community; and working with industry stakeholders via the HESI project committees. One interviewee noted, "Even internal review by CDER and CVM would be better than no external review."

When interviewees were asked if there is **an alternative to the lengthy guidance procedure**, there were two broad categories of responses: those responding specifically in terms of alternatives to current guidance procedures, and those responding in terms of the Agency's system of approving and issuing guidance.

With respect to the Redbook, some interviewees felt that the lengthy guidance procedure was a necessary part of the regulatory process for establishing safety, as a means of: improving consistency in data submissions; maintaining continuity with changing personnel; and weeding out companies who are not really invested in the process: "The guidance procedures are in place for good reason, and are not too lengthy--some might say too brief. If we need to make changes, we do." One interviewee noted that, although the Agency would like to allow some flexibility for toxicology testing, "industry wants to know exactly what [we] want." In terms of improving the guidance procedures under the Redbook, interviewees suggested: developing flow-charts, decision trees, or brief overviews to clarify the system and direct stakeholders to the appropriate section of the guidance; adding the "Emerging Issues/Trends" chapter back into the Redbook; developing a handbook of validated tests for organ systems; and use of cookbook-type formats for protocols.

Additional suggestions for improving guidance without going through the rigorous guidance approval process included: incorporation of informal case-by-case safety evaluations into the review process (e.g., adapting exposure assessments to include infants and children); expanding consultation with industry to tailor guidance and improve submissions; and developing "Points to Consider" documents that would cover areas of interest but would not be issued as guidance. Another recommendation was to write guidances in more general terms with the focus on: the information that is needed, recommendations concerning the type of study that might be

conducted to get this information, an allowance for alternative study designs, and a recommendation that any potential alternative approaches be discussed with the Centers.

Interviewees within CHAT and OCAC felt that their guidance did not need to be as extensive as the Redbook and proposed white papers or short manuals indicating how to do evaluations and identifying relevant procedures that are broadly available.

Interviewees commented that the system for approving and issuing guidance was a major deterrent to updating and generating guidance, with Guidance for Industry (GFI) taking as long as 2-3 years to be cleared and issued. Several interviewees noted that, although guidance isn't law, it does undergo rigorous and time-consuming legal review. Some alternatives to this process that were suggested were: issuing "draft" guidance and opinion pieces; allowing publication on the FDA website, in a peer reviewed journal, or as an OECD test guideline to take the place of Level 1 guidance; and increasing involvement with international organizations (e.g., OECD) to gain access to additional methods that have already been validated and approved. One interviewee proposed an open forum approach via the Internet to allow broad participation in developing guidance. Within CVM, the publication of FOI Summaries which identify the methods used for risk assessment, allows sponsors to see what someone else did successfully: "This is a good way of showing different, current options that were used successfully. It doesn't necessarily include specific methods, but does identify what was important in the risk assessment."

2.1.9. Question 9: How can CFSAN/CVM/OF be more proactive in identifying compounds or issues of emerging safety concern (for example, contaminants, endocrine disruptors, dietary ingredients in conventional food)?

When asked how the Centers could be more proactive in identifying compounds or issues of emerging safety concern, many interviewees maintained that being proactive is not the mandate of the Agency, citing resource issues including funding, manpower, and time. One interviewee noted that the problem may not lie so much with identifying compounds or issues, but with making sure they do not get "buried in the wash of priorities." Others noted the difficulties of predicting emerging safety concerns, particularly contaminant issues, while still others voiced the frustration of having emerging issues identified for the Agency by outside groups and the media, sometimes regardless of scientific merit. Nevertheless, most interviewees provided at least one suggestion for improving the Agency's ability to identify emerging issues. Suggestions for improvements in being proactive follow.

Suggestions for improving the Agency's ability to identify compounds or issues of emerging safety concern	Responses (% of 82 interviewees)[1]
Maintaining or increasing attendance at meetings and conferences and monitoring the literature to keep current on emerging issues	~34%
Assigning dedicated staff	~20%
Improving internal communication	~16%
Increasing outreach to industry	~12%
Increasing post-market surveillance	~9%
Maintaining a watch or alert list	~9%

[1] Up to 2 responses/ideas captured per interviewee as follows: 30 interviewees had ≥ 2 responses, 43 had 1 response, and 9 and no response.

In discussing **attendance at meetings and conferences and monitoring the literature**, interviewees noted that it has become more difficult to attend meetings due to limited funding and the requirement that persons attending be invited or presenting a paper. They also indicated that access to scientific journals has been limited due to reduced funds. Meetings and conferences, as opposed to training, were seen as important ways of keeping current with developments, being active in the scientific community, and networking with scientists at universities and in industry. These interviewees tended to feel it was their obligation as individuals to be aware of evolving science and to assess its impact on their work.

Interviewees who recommended assignment of **dedicated staff** to the task, felt this would be an effective way of allocating resources to identify emerging issues. Recommended staff sizes ranged from 1-2 people to work groups or committees, and recommended focus areas included: searching the scientific literature/conducting cyclic literature review and processing information from meetings/conferences; implementing signal detection and data mining efforts; searching the Internet (blogs, consumer web pages, etc.); monitoring post-market issues and adverse events; monitoring emerging threats by watching EFSA and other agencies; and managing the Agency's response to new safety issues that are identified during day-to-day operations (e.g., new toxicity equivalent factor (TEF) for dioxins). Interviewees felt that the effort should cross offices and centers and stressed that the functions of the group(s) must include dispersing/disseminating relevant information and data within the Agency.

Interviewees who felt that **improving internal communication** would improve the Agency's ability to be proactive recommended more communication/collaboration/integration across disciplines (e.g., toxicology and chemistry), offices, and centers. Suggestions included: utilizing existing knowledge from different disciplines to take a whole food focus rather than a single compound approach; providing a mechanism for discussing and ranking issues/setting priorities; improving communication between program and research offices to capture issues identified at the research level; establishing focus groups to get started on issues (even small ones) earlier in the process/before products come in; establishing internal forums or regular meetings within and/or across disciplines to share issues of interest and concern and discuss potential approaches; and establishing a "listening post" to bring emerging issues to the attention of scientists.

In terms of improving **outreach to industry** interviewees suggested the following: improving interaction via attendance at trade meetings (e.g., food manufacturing conferences) and reviewing trade literature; considering memoranda of understanding (MOUs) and confidentiality

agreements to encourage sharing information on sensitive issues; and sending expert panels to industry (e.g., ingredients suppliers) to get exposure to new techniques and ingredients. Several groups felt that they were already making improvements in this area. Within CVM, interviewees cited several initiatives intended to improve interactions with industry, including: quarterly portfolio meetings to talk about what is in-house and what is coming up prior to submitting data; seminars and meetings with the InnoVation Exploration Team (IVET); and establishment of "tech teams" to work with industry on new technology. They felt this had enabled them to reach a consensus and understanding on technology, identify the risk questions, assemble new questions appropriate to the new technology, identify relevant data requirements, and identify appropriate program paths for new technology.

Interviewees felt that being more proactive in **post-market surveillance** could improve the Agency's efforts to be proactive in identifying emerging issues. One example of a successful proactive effort was the identification of melatonin being used in foods when it had only been approved for use as a supplement. Recommendations included: establishing active surveillance the first year or two a product is on the market; instituting a cyclic review of previously approved or notified products to incorporate emerging science and help identify the need for further testing before an issue arises; being more aggressive in testing products on the shelf to reduce the amount of adulteration; allocating specific resources for post-market work; and increasing focus on the CFSAN Adverse Event Reporting System (CAERS) as a post-market surveillance tool via e-mail updates to scientists (e.g., a monthly summary of complaints). "Because we don't require human data before a substance goes out, the human data are people being exposed post-market."

Although there appeared to have been some problems with support for this approach in the past, many interviewees supported **maintaining a watch or alert list** for post-market issues as well as anticipated new contaminants and dietary ingredients. Suggestions included: obtaining a "Top 5" list of chemicals of concern from each program and research office to identify a "Top 20" for the Agency and then prioritizing; seeking volunteers or assigning personnel to identify and/or take responsibility for a compound on the list and follow up regularly (e.g., once/month) via a literature check and/or data mining news releases, social media etc.; and obtaining support for coordination of this effort from higher up.

Additional suggestions included: providing incentives/rewards for those identifying emerging issues; developing in-house databases to track issues such as dietary supplements; improving response time on new scientific findings indicating potential risk from foods or food contact products; monitoring where other agencies or countries are spending their resources; increasing use of QSAR models to identify compounds of potential concern; establishing/expanding cumulative exposure assessments; obtaining more consumer data; establishing a website to solicit public comments; and paying attention to influencing factors (e.g., weather conditions for mycogens in grain).

2.1.10. Question 10: What internal processes are in place to ensure appropriate quality assurance and peer review on chemical safety matters? How well are we implementing these processes? What additional processes, if any, do you recommend?

When asked about **internal quality assurance and peer review processes**, ~92% of interviewees indicated that there were generally established processes in place, and ~71% felt that the processes were implemented adequately to very well. Only two interviewees felt there were no processes in place (one each in CHAT and OCAC). Among those who felt the processes needed improvement, seven were toxicologists in OFAS, four were OFAS interviewees in areas other than chemistry, two were OARSA interviewees, and one each was from CHAT and CVM. Two OARSA interviewees and one interviewee each from CHAT and OCAC felt that the procedures in place were poor. We note that in responding to this question, few interviewees made a point of distinguishing between quality assurance and peer review.

Among those conducting petition reviews, it was generally felt that the procedures in place were acceptable, with the supervisor acting as the first line of QA, and higher levels of management being involved for bigger issues. Interviewees noted that support from other offices was available when needed and that there were procedures in place for resolving issues with international entities. However, one OFAS toxicologist stated, "For regulatory scientists, there is a questionable peer review process. For big petitions, different studies are done by different scientists working independently. They are not encouraged to communicate with each other in such a way as to improve quality of the review. There is a lack of exchange even between toxicologists, which can reduce the quality of the review." Among those involved in notification programs, interviewees also felt there was an acceptable process, including SOPs and provisions for dispute resolution, with different disciplines involved, and different levels of review through convening boards of experts if needed. These interviewees also mentioned that their source data, typically from the scientific literature, reflected an additional level of peer review. Similar processes were described by CVM personnel. One CVM interviewee noted that while there is a traditional review process through a review team, team leader, and division director, "Past that, it is difficult to balance a transparent peer review process against a timely and proprietary review."

Within OARSA, there appeared to be discrepancies in perception as to whether there were processes in place and how effective they were. Some interviewees identified a QA program with inspections of labs, notebooks, and records, while others seemed unsure of the procedures, and still others felt that the labs were "sloppy" in adhering to QA procedures. Interviewees in CHAT and OCAC cited the following deficiencies: no SOPs for review and compilation of contaminants data; no cross-check of data that are compiled; no second level of review or only one level of review of safety assessments prepared by a single reviewer; and/or no oversight on decisions. One CHAT interviewee stated, "Some of the major risk assessments have been subject to peer review. Other than that, it is not clear that there is a formal mechanism for peer review." Another CHAT interviewee stated, "It is a small group and growing smaller. The number of employees is not adequate to cover the issues coming to us . . . . The reviewers feel they are short of guidance because the supervisors [detailees] don't have specific knowledge or the expertise to confirm that their work is adequate."

In terms of **how well the processes are implemented**, most interviewees felt this was done well; however, there were a few areas where they felt improvements were needed, including: dispute resolution between reviewers or offices; coordination of efforts between offices ("Sometimes documents from other offices are finalized before we see a draft in OFAS, and this can be too late for review"); coordination on issues between different disciplines ("Often other reviewers are not aware of the issues because we work in silos"); and maintaining a consistent historical approach for regulatory decision-making ("[We have] done well in having quality assurance and having SOPs, but on our decision-making, we don't have a consistent approach").

Most of the recommendations for **additional quality assurance and peer review processes** fell under the general areas of: improving peer review (~16%), improving access to outside or subject area experts (~12%), establishing more formal processes or SOPs (~10%), and improving internal communication (~10%). The suggestions are summarized below.

<table>
<tr><th colspan="2">Suggestions for additional quality assurance and peer review processes</th></tr>
<tr><th>Peer review</th><th>Access to outside or subject area experts</th></tr>
<tr><td>Establish a Center-wide committee/panel to review overall decisions when there is a new entity or substantial questions.
Select a secondary review team from a different office or division than the one that did primary review.
Exchange reviews between team leaders/managers or have leaders from both teams review each product before it is released.
Select personnel for peer review who are qualified in the relevant scientific area they are reviewing.
If supervisors are to provide critical review, ensure that they have the required scientific expertise.
Allow the primary reviewer to select someone to read over the review and ask questions..
Achieve consensus between disciplines before going to the next level of review.</td><td>Establish a system within the office to make it easier to identify/contact the correct person.
Assign an experienced "head scientist" to serve as the focal point for questions.
Allow a qualified subject matter expert to substitute for the tiered review process for special cases.
Provide a list of experts in various fields who are available to answer questions quickly.
Make more use of external food advisory panels to vet FDA decisions.
Within groups, allow more dedication to specialized topics.
Make wider use of the Carcinogenicity Assessment Committee (CAC) where appropriate, or establish a CAC-type function for other areas.</td></tr>
<tr><th>Formal processes/SOPs</th><th>Internal Communication</th></tr>
<tr><td>Incorporate QA into general processes--not just by study but as a big-picture approach.
Re-invigorate the CFSAN Bioresearch Monitoring Program or run the program jointly with CVM.
Establish SOPs within those offices that are lacking.
Establish SOPs to improve consistencies across offices.
Establish a science-oriented committee to deal with inter-office disputes.</td><td>Do not wait for a formal update meeting to raise and discuss issues.
Encourage weekly meetings within disciplines and across offices to discuss broader issues and improve consistency.
Consult across centers and offices for common compounds; consult across the Agency for larger issues (e.g., endocrine disruptors).
Include research scientists in the review process.
Establish contacts within other centers and/or have other centers review risk assessments more routinely.</td></tr>
<tr><th colspan="2">Other</th></tr>
<tr><td>Establish interdisciplinary teams or committees for assessments for other toxicities that impinge on the public health.
Place more scientists in top positions.</td><td>Publish all post-market reviews for public review.
Post chemical safety reviews on the website for review and comment.</td></tr>
</table>

Suggestions for additional quality assurance and peer review processes	
• Establish regular meetings with industry for feedback. • Institute regular 5-year review of chemicals and publish the results in a docket to encourage external peer review. • Establish a mechanism for handling products that are evaluated/approved internationally.	• Avoid sacrificing science integrity to the template format. • Conduct QA of any letters or reviews that are issued to check details (dates, names, pg. nos.). • Bring in technical editors to prepare documents to be posted on the web.

2.2. Communication and Collaboration

2.2.1. Question 1: How effective is the coordination and collaboration across offices and centers on cross-cutting issues? If not, what are the impediments? What can be done to improve coordination and collaboration?

When asked about the **effectiveness of coordination and collaboration across offices and centers**, interviewees were nearly evenly divided between those who felt the situation was improving to very good (~48%) and those who felt it was poor or needed to improve (~46%). Interviewees on both sides of the issue commented that success tended to depend on the personnel involved and often was the result of individual initiative, with few formal processes and/or too much red tape involved.

Interviewees within CFSAN who felt that coordination and collaboration across offices was **effective**, identified good relationships between the chemists within OFAS and researchers in OARSA and between the dietary supplement and food additive groups. The FVMP Strategic Plan, the efforts of the Office of Communications, and a successful detail in which an OARSA scientist served as an OFAS office director were cited as specific examples of improvements at the inter-office level. These interviewees indicated that it was easy to get information from other offices. Those who felt coordination and collaboration was effective across centers noted that there have been improvements in communication between CFSAN and CVM to solve regulatory issues and that there are clearly identified points of contact within other centers for when cross-cutting issues arise. The establishment of the OFVM was felt to have improved coordination between the Centers. Personnel within OARSA cited a new division director, a monthly seminar system for CFSAN and CVM, and improving coordination with NCTR as advances. Interviewees within CVM who felt that coordination/collaboration across offices was effective, noted the collegial atmosphere within the Center and stated that interaction was more successful when personnel were involved early. Regarding coordination/collaboration between centers, interviewees cited good interactions with NCTR and CFSAN. One CFSAN interviewee reported a successful interaction with CVM on a biotechnology review in which "there was an impasse because the technical requirements for the experts at CVM were very different from the CFSAN side of things" Over the course of several meetings, the group adopted the "Six Thinking Hats" approach and was able to resolve their issues despite having two different approaches and two different audiences. A CVM interviewee stated, "It is really good when one side reaches out and asks for help (CFSAN, NCTR, CDER, and CBER). Lacking outreach it is poor . . . . There is great desire for bettering cross-communication, but a dearth of good answers." Interviewees from both CFSAN and CVM identified sharing pathology expertise between centers as a good example of coordination.

Interviewees who felt that coordination/collaboration across offices was **poor or needed improvement** noted that there were few opportunities/occurrences at the staff level and that it was difficult to achieve due to: little outreach across offices; differences in office structures, opinions, and policy decisions; problems with identifying partners; and difficulties in navigating the office hierarchy. One CVM interviewee commented, "Offices seem to have a wall between them . . . . There tends to be butting of heads and lack of communication that make it hard to move on to the science." When addressing poor coordination/collaboration across centers, interviewees reported the following issues: a general lack of information concerning what is going on in other centers; difficulties in identifying the lead in inter-center actions or in resolving territorial disputes; difficulties in accessing each other's data (especially with respect to CDER); and little "forward-looking" between centers to identify potential areas of concern. One interviewee noted, "Sometimes companies get a rejection from CFSAN, then turn around and submit to CVM. If [the Centers] communicate, they can catch the double dip."

In terms of **impediments** to coordination/collaboration, poor communication was cited most often (~34% of responses), followed by time constraints (~23%), lack of support or mandate (~21%), physical separation (~12%), and nature of the work (~12%). Improving communication in general and increasing inter-group meetings and talks were also the top suggestion for **improvements** to the process (~49% of responses), followed by more support from the top (~17%), and exchange of staff (~7%); however, interviewees acknowledged that limited resources, primarily in terms of staff availability and time, were among the most serious and least fixable impediments. Relevant comments and suggestions are summarized below.

Coordination and Collaboration: Impediments and Improvements	
Impediments	**Improvements**
Poor communication across offices and centers: • Communication outside the division is not encouraged; need supervisor's approval • Lack of knowledge on focus, common issues, and expertise of other groups • Insufficient communication between the laboratory and regulatory review teams • Lack of understanding of other centers' policy issues • Organizational structure is all linear (stovepipe model). **Time constraints:** • Collaboration is discouraged by the focus on "moving the freight", dealing with crises • Need to have coverage if you go on details • Difficult to coordinate individual time frames/priorities between groups • Helping another office/center meet their deadline may not be a priority. • Timing is difficult to coordinate: make sure everyone is invited, make the offer, alert them to the purpose of the meeting. **Lack of support or mandate:** • No formal processes in place • Not enough encouragement from office leadership • Problems with dispute resolution between offices/centers **Physical separation:** • FDA is a large agency; staff are physically separated. • There is separation even between the laboratories that are next door to each other. • Different buildings and the lay-outs within buildings do not facilitate collaboration. **Nature of the work:** • Difficult to get data/information that other centers have (e.g., CDER) due to proprietary nature • Interest/concern on a given issue rarely coincides temporally between offices and centers. • It can be difficult to identify cross-cutting issues due to differences in product categories. **Other:** • Lack of follow-through on collaboration projects • Deliberate blocking due to territoriality, misunderstanding	**Communication:** • Develop technology/database (similar to the CFSAN Automated Research Tracking System; CARTS) to track what is being worked on, where, and by whom across offices and centers. • Assign "communications officers" to certain issues to coordinate meetings, summarize issues. • Increase opportunities for informal interactions. • Establish focus groups/small group meetings for staff within scientific disciplines who have shared interests and objectives (e.g., epidemiology, toxicology, compliance interest groups). • Establish more opportunities for interaction within/across centers (events, workshops, talks, poster sessions, science days, retreats). • Establish regular meetings (monthly, quarterly, biannual) to bring people together to discuss current issues. • Establish all-hands meetings for offices and across the Centers. **Support from the top:** • Begin with clear commitment and active involvement at the highest level of management. • Make coordination/collaboration a priority at all levels of management. • Establish a cross-cutting management system to encourage harmonization across offices/centers. • "Put in writing" what is allowed/encouraged in terms of collaboration. • Establish a system for addressing supervisor approval concerns. **Exchange of staff:** • Increase interchange of staff across offices and centers via the formal detail process, including exchange of personnel between related offices (e.g., ONLDS and OFAS), and between laboratory and regulatory groups. • Expand cross-training in different offices and centers. **Other:** • Establish an index of expertise throughout the Centers to facilitate sharing skills. • Address data sharing/confidentiality issues between centers. • Provide limited but regular direct collaboration opportunities (e.g., between toxicologists and NCTR) for special projects. • Ease restrictions on publications by establishing an independent "courtesy review team" that is not office or division based. • Create incentives for collaboration.

2.2.2. Question 2: Are there sufficient opportunities for collaboration internally and externally and if not what are the gaps? What collaborations would improve/benefit the programs?

The majority of interviewees felt there were sufficient opportunities for collaboration internally (~54%) and externally (~42%), ~22% felt there were insufficient internal opportunities and ~32% felt there were insufficient external opportunities, while ~18% and ~15%, respectively, felt internal and external opportunities varied, depending on factors including whether partners could be identified, management approval, time available, how well the different factions worked together, and whether the outcome of previous collaborations had been positive. Interviewees felt there were good opportunities for internal collaboration between: members of review teams, OFAS chemists and OARSA, OFAS and ONLDS, CFSAN and CVM, CVM and OR, and OR and NCTR; for big issues/projects; and on internal details at other centers/offices. Only a few external collaborations were cited under this question (for CFSAN with EPA on antimicrobials and USDA on meats, and for CVM with AFCO); however, this topic was addressed in more detail under Interactions with Other Programs/Agencies/Public. There were mixed responses concerning whether the impact of the following factors on collaboration was significant or not: identification of and access to internal and external expertise; lack of formal procedures for collaboration; supervisors' approval/encouragement; and favoritism toward certain projects or personnel. Interviewees tended to feel that collaborations were neither discouraged nor specifically supported, and that, aside from formal details and shadowing, they were not easy to participate in. External opportunities were felt to be more difficult to achieve due to: restrictions in FDA's relationship with industry; travel and time restrictions; the rules and regulations governing the clearance/approval process; and the perception that such collaborations might be outside the scope of the Centers' mission and resources.

One interviewee addressed the need for incentives to encourage collaboration, both for supervisors and reviewers (via writing collaborations into IDPs and PMAPs), with resulting bonuses for successful collaborations: "The obstacle here is that supervisors will lose effort towards regulatory review assignments, so they need to be given incentives (people, performance bonuses) too. There needs to be buy-in throughout the supervisory chain that diverting resources now committed to regulatory review into these collaborations is supported."

Some of the **gaps** identified for internal and external collaboration were similar to those listed above for internal coordination and collaboration, including lack of communication (~16% of responses) and resource issues (coverage/time constraints and funding, ~18%); however the hierarchical nature of the Agency was mentioned as the primary gap (~28%), and difficulties identifying partners (~11%) received more attention when addressing internal/external collaboration. In terms of hierarchy, interviewees commented:

The management structure tends to be vertical and hierarchical both for offices in CFSAN and between centers. This is inevitable due to human nature in the absence of any proactive upper management attempt to foster a cooperative, interdisciplinary climate.

The hierarchical nature of the organization means you have to go to your supervisor to ask for the time, through the division head, and then maybe you can talk to someone.

We do have multiple groups working on chemical safety of particular chemicals; however, each group is an entity unto itself and only the people working in that group and the managers know what is being discussed. There is no information sharing. The managers are aware of the information from all the groups, but that stays with the managers. The policy is a need-to-know basis.

Collaboration generally occurs only through personal networking. Although there is "lip service" about regulatory staff working with laboratory scientists, there is no management interest in, much less requirement for, attendance of the respective staff at each other's meetings.

I often feel that that I have to justify my collaboration with other centers. When I joined the Agency I thought collaboration was my number one measuring stick. Now I think it is the opposite. If you want to collaborate with another center, you have to make sure you take care of everybody in your own office first. You also have to defend it or justify it now.

The Agency does not want to say anything or work with anybody from the outside that may interfere with our making enforcement decisions or regulatory actions. We don't have a grant/funding mechanism that is very robust for getting research done with the outside.

In discussing the difficulty in identifying partners for collaboration, interviewees commented on the apparent difficulty in maintaining a directory of scientific expertise to identify the knowledge, skills, and abilities of staff in other centers and offices. Difficulties included keeping such a list current, and vetting self-identified experts. The "Traction" system within CVM was cited as a possible means of establishing such a listing.

When asked what **collaborations would improve/benefit the programs**, responses tended to be general rather than specific. In terms of internal collaborations, recommendations included: increasing detail opportunities; working with the labs (OARSA, OR, and NCTR) to gain additional information on new chemicals; increasing collaboration between chemists and toxicologists within OFAS, between OFAS and ONLDS, and with NCTR; increasing involvement of management in identifying opportunities for collaboration; increasing topic-based collaboration; and reducing bureaucracy in arranging collaborations. One specific suggestion for increasing internal collaboration, which would also highlight ongoing research in the Centers, was to offer the opportunity to write mini-grants to pursue work with others. In terms of external collaborations, recommendations included both general and specific suggestions. General suggestions included: expanding opportunities for personnel to give talks/presentations in their specific areas of expertise (with additional review or vetting to screen for sensitive issues), rather than restricting them to general topics; providing notice when Agency personnel have papers accepted for publication; and increasing contracting by improving the

contracting process to be more efficient and transparent. More specific suggestions included increasing collaboration with: academia (e.g., UMD and JIFSAN, and other local universities); other regulatory science agencies (e.g., EPA, EPA ORD, and EFSA); and organizations including ILSI. Several interviewees suggested applying an inter-agency approach similar to that used for the IRAC to other areas (e.g., toxicology or chemical safety review). One interviewee stated, "We don't always exercise our options [for collaboration with other international agencies]. If we have agreements with them, we should consult with them on decisions." Another noted that the Agency could investigate adopting EFSA's practice of consulting with academic experts on regulatory decisions.

2.2.3. Question 3: What toxicology research could NCTR do for CFSAN or CVM that it is not doing for either CFSAN or CVM?

When asked about NCTR, over ~65% of interviewees were unfamiliar with NCTR's role or had no suggestions for additional research. Those who were familiar with NCTR felt that the Center performed its research functions well, including conducting larger and long-term toxicology studies, and that there have been recent improvements in communication and collaboration between CFSAN/CVM and NCTR. Several interviewees noted that NCTR has been proactive in asking the Centers what additional work can be done (e.g., research in cosmetics, dietary supplements, botanicals). One interviewee commented, "NCTR operates at a different level. They have their finger on the pulse of science: cancer induction, generational toxicology, genetic mutation micro-arrays . . . . It would be beneficial to join a core group at NCTR on a specific topic and collaborate with them on that kind of research." Another stated, "NCTR is still under-utilized. They are our best collaborator." A few concerns were voiced concerning the potential for over-lap of efforts between NCTR and OARSA/OR or stakeholders. Within OARSA, some interviewees commented that the need for large-scale studies at NCTR should be assessed after small-scale pilot or exploratory work had been done within OARSA, and a few interviewees noted that communication/coordination between the laboratories could be improved. Suggestions for additional toxicology research for NCTR are summarized below.

Suggestions for additional toxicology research that NCTR could do	
Research on Compounds/Chemicals/Components	**Methods development/validation**
• Resolution of pre- and post-market safety issues • Evaluation of perfluorinated compounds and perfluorohexanoic acid (C6) • Endocrine disruption testing • Investigation of already regulated substances (e.g., JECFA recommendations for future work) • Toxicology research on allergenicity • Nanotechnology research • Evaluation of mixture exposure of multiple components • Mycotoxins class research • Dose response investigations • Development of human serum data bank	• Evaluation and validation of new toxicity testing methods in support of Tox21 for applicability to chemical safety review • *In vitro* testing, genomics, proteomics • Development of immune detection methods • Refinement of current animal testing systems to better reflect human toxicity • Method validation for new and alternative methods (e.g., as center of ring trials) • Methods/techniques training

2.3. Interactions with Other Programs, Agencies, and the Public

2.3.1. Question 1: Are those conducting chemical safety risk assessments and safety reviews obtaining the type and quality of toxicity and exposure data they need from laboratories in CFSAN, CVM, ORA, and NCTR? Do FDA scientists have access to information from databases at NTP, NHANES and other agencies/sources? What additional databases would be beneficial? What do you see as barriers to us getting this information?

The majority of interviewees (~67%) felt that those conducting chemical safety risk assessments and reviews generally were obtaining the data they need from FDA laboratories, especially in terms of traditional toxicology studies, exposure data, and post-market data (e.g., Health Hazards Assessments). This was felt to be true despite comments that regulatory personnel might not always get all of the data they wanted and that there are sometimes delays in getting the research approved and started. Laboratory efforts on BPA, melamine, acrylamides, and furans were cited as specific examples. Many of the remaining interviewees were involved in programs for which data were generated or provided by the stakeholders, and thus indicated that they did not need to obtain data from the laboratories.

The FVMP Strategic Plan was mentioned both as an asset in keeping research mission-oriented and as an impediment in limiting the type of research that can be done. The following concerns were expressed: that new scientists emerging from academia are not being trained in the methodology accepted by FDA (e.g., *in vivo*, animal models); that not all of the research conducted by OARSA is mission-relevant; that regulatory staff does not have sufficient input concerning which research will be funded; that regulatory staff is not always aware of priorities or the chain of command for making requests; and that there is not always sufficient time to wait for data from the laboratories to help with assessments. In addition, two interviewees commented that exposure assessments might not be as robust as they could be due to agency bias against acquiring more data and/or lack of market-based data.

Interviewees within OARSA felt that interaction with the regulatory staff was improving due to improved interaction between offices, but indicated that they could do more for the program offices, including: contributing to smaller, faster, still informative studies; expanding projects based on program office needs (e.g., cosmetics, nanotechnology); bringing in additional expertise (e.g., via ORISE fellows) to address special research projects with targeted outcomes outside traditional areas of expertise; and participating in selecting compounds for NCTR to investigate and for inclusion in NTP's Report on Carcinogens.

Nearly 88% of interviewees indicated that they had **sufficient access to information from databases at NTP and NHANES** and to FDA library resources. In addition to NHANES, the following additional databases were mentioned: EPA's IRIS database and related toxicological reviews; ToxBase; ToxNet; NAS documents; PubMed; Agricola; International Agency for Research on Cancer (IARC) databases; OECD's Screening Information Data Set (SIDS); and Mintel, Gladson, and Nielsen (market databases). Interviewees noted that access to databases in other agencies (e.g., EPA) is more difficult to obtain and indicated that it is difficult to get access

to raw data from many sources (including toxicology data from CDER). Interviewees stressed the importance of having continued access to databases.

Suggestions for **additional databases** included both specific databases and suggestions for different types of databases that would be helpful. There appeared to be knowledge gaps concerning which databases were and were not currently available within FDA. One interviewee stated, "It would be helpful to organize the [databases] we have so that we know what is available." Many interviewees commented that not all databases are useful and/or reliable, depending on the source of information and whether they are kept up-to-date. Others commented that databases are not as useful as primary data and noted data-sharing issues with CDER, NTP, and EPA due to CBI issues.

<table>
<tr><th colspan="2">Suggestions for additional databases</th></tr>
<tr><td colspan="2">Specific databases</td></tr>
<tr><td colspan="2">• QSAR (Quantitative Structure-Activity Relationship) databases
• TOXNET, PUBMED (full access vs. restriction to abstracts)
• RITA (Registry of Industrial Toxicology Animal) database</td></tr>
<tr><td colspan="2">Types of databases</td></tr>
<tr><td>FDA Available:
• Full access to CFSAN (by CVM) or CVM (by CFSAN), CDER, and CDRH databases
• Access to CFSAN/CVM intranets
• Access to search function for in-house reviews
Internal FDA Databases to be Developed:
• Database of product labels (to be developed and maintained by FDA, filled by industry)
• Database of chemicals reviewed in other centers
• Database of analytical methods</td><td>Other Agencies:
• USDA market basket/food consumption data
• EPA exposure data
• IARC data
• ATSDR data
• Databases related to ToxCast and Tox21
Industry:
• Industry use database
• Nielsen market sales data
• Market share data on uses on food and packaging
• Market reports for processed foods</td></tr>
<tr><td colspan="2">General Suggestions:
• Longer-term food consumption data
• Label information databases
• Data on sub- or sensitive populations and high risk groups
• Mixture toxicology data
• Longitudinal extant data
• In silico predictive toxicology databases
• Protein and DNA databases
• International food, labeling, and drug databases, and basis-for-approval databases</td></tr>
</table>

The major identified **barriers to getting needed information** were: lack of knowledge of what is available, funding issues, confidentiality issues (with other centers, agencies, and with industry); access to primary vs. summary data; data sharing issues (e.g., reluctance to share and lack of mandates or procedures to obtain data); confirming data quality (e.g., source, validation); and obtaining data in a useful timeframe. In addition, several interviewees commented that there may be problems manipulating and/or using the data that are obtained, in terms of adequate training, tools, or computer programs. NHANES was identified as a specific example of a database for which there is good access but possibly inadequate training in its use.

2.3.2. Question 2: Is there a reason for different safety assessment approaches/methodology between regulatory agencies? Could it be possible to harmonize safety assessment methodology with other agencies to avoid confusion? If so, what ideas do you have to reach this goal?

Over ~90% of interviewees felt there were good **reasons for different safety assessment approaches/methodology between regulatory agencies**; only ~4% felt there were not good reasons for differences. Among the reasons identified for the differences were: different regulatory mandates, different timelines, different types of products regulated (foods and food additives vs. drugs and pesticides), different routes of exposure (ingestion vs. contact or inhalation), whether exposure is intentional or incidental (food additive vs. contaminant), different types of data or studies submitted (clinical vs. non-clinical, dosing by gavage vs. ingestion), different assumptions, and different paradigms (safety vs. risk/benefit vs. environmental risk). The Delaney Clause was cited as a specific differentiating factor which affects FDA but not EPA.

When asked whether it would be **possible to harmonize safety assessment methodology with other agencies**, ~72% of interviewees felt it would be partly to mostly possible, ~7% felt it would definitely be possible, and ~13% felt it would not be possible. Interviewees tended to believe that harmonization of methodology *per se* is possible, and that some harmonization has already been achieved: e.g., CFSAN guidelines for reproduction and teratology testing are harmonized with EPA and OECD guidelines; EPA and FDA use similar approaches to calculating exposure; and data gathering for food additives between the U.S. and EU is being harmonized. Interviewees agreed that, in broad terms, safety and risk assessment methodologies are the same, and that, in some cases, outcomes are the same or similar (e.g., toxic endpoints, ADIs). Interviewees generally felt that harmonization of new methods and technology (e.g., nanotechnology and Tox21) would be easier to achieve because these "do not fall under outdated guidances"; however, one interviewee noted that the relatively small size of FDA's foods program relative to the other participants (e.g., EPA's Office of Pesticide Programs) may be problematic for FDA's participation in this effort. There was also felt to be good potential for harmonization of the data analysis efforts between agencies (e.g., sharing market sales and label data with USDA and CDC).

Even given the adoption of similar methodologies to collect similar data sets, interviewees felt that different statutory directives, different goals and objectives (including the differences listed above), and differences in how the data are interpreted and the results are applied to the product that is being assessed, reviewed, or approved, precluded complete harmonization within FDA and between FDA and other Agencies. There appeared to be opposing views as to what could and should be harmonized. Several interviewees noted that the science can be harmonized, but the regulatory mission/practice needs to be specific to the program: "There are different programs for a reason." However, another interviewee stated, "Part of the confusion is that people keep trying to harmonize things that shouldn't be harmonized. We need to separate the science from the policy. Harmonizing policy may be necessary, but you need to make sure it's a policy question."

There were differing opinions between CFSAN and CVM regarding the potential for international harmonization. Within CVM, where harmonization has begun with the adoption of the VICH guidelines, harmonizing internationally with agencies regulating the same type of compounds was felt to be more possible (e.g., harmonization for animal drug approval between CVM and the EU and Japan) than harmonization with OFAS. Harmonization is also being attempted by CDER, CBER, and CDRH via the International Conference on Harmonization (ICH) to create one uniform standard of toxicity testing. However, CFSAN interviewees noted that attempts at harmonization with the EU, Health Canada and other countries has improved understanding and communication, but has been unsuccessful due to use of different consumption levels, use of different safety data, and different standards.

A number of interviewees felt that harmonization was not necessary and that the emphasis on harmonizing was the result primarily of consumer pressure and a lack of understanding, rather than a scientific need: "We would not regulate our food chemicals the way pesticides are regulated." These interviewees offered alternatives including educating the public and making the processes more transparent to clarify why different agencies do things differently.

There were few **specific ideas to reach the goal of harmonization.** Most interviewees responded that more communication, collaboration, coordination, and interaction, with a willingness to compromise, was needed via: informal or formal discussions; meetings between affected groups or agencies (with the "people in the room who can make the decisions"); sharing information ("we need to find ways that all of this information is readily shareable in real time"); cross-training or exchange of staff, joint working groups/committees (JECFA model); and attendance at scientific meetings (and sending the "right people" to the meetings). Interviewees felt these efforts would help to establish relationships, address different perspectives and terminologies (a workshop with EPA on different subpopulations was cited), identify areas of common ground (e.g., work with EPA on antimicrobials), and assess differences in methods or protocols and determine whether the differences are necessary or appropriate and whether the methods can be applied to different endpoints. IRAC was cited as a good model for harmonization efforts, and the collaboration between CVM and CFSAN in setting up CVM's GRAS Notification program was cited as a successful outcome.

Many interviewees also felt that harmonization could only be achieved through efforts made at a higher level of government (i.e., upper management, Congress, the White House) and not at the staff level:

> *You need someone with clout heading the effort.*
>
> *First we need to convince management and the lawyers that they agree to . . . change the Agency's perspective on [a harmonization issue].*
>
> *There have been efforts at the level of the risk assessors to try to communicate between the agencies, but that has been limited because of the different regulatory authorities, different cultures in the agencies, and the short-term focus of the political people who are appointed to run the agencies.*

One specific suggestion for harmonization of risk assessments between EPA and FDA was to set up a situation in which FDA scientists or regulators could participate in an EPA review of a chemical of common interest, so that FDA could rely on the review and have confidence that the review addressed FDA objectives: "EPA has the resources to do these very extensive risk assessments, [while] FDA does not have these resources (personnel or time)."

Here again, some interviewees maintained that harmonization *per se* should not be the main focus of the Agency's efforts:

> *It is more important to explain the differences and why they are necessary than it is to harmonize methods.*
>
> *We need to explain the government risk assessment process to consumers to get their feedback on what they're willing to pay for [harmonization].*
>
> *We need to do a better job of letting the public know that science doesn't get you to one number agreed upon by everybody.*

2.3.3. Question 3: At what levels and in what manner does the program interact on significant chemical safety and risk assessment issues with NIEHS, CDC, EPA, USDA, other federal agencies, and international bodies? What has worked well in this regard? What improvements are needed, and how can we best achieve these improvements?

There was a broad range of responses concerning the levels and manner of **interaction between CFSAN/CVM and Federal agencies and international bodies**. Interactions were variously described as: close relationships; effective but affected by priorities; occurring when necessary and when regulations and law demand; occurring at all levels for significant issues; more effective when initiated at higher levels; limited to designated people selected by management; effective when occurring as informal interactions between reviewers; limited by the confines of each Agency's rules and regulations; limited in general, but with established points of contact for cross-cutting issues; more likely to occur after FDA decisions have been made; occurring as regular meetings with team leaders and management; occurring as telephone conversations on specific issues; not occurring as frequently as they should; and virtually nonexistent at the staff level. The Delaney Clause was cited by several interviewees as negatively affecting interaction with other agencies and organizations. Specific interactions that were mentioned by interviewees are summarized below.

Specific interactions between CFSAN/CVM and Federal Agencies and international bodies identified by FDA interviewees	
Federal Agencies	
NIEHS • Through NTP: recommending compounds for Report on Carcinogens; scientific review meetings with intramural programs • Consulting on carcinogenicity studies • Participation in Tox21 working committee • Sharing databases and products • Individual staff contacts **CDC** • Trans fats and sodium reduction initiatives • Participation in NARMS (National Antimicrobial Resistance Monitoring System) Program • Rulemaking on bovine spongiform encephalopathy • Conducting document review **EPA** • Post-transfer consulting on antimicrobials • Developing crop regulations • Biotechnology: exchange of information and technology • Liaisons for questions on cross-cutting issues • Conducting/sharing food safety document review • Participation in Tox21 working committee • Work under NEPA for veterinary drugs and food additives • Individual staff contacts • Working group on drug and pesticide residues in agricultural products	**USDA** • Developing crop regulations • Conducting safety and suitability assessments for food ingredients in meat, poultry, and egg products • Assessment of processing plant materials • Tissue residue monitoring • Assessment of vaccines • Review of World Trade Organization (WTO) Sanitary and Phytosanitary (SPS) Notifications • NAHMS (National Animal Health Monitoring System) program • Assessment of animal biologics • Rulemaking on bovine spongiform encephalopathy • Working with the Foreign Agricultural Service • Working group on drug and pesticide residues in agricultural products • ICCVAM (Interagency Coordinating Committee on the Validation of Alternative Methods) **NIST** • Working group on nanotechnology
International bodies	

EFSA
• Liaison in-house
• Sharing reviews and exposure data (MOU)
• Harmonizing guidelines
OECD
• Participation in Task Force for the Safety of Novel Foods and Feed
• Methods/techniques training
World Organization for Animal Health (OIE)
• Rulemaking on bovine spongiform encephalopathy
	WHO (World Health Organization) and FAO (Food and Agriculture Organization of the UN)
	• JECFA and Codex Alimentarius
	  • Participation in committee activities
	  • Participation of scientists in individual, independent, safety review assessments
	  • Consultation on food additives contaminant
	  • Harmonizing guidelines
	• Providing expertise for food additives, contaminants or impurities
	• Participation of scientists in individual, independent, safety review assessments
	• Conducting document reviews
	• Review of World Trade Organization (WTO) Sanitary and Phytosanitary (SPS) Notifications

When asked **what has worked well in terms of interactions**, addressing **special issues** (primarily with other Federal agencies) accounted for ~67% of responses, **harmonizing standards and policy** accounted for ~13% of responses, and **methods development and validation** under ICCVAM accounted for ~6% of responses. Approximately 11% of interviewees commented that these interactions worked best when initiated at higher levels.

In terms of **special issues**, good interactions between Federal agencies were noted with: EPA on BPA and 4-methylimidazole in caramel color; EPA on Tox21; USDA and FDA on risk assessment for cyanuric acid and melamine; CDC and USDA on food-borne illness attribution and bovine spongiform encephalopathy (BSE); CDC on addressing food allergy issues in schools under FSMA (Food Safety Modernization Act). Interactions with international bodies on safety reviews (e.g., with EFSA on feed additives) were also felt to work well, with several interviewees noting a higher level of data sharing between FDA and international bodies than between FDA and Federal agencies. Interactions on special issues were believed to be important in saving resources, leveraging reviews that might have been done elsewhere, and obtaining additional reliable information and sharing institutional knowledge on current topics and issues.

In terms of **harmonizing standards and policy**, interactions at the international level, including those with WHO (JECFA, Codex), EFSA, and VICH to set international standards were felt to be the most successful due to better data and information sharing and more common ground on types of products to be regulated, while interactions with EPA and USDA were described as "more situational." In terms of harmonization with Federal agencies, interviewees specifically noted efforts between CVM and USDA to develop common approaches to regulating contaminants and between CVM and EPA to establish an import tolerance program and a microbial risk assessment framework.

When asked **what improvements are needed**, the most common responses were **improved communication** (~30%), **more support from the top** (~11%), **improved data sharing** (~10%), **better identification of relevant staff** (~6%), and **resolving differences in decisions** (~4%).

For improving **communication**, in addition to general recommendations to maintain or increase opportunities for communication (via committees, meetings, teleconferencing, e-mail), interviewees commented specifically that they were unaware of what EPA and USDA might be working on, that there was insufficient communication with NTP regarding identification of carcinogens, that communication with EFSA tended to be "fragmented" and not timely, and that relevant rulings and decisions were often not communicated down to the reviewers. Staff exchange between agencies was also seen as a way to increase communication. Better s**upport from the top** was felt to be needed primarily for allocating time and resources to these efforts and for identifying a broader range of personnel for these opportunities. One interviewee noted "Some feel the international connection is not in line with the mission, but it is because we need to represent the U.S. in international trade." Another commented, "[Our senior management] needs to take a long-term, integrated point of view as opposed to a short-term immediate problem-solving view-point [when it comes to these interactions]. Better **data-sharing** was seen to be a particular issue with EPA, but was also mentioned for other agencies. Interviewees mentioned the need for more data-sharing agreements for CBI. One CVM interviewee mentioned that the Center is setting up confidentiality agreements with Canada (Veterinary Medical Association; VMA, Canadian Food Inspection Agency; CFIA, and others) to enable data sharing. In terms of identification of relevant staff, interviewees mentioned the need for clearer guidelines on when and how to contact other organizations for a given issue, and the need to maintain a current list of contacts within other organizations.

Several interviewees mentioned the need for a mechanism for **resolving differences in decisions** between agencies or organizations. Regarding cases in which there are differences in safety decision on products (e.g., between JECFA or EFSA vs. FDA), one interviewee commented that depending on whether JECFA/EFSA's position was more relaxed or stricter than FDA's decision, the reviewer might be urged to accommodate their decision or stick with FDA's decision, respectively. Another noted, "We cannot let one country dictate what we do and we cannot dictate to another country what needs to be done; we have to abide by our own rules."

There were few specific suggestions for how to **achieve the needed improvements**. Suggestions included hiring more people, increasing FDA participation in meetings at other agencies, increasing efforts of the Senior Science Advisor staff and relevant offices to develop ways to create and communicate priorities and to establish a method for allocating time and travel resources to these efforts; and overcoming historical barriers. A CVM interviewee mentioned the International Programs Team (IPT) as a good example of the efforts this Center has made to "be at the table" with other groups on veterinary drugs.

2.3.4. Question 4: What is the current state of scientific transparency and engagement internally and between FDA's chemical safety scientists and programs and the external scientific community? How satisfied do you feel with the current state? What, if anything, needs to be done to improve transparency and engagement?

[Note: Although it appears this question was targeted to investigate external transparency with the scientific community, because of the way it was written (internal vs. external transparency) the majority of interviewees also answered the question in terms of transparency with consumers and the public. Therefore, we have included this information in the report.]

Regarding the state of scientific transparency internally between FDA's chemical safety scientists and programs, most interviewees (~52%) felt transparency was improving to very good, while ~16% felt internal transparency needed to improve, and only ~7% felt it was poor (~24% of interviewees did not offer an opinion on internal transparency). Regarding scientific transparency externally between FDA's chemical safety scientists and programs and the external scientific community [and the public], the distribution of responses was: ~48% for improving to very good, ~33% for needed to improve, and ~9% for poor (~10% offered no opinion). The relative distribution of responses was similar across offices and centers, although there was a difference between the issues identified by OARSA staff and regulatory staff within CFSAN and CVM. When asked if they were satisfied with the current state of transparency, ~55% of interviewees said they were satisfied to very satisfied, ~38% said they were not satisfied, and ~7% offered no comment.

Those who felt **internal scientific transparency was improving to very good** were generally addressing transparency within their office or center and offered the following supports: access to any information/memo that is needed on any safety issue (within the Center), good communication/consultation across offices and divisions, good means of tracking research (e.g., CARTS system), willingness to answer questions openly, and establishment of more focus groups for similar products (within CVM). Those who felt **internal scientific transparency was poor or needed to improve** commented that most people don't know what other centers are doing unless they're on committees; that there is a lack of transparency across centers about how and why decisions are made; and that reviews are not made public to other groups. Interviewees

also cited the lack of a resource list of expertise ("When I came in, I received a list of experts, but probably 90% of those people are gone"). OARSA interviewees commented that there seems to be competition between OARSA and NCTR; that information for attaining equipment or materials tends to be spread only by word of mouth; that information appears to be provided on an as-need basis or worse; and that they tend to find out about decisions after the fact, with no opportunity for input. Areas in need of improvement included: finding information in-house (via contacts, supervisors); accessing older decisions/information; explaining decision-making processes in-house (e.g., (b) (5)); identifying who does what in different buildings/offices/centers (organizational directory); and sharing information across centers for overlapping programs.

When addressing **external scientific transparency**, interviewees felt, in general, that the Centers were not as successful as they could be in communicating information to the public. Feelings concerning interactions with the scientific community were mixed as to how much of the problem should be attributed to the Agency. As stated by one interviewee, "Within the external scientific community, there are two groups: groups that understand the regulatory scientific process seem to have better and more productive interactions with FDA; groups that expect FDA to regulate on the "precautionary principle" or on science with high uncertainty have difficulty in FDA interactions. Another commented, "If you are feeling adversely impacted, you think we are anything but transparent."

Interviewees within OFAS and CVM who responded that **external scientific transparency was improving to very good** indicated the following: information can be obtained via FOIA; the Centers are trying to post as much information as possible on the website in addition to FOIA (e.g., most GRAS memos and letters currently appear on the website); most of the environmental decisions and supporting memoranda are already available; and decisions and final regulations are published in the Federal Register (FR). Several interviewees noted that transparency is much better when FDA has completed its assessments; however, during the process, there is not and cannot be much engagement with the external community due to proprietary issues. One interviewee commented, "I do not think it is a good idea to have people intersect the review process at any level. Disclose if asked, that's transparency." Another stated, "Agencies have to be given the opportunity to conduct their own deliberative processes without interferences. [I don't know of] any one agency that has yet perfected either pre- or post-decision information sharing with the external public in a way that satisfies anyone."

Regarding accessibility of information through FOIA, although many interviewees felt this was sufficient for providing transparency, others commented that releasing information through FOIA does not constitute transparency because information is difficult to obtain and may not be comprehensive or easy to interpret. Within CVM, this issue has been addressed by publishing an FOI Drug Summary with every approval which is issued before there are FOI requests. The summary identifies key reports/data and provides a road-map to the decision. Regarding accessibility of information in the FR, one interviewee commented, "I am not sure that the public or a lot of the scientific community understands that the Federal Register exists, and [publication in the FR] is not a good way to help people understand how we do a review, what we take into account, what types of back-up and checks do we do on our reviews. We need to find a better way to communicate with the outside world."

Means by which interviewees felt the Centers have been trying to improve external transparency included: investigating how to post more information on the website; participating in the Pew review; presenting webinars (e.g., on *trans* fats) and seminars; presenting posters at ACS; and participating in international meetings. In addition, one interviewee noted that the Office of Communications has been trying to address potential issues either before or when something becomes an issue. It was noted that efforts to improve transparency don't always occur in the time-frame required by the external community.

Those who felt **external scientific transparency was poor or needed to improve** noted the following: there is a lack of awareness/understanding among non-scientists concerning FDA's science-based policies and how the regulatory side of science works; the lack of communication within the Agency can lead to contradictory findings, which can lead to a bad public impression; when issues get "blown out of proportion" (e.g., BPA), we cannot/do not always react properly; and the Centers' overly cautious position on sharing information via publishing, poster presentations, and/or asking questions or making statements at scientific meetings make it difficult to improve engagement and transparency with the scientific community. Regarding publishing and interaction with the scientific community, interviewees within OARSA tended to be more likely to feel that there were sufficient opportunities for scientists to publish, attend meetings, present posters, and interact with the external scientific community than regulatory personnel within CFSAN and CVM. Areas in need of improvement included: improving accessibility of information in terms of releasing more information, making it easier to find on the website, and making it more "public-friendly"; and achieving real-time interaction with the scientific community.

The lack of transparency was felt to lead to issues of mistrust with the scientific community and the public. Interviewees commented:

> *If we change our minds [due to change in policy], there is a perception that we are not being honest.*
>
> *CFSAN is not transparent, which has created a serious breach with the external scientific community and the public. This is a great hindrance to our credibility. Openness makes us vulnerable, which tends to be avoided if at all possible. Denial is the most common defense, as if publication of final regulations in the Federal Register meets the criteria for transparency. It does not by a long shot.*
>
> *Part [of the problem with transparency] is how the Agency thinks of itself as a regulatory policy agency and the restrictions that it places on being transparent. That is not an issue for scientists, so much as a broader policy (legal) approach within the structure. It's easy to use those restrictions as an excuse for not doing anything . . . .*

Another interviewee noted that the issue of transparency goes both ways, commenting "When industry comes to FDA for premarket meetings, they are not very transparent with us . . . . Industry wants information from FDA, but doesn't want to give up any information."

When asked **what needs to be done to improve transparency and engagement**, the main suggestions included improving **interactions with the public** (~33%), improving the FDA **website** (~16%), improving **internal communication** (~15%), increasing **publishing and**

attendance at scientific meetings (~11%), and having **more involvement from the top** management at FDA (~6%). Two other suggestions for improving transparency were to increase **external peer review of Agency decisions** (by other government agencies or the NAS) and to increase **engagement with industry** (e.g., via more attempts to provide the regulatory perspective on a prospective submission before action is taken or by establishing regulatory liaisons within industry).

In terms of improving **interactions with the public**, interviewees felt strongly that the Centers were not doing a good enough job of interacting, either directly via talks or presentations or indirectly via making information available on the website or through publishing. Suggestions for improving direct communications included: providing additional training for scientists in how to address the public (i.e., to talk and ask/answer questions without risking negative impact on the Agency); expanding outreach efforts by organizing special interest groups to ask the public what they want (e.g., the National Conversation on Public Health and Chemical Exposures); and increasing educational outreach via regulatory and risk assessment course work, seminars, and guest speakers to convey how the process works. Although interviewees recognized the contributions of the Office of Communications, some felt that Office of Communications personnel might be too far removed from the actual work to be clear on the results. They suggested establishing Office of Communications personnel within programs so that they would more fully understand the issues before speaking to the public. Suggestions for improving dissemination of information included: making more memos available publicly (after redaction to remove confidential information); publishing editorials and articles in media other than the FR, including magazines and trade journals; presenting more information in a consumer-friendly format (using plain language or layman's terms); improving turn-around time on posting documents; expanding the type of information released to include issues that the Agency may be looking at and how they are investigated; and developing programs to educate the public on where to find information. Another suggestion was to benchmark other agencies and how they work with the public. EFSA, NICEATM (The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods), and ICCVAM were cited as examples of organizations who publish their reviews, including full reports, reflecting the agreed-upon approach as well as dissenting information and identification of all panel members. Several interviewees noted that one down-side to increasing transparency via increasing accessibility to information has been that more time needs to be spent on preparing files for release to the public (e.g., expanding and clarifying information, cleaning up formatting, etc.).

Some additional comments included:

> *If [the public] could get their information from us, it would increase our transparency and also help them understand that we are trying to protect people.*
>
> *The biggest issue is perception. Maybe we should tell people how many compounds are not approved to show that it is not a rubber stamp program, or have them look at how few have been withdrawn once approved.*
>
> *We need to try to create fewer response-only situations, which gives the impression we're only speaking up because there's a problem. There should be more free-flowing information, maybe via Twitter, Facebook, or other routes, to establish more continuous interaction.*

Regarding improving the FDA **website**, many interviewees commented that the website is difficult to impossible to navigate and commented that, even when information is there, it is very difficult to find. Suggestions included: making the website format more user friendly (maybe via the press office); establishing a Center-based website separate from the FDA website; and providing a list of products being reviewed or worked on, along with supporting information, rather than simply pointing users to FR entries.

The issue of **improving internal communication** remained a common theme, especially in terms of internal engagement and transparency. Interviewees commented:

> *I have never seen a formal chemical risk assessment that has been distributed or made available to the whole Center. There is no place for it to happen.*
>
> *We need to do a better job of sharing in-house what's been decided and why. Once a decision has been made, there should be a discussion. It's not enough to just make the information available.*
>
> *Improving internal transparency would help to expedite the review process and get more deserving products approved.*

Interviewees who suggested **increasing publishing and attendance at scientific meetings** commented that FDA has too little exposure in the scientific community. Regarding publishing, interviewees indicated that getting publications through the system was very difficult, mainly due to an over-cautious approach by the Agency to releasing information. One interviewee noted, "The safety information and a lot of the other information in these submissions are clearly public to anyone who has looked at the question." Interviewees felt that there should be more publishing in appropriate and widely read journals; more information/articles published in the trade press; more position papers and editorials; and more efforts made to summarize the research being done on hot-button issues, possibly via newsletters at the center or FDA-wide levels. Several interviewees also noted that more information should be released concerning the basic methodology used by the Centers (e.g., for calculating exposure estimates or combining EDIs with ADIs): "We should expose more about the steps we take and how we draw our conclusions. Regulations may change, but the science stands." One interviewee commented,

"There should be a mandate from above to publish everything that is done in some form. If we're going to use it, and we're going to expect other people to use it, then we should publish . . . The science is the science, and it is sound." Regarding attendance at scientific meetings, interviewees suggested sending people to meetings who are actually doing the work (vs. the "big name"), increasing attendance at "big" scientific meetings and trade conferences; and increasing opportunities to serve on panels. Several interviewees commented on the general prohibition against making public comments at meetings. As stated by one interviewee, "I'd like to see this unofficial "gag order" on FDA scientists [speaking at scientific meetings] replaced with some training in how to ask probing questions that bring out the meat of the matters in such a way as to promote discussion, consideration, growth, and learning for everyone's benefit and more opportunities to actually speak at meetings."

A number of interviewees felt that improvements in transparency should come from the **top management at FDA**. These interviewees commented:

Sometimes transparency and engagement issues are the responsibility of upper management (the Agency) rather than at the Center level. We must have the support of the Agency level because they understand what is secret and not secret.

Change needs to come from above. We need to remove some red tape, or maybe have an office liaison to get things through in a timely manner.

There should be more official commentary from the top. Further down, we can address the technical issues.

2.4. Expertise/Training

2.4.1. Question 1: Do CFSAN and CVM have the scope and depth of expertise they need to fulfill their chemical safety regulatory obligations and meet today's (and future) chemical safety challenges? In what areas do we have greatest expertise? Where do we most need to increase our scope and depth of expertise to improve our programs?

The majority of interviewees (~54%) felt that the Centers have adequate **scope** of expertise to fulfill regulatory obligations and meet today's and future challenges; ~11-22% of interviewees felt that the scope of expertise was partly to mostly sufficient, and ~12% of interviewees felt the scope of expertise was inadequate. There was more concern over **depth** of expertise: ~37% of interviewees felt depth was adequate, ~18-21% felt it was partly to mostly adequate, and ~21% felt it was inadequate. Within CFSAN, smaller offices/teams (e.g., CHAT and OCAC) tended to be less likely to feel that scope of expertise was adequate, while interviewees in all offices expressed concern about depth of expertise. Within CVM, all interviewees felt both the scope and depth of expertise were partly adequate or better; this seemed to tie in with the relatively recent expansion of hiring within that Center. Regardless of their stated opinion, many interviewees commented that the Centers can always use more qualified personnel in general and especially in response to expanding areas, such as post-market review.
Concerning **scope of expertise**, many interviewees commented that the Centers have a good ("impressive") range of expertise across different technical areas and fields, represented by

qualified scientists (mostly Ph.Ds.) who are able to move into or understand new areas as needed. The ability to access additional expertise, either across offices or centers or externally, was also considered to be a contributor to the scope of expertise. Several interviewees commented that the scope of expertise reflects what is practical or needed for current regulatory obligations, and noted the difficulties in "staffing up" ahead of potential issues. Those interviewees who felt that the scope of expertise was inadequate or not completely adequate noted the following:

- Difficulties in hiring new expertise, both in terms of the hiring process itself and in terms of attracting qualified personnel to government vs. industry, to address emerging issues (e.g., Tox21);
- Difficulties in retaining expertise in areas of emerging technologies when new hires, who are familiar with new science and techniques, find that FDA is not involved in these areas;
- Difficulties in utilizing available expertise due to lack of an effective system for identifying and locating expertise within the Centers and lack of communication, coordination, and collaboration between offices and centers to maximize sharing expertise; and
- The need for a means of defining or vetting expertise (i.e., "an expert should have an in-depth understanding of both history and emerging aspects of an area", not just an area of interest; "publications aren't always sufficient to confirm someone as an expert").

One interviewee commented, "The problem I see is people get hired for their expertise, and as soon as you are part of this institution, you are not considered an authority to listen to anymore. They hire an expert and then don't want to listen to them."

Suggestions for improving the scope of expertise, in addition to addressing the issues noted above, included: allowing staff to maintain their expertise (and credentials) by participation in professional meetings; developing a more coordinated approach to hiring that encompasses program needs as well as individual group needs; expanding flexibility in management to increase utilization of expertise (matrix management vs. "pigeon-holing" or "stovepipe" mentality); increasing the use of "integrated teams" to address specific issues; and increasing the level of scientific expertise in management.

Concerning **depth of expertise**, the primary concerns were the loss of expertise due to retirement without sufficient "back-filling" and the changing perception of what constitutes depth of expertise, particularly within CFSAN. Interviewees commented:

There is a big gap in age and expertise. There are people with 30+ years of experience who are leaving or have left and cannot be replaced or back-filled. We don't have mid-career people in our branch. Many positions are 1-person deep.

There is definitely a depth problem: we have few people and we all have to be general toxicologists. Forget about redundancy in expertise, we are lucky to have one expert.

Junior employees should be trained to replace senior employees (when they change position or retire) so that we have continuous expertise in all areas.

We have this idea about having one expert per specialty area. When one person with expertise leaves or is missing, no one else can step in and help out if there is more work to be done in that particular area.

One or two experts are not enough. For example, now there are two pathologists, formerly there were 19. Two cannot look at the actual slides or raw data in making their decision, but it appears that they used to do that. Memos from the 1970s and '80s were more thorough, filled with content and facts. These types of memos are rare now. In addition, with a large group, you would need to convince 19 people of your decision. Now you need to convince only one.

The following specific areas were identified by interviewees in response to the questions "**In what areas do we have the greatest expertise?**" and "**Where do we most need to increase our scope and depth of expertise to improve our programs?**"

Areas of Greatest Expertise	
Chemistry • General chemistry • Organic chemistry • Polymer chemistry • Lipids/foods chemistry • Analytical chemistry **Toxicology** • Traditional toxicology • Reproductive toxicology • Developmental toxicology • Carcinogenicity • Whole animal toxicology • Genetic toxicology • Immunotoxicology • Neurotoxicology • Dermal toxicology • Molecular toxicology • Heavy metals toxicology • QSAR and *in silico* modeling **Biology/Medicine** • Molecular biology • Microbiology • Neuroscience • Immunology • Endocrinology/endocrine disruption • Allergenicity **Environmental science** **Nanotechnology** **Exposure/Safety/Risk/Hazard Assessment** • Exposure assessment for food additives, ingredients, and packaging • Human intake exposures • Dietary exposure modeling • General toxicology risk assessment • Carcinogenicity risk assessment • Contaminant safety hazard assessment • Trace elements assessment **Analytical methods** • *In vivo* toxicology methods • *In vitro* toxicology methods • Dose response investigations • Development of human serum data bank **Mathematics** • Biostatistics	(Shading indicates area not listed in first column) **Chemistry** • Industrial chemistry **Toxicology** • Modern toxicology • Reproductive toxicology • Developmental toxicology • Carcinogenicity • Immunotoxicology • Neurotoxicology • Renal toxicology • Toxicogenomics • Mixture toxicology • Metabolism • Food packaging toxicology • QSAR interpretation **Biology/Medicine** • Molecular biology (large molecules, systems tools) • Microbiology • Immunology • Endocrine disruption • Developmental biology • Modern biochemistry • Biological systems modeling • Pharmacology • Pharmacokinetics and modeling • Epigenetics (mechanisms of carcinogenesis) • Biotechnology& • Physiology • Genetics • Proteinomics • Interspecies extrapolation • Gastroenterology • Pathology • Oncology • Neurology • Stem cells research **Nanotechnology** **Analytical methods** • *In vitro* toxicology methods • Interaction between *in vitro* and *in vivo* models • High throughput methods • Analytical methods development **Mathematics** • Mathematics (data analysis) • Statistics

Areas of Greatest Expertise	Areas Where We Need to Increase Our Expertise
Food Sciences • Food technology **Animal Sciences** • Physiology • Animal feeding • Aquaculture (drugs in fish) **Regulatory Areas** • Residue chemistry • Human food safety • Small chemical entity food safety • Specifications for purity of food additives • Conducting food additive and food packaging material reviews • Developing specifications for purity of food additives • Regulating veterinary drugs • Regulatory writing	**Food Sciences** • Food science • Produce expert **Animal Sciences** • Skilled technicians • Genetically engineered animals **Regulatory Areas** • Scientific/technical writing • Technical editing

In discussing areas of greatest expertise interviewees commented that: the Centers generally do a good job of balancing scientific strictness with the needs of regulatory safety, and do a good job of maintaining well-balanced teams. Consumer safety officers were identified by a number of interviewees as having wide areas of expertise.

In discussing areas where expertise needs to be increased, a number of interviewees addressed the need to integrate available expertise to address emerging areas:

> *While there is always a need for more expertise in the complex interdisciplinary area of risk/safety assessment and all the related disciplines, the real need is to integrate the expertise that we have by recognizing the profound interdisciplinary nature of this activity. Such recognition would galvanize the need for mutual team efforts to solve difficult scientific and policy issues.*
>
> *To address emerging issues, genetic, molecular, and chemical capabilities are needed. Not many scientists are able to integrate this type of information. We need seasoned individuals to assist new hires.*
>
> *We need more risk assessors who aren't expert quantitative modelers, but actually know how to talk a toxicologist or scientist through a risk assessment paradigm for the first time. We need to have some bridge between the analytical quantitative risk assessors and people that are actually doing safety assessments and risk-based and weight of the evidence assessment.*

Another area in which additional expertise is needed that was identified by a number of interviewees was mathematics and statistics. Interviewees noted that, although there is a mathematics component to safety assessments, the Centers do not typically hire mathematicians *per se*. The need for mathematicians was seen not only for performing calculations for exposure estimates, etc., but for interpreting data received from the sponsors. One interviewee noted, "A

lot of the number work can be done in 5 minutes, not 5 months, if the right expertise is available."

2.4.2. Question 2: Can CFSAN/CVM get adequate external expertise when needed? Why or why not?

The majority of interviewees (~77%) felt that **CFSAN/CVM were generally able to get adequate external expertise** when needed, despite a number of impediments, including:

- Availability of funding: for contracting/consulting;
- Time constraints: "consulting services take time to obtain when you need answers right now";
- Difficulties in identifying contacts/experts: no mechanisms or SOPs in place;
- Conflicts of interest: with academia and industry, and due to working with proprietary information;
- Complicated clearance procedures: e.g., Food Advisory Committees can be obtained but are difficult to assemble; and
- Public perception: "[People will wonder;] did we pay them to do that study?"

A number of interviewees felt the easiest way to obtain external expertise was though personal contacts. One interviewee commented, "There is no reason why we cannot get any special expertise we want within government. It is a matter of process and making it happen. There is so much expertise within the government scientific agencies themselves, and they seem eager to help us. But we need to ask, and not cower behind some insecurity complex that makes us reluctant to ask for help."

Only ~10% of interviewees felt that the Centers were not able to get external expertise when needed. Several interviewees spoke of being discouraged from obtaining external expertise at the staff level ("I was told we don't do that"). Others felt it was not attempted. Additional comments included:

The process is cumbersome and time-consuming. There is no structure for grants or contractors, and it is difficult to get grants through. We need to evolve a way where we can do this at the center level.

We should be able to invite scientists here and pay for them to streamline the process for getting an expert opinion.

We rule out industry because of COI, but the EU does use industry. We need to figure out how to change this.

We don't work hard enough to obtain this, probably because we don't feel it is necessary.

It is difficult to pick up the phone and talk to two or three experts and be able to tell them enough to get input in a useful way. There are a lot of understandable but very difficult restrictions placed on our ability to do that.

2.4.3. Question 3: To what extent should we focus on acquiring general as opposed to specialized toxicology expertise?

[Note: Although this question was targeted at toxicology expertise, it was often answered by interviewees in other disciplines with respect to their own areas of expertise. These responses were included].

When asked whether the Centers should **focus on acquiring general or specialized expertise**, the distribution of responses was: ~18% for general, ~22% for specialized; and ~43% for both or a balance between the two; however, even within these response groups, responses were often mixed. Approximately 17% of interviewees offered no opinion. Many interviewees commented on the merits of training available staff to expand their expertise as an alternative to hiring.

Interviewees in favor of obtaining more **general expertise** cited the following advantages: general experts are better able to take an integrated approach to interpretation of toxicological signals; general experts are more likely to be able to address a range of different compounds/issues, to get the group more involved, and to apply a more diverse knowledge base to an issue; they are a safer hire because it is difficult to anticipate what special issues will arise; they are likely to develop specific expertise on the job as needed. The only specific drawback to obtaining general expertise that was stated was that a generalist may not be able to do a specific study type. One interviewee commented, "General toxicology expertise is seasoned and is gained from people working in interdisciplinary environments that foster such seasoning. These people are scarce. We need to develop them ourselves, not think we can steal . . . them from somewhere else."

Many interviewees in favor of obtaining more **specialized expertise** indicated that the Centers have enough generalized expertise already. The following advantages to obtaining specialized expertise were cited: specialized experts are needed to address emerging trends and remain current; having groups comprised of scientists with different specialties is an advantage; anyone with specialized expertise will have had general training before that; using specialists can save time because they know where to find information on a given issue; and they are likely to develop generalized expertise over time. Drawbacks to obtaining specialized expertise included: potential difficulties for specialists to adapt to general work and the need to train them in the fundamentals of review; difficulties in choosing which area of expertise is the greater priority (e.g., reproductive or liver toxicology?); specialists may not be used to best advantage because of their narrow range of expertise; and if too many specialists are hired for a given issue, they may not be needed in a couple of years.

In response to this question and Question No. 1 of this section, a number of CFSAN interviewees also commented on the need to acquire more toxicologists of any type, noting that there seems to be a shortage of true toxicology programs in academia, and a perception that the Center has de-emphasized the importance of toxicology within its programs: "Since I have been here, toxicology has atrophied badly . . . . We used to be the nation's leader and global leader in toxicological assessments . . . . The entire toxicology concept at FDA needs to be revised, re-envisioned, and revitalized."

2.4.4. Question 4: Are the staff and resources currently devoted to chemical safety reasonably deployed and efficiently used across the Foods and Veterinary Medicine Program? What ideas do you have for improving the allocation of staff and resources?

When asked if staff and resources devoted to chemical safety were **reasonably deployed and efficiently** used across the Program, ~62% of interviewees felt this was generally true; ~11% felt this was not the case; and ~27% offered no opinion. Many interviewees felt this question could not be addressed by someone at the staff level, and others responded in terms of deployment and use across their division or office.

Although many interviewees commented on staff shortages, budget constraints, fluctuations in the workloads within the Centers, and the need to address emerging issues, these were generally felt to be minor obstacles. Most interviewees felt that their office, division, or the Centers were doing the best they could to maximize the efficiency of the available staff, and that regulatory obligations were being adequately addressed. Even the increase in post-market review work was not seen as a major issue, due to the allocation of additional funds to recruit temporary assistance for this type of work. Increased bureaucracy associated with the establishment of the OFVM was also identified as a minor impediment to efficiency, as was the increase in administrative duties assigned to scientists to support efforts to address/improve transparency (responding to FOIA requests, preparing FOI Summary documents).

The following issues were identified as more serious impediments to the efficient deployment and use of staff:

- The shift across the Centers to an integrated review team/interdisciplinary approach by work product vs. the "pool" approach which grouped reviewers by discipline;
- The lack of sufficient means of identifying expertise within the Centers;
- Insufficient communication and integration across offices and centers;
- The allocation of effort between "moving the freight" and addressing special projects: "special projects get noticed; moving the freight, only if it's not done";
- Improper utilization of expertise, including problems finding the balance between staff who are more expert in a limited field vs. those with broader experience, and insufficient or inefficient use of specialized expertise (e.g., failure to consider expertise within OARSA in program decision-making);
- Lack of flexibility in deployment and use of staff; and
- Too much focus on building programs vs. doing the work: "We are way too top heavy."

Ideas for improving the allocation of staff and resources fell under the following general areas: revisiting the current integrated team approach; increasing details and/or cross-training; increasing communication and integration across centers; improving means of identifying expertise; addressing post-market obligations; establishing "strike teams" to address special issues; adjusting workloads; improving hiring practices; and finding help elsewhere. The need for a means of identifying expertise within the Centers has been addressed elsewhere, and will not be discussed further here.

There did not seem to be a simple answer to the question of whether use and deployment of staff would improve if the **integrated review team approach** were to be replaced by the pool approach. Although several interviewees saw the integrated approach as decreasing efficiency due to a loss of cross-training on other products, loss of ability to shift assignments within the group depending on work-flow, and the loss of critical analysis of reviews by other experts within the same discipline, others maintained that there were efficiencies in the current approach. Along these lines, many interviewees suggested **increasing details, shadowing, or cross-training** to expand the breadth of expertise across review areas: "Meaningful cross-training is a great idea. Once you have a fully trained and educated risk assessor, toxicologist, exposure assessor, pharmacologist, have them trade jobs . . . for 6 months to a year to learn people and practices that they might want to bring back to their parent Center. Then if there is a true emergency . . . these people could seamlessly enter [the work-flow] because they have already done something like that."

In addressing the need to increase **communication and integration** across centers, interviewees commented that better communication and integration across the Centers would enable better leveraging of staff and resources, enable better identification of needs in terms of both manpower and expertise, potentially reduce the need to hire individual expertise, and make the assessment process more transparent. Interviewees commented:

> *Harmonization with CFSAN's toxicologists would be good so that we can better utilize resources depending on level of work in each Center. We could shift around if needed. The regulations are different, but the approaches could be harmonized and expertise leveraged across the Centers.*
>
> *First we need to define scope and needs for the next 5 years. That is difficult because our budget is from year to year. We need to look at the overview, emerging issues, basic objective, overall goal, and then analyze what we have and what are our deficiencies are. From there, we can define what we need to do, then allocate resources (shifting or maintaining) for these programs or new programs.*
>
> *We need to get rid of silos and start working on a matrix-managed approach. We've got lots of resources scattered all over the place but we don't know where they are. We don't always bring the best people to bear because something has to go through a particular administrative route that limits the extent to which you can pull people in. We need to understand that these are Agency resources, not branch or division resources. Expertise needs to be deployed to serve the public not to meet an administrative quota.*

In addressing the impact of **post-market obligations** on use and deployment of staff, interviewees suggested assigning dedicated staff to address post-market issues: having designated staff for both with sufficient cross-training to handle fluctuations in workload; or increasing staff so that there is time to handle both. "We are Congressionally mandated to do premarket review on a strict timeframe. It is very difficult to also do the post-market issues when they come up." The idea of establishing "**strike teams**" to address special issues was mentioned by several interviewees. These "*ad hoc* specialty groups would be formed and provided with sufficient support to address a high priority issue within a specific time frame; a similar approach is taken within EPA's ORD. The need to **adjust workloads** was perceived to

address the relatively minor issue of staff who are under-utilized or not working to capacity. Interviewees felt it was the responsibility of division directors to identify these personnel and shift or re-prioritize workloads to improve their utilization. In terms of **improving hiring practices**, interviewees commented that the Centers need to focus on hiring the right personnel and filling the right positions: "Every time you have a fillable position, you need to do an assessment for where that position is needed. We need to get away from the mind-set of 'I lost a person, I get to hire a person.'" For **finding help elsewhere**, interviewees suggested the need for finding ways of going to academia with questions or asking questions in a public forum without compromising FDA's position. Another idea was to use ORISE fellows as resources for in-depth projects or literature reviews, with subsequent QC by senior personnel.

Other suggestions included: addressing the problem of reacting to issues that have already been resolved simply because someone important raises the question again; motivating staff to a common goal and specific outcome; and bringing in contractors for processing FOI requests so that scientists can do their jobs.

2.4.5. Question 5: Are our training needs being met and if not what training types/topics would be most beneficial to the programs? Are there outside entities we could partner with for more training opportunities? How can we better ensure professional development needs are being met to ensure development and retention of qualified scientists?

The majority of interviewees (~85%) felt that, in general, their **training needs were being met**; only ~10% of interviewees felt their training needs were not being met. Although the response to this question was generally positive across all offices and centers, it appeared that there may be a stronger commitment to providing training within CVM, where interviewees commented that training "goes beyond what we ask for" and that it is "more than adequate for training in doing the job as well as beyond to areas of interest."

While several obstacles to meeting training needs were mentioned, including funding, time constraints, and communicating available opportunities to the staff, the main problem was seen to be budget constraints and allocation of funds for training and travel: maintaining a training budget was seen to be essential for the Centers to remain current with the science. Several interviewees commented on the coincidence of summer training opportunities (e.g., JIFSAN courses) and fall meetings with the end of the fiscal year and funding shortages. These interviewees recommended better allocation of funds, including: long-range development plans incorporating odd-year "big" training opportunities with alternate-year smaller opportunities. Other suggestions for cost savings included: offering more training opportunities via webinars and online classes; expanding training to other centers or making it available FDA-wide; recognition of/encouragement for people paying their own professional society memberships; and making more efforts to bring in or partner with professional societies, rather than sending staff to meetings. As a potential cost-saving measure that could be utilized more within the Centers, several interviewees mentioned in-house training that had been offered in the past, including: seminars with OARSA on new techniques and analytical methodology; a training series on different methods of risk management and exposure assessment; a lecture series offered by the pathology group in CFSAN; immunology classes organized within OFAS; a lecture series on genetic epidemiology; and re-establishing "Grand Rounds" training to bring experts in-house.

One interviewee noted that these were typically individual efforts, and suggested having an *ad hoc* group that might meet on a regular basis (weekly or monthly) to identify areas that need to be addressed, recommend courses to be taught, and help organize them.

Suggested **training types/topics** included:

- Analytical methods training, including: hands-on training in techniques and methodology (e.g., *in vitro* methods, high throughput screening techniques);
- Training in safety and risk assessment and management technologies including exposure assessment technologies;
- Training in emerging technologies, including nanotechnology and nanotoxicology, mixture toxicology, PK (pharmacokinetics) profiling, PBPK (physiologically based pharmacokinetic) modeling, systems biology modeling, epigenetics, genomics, and toxicogenomics;
- Training in data management, including analysis of raw data, introduction to databases, and statistics software (e.g., SAS);
- Training in quality assurance, quality control, GLPs, and GCPs;
- Toxicology training including courses in general toxicology, pathology, neurotoxicology, developmental toxicology, as well as prep courses for DABT (Diplomate of the American Board of Toxicology, including overviews of topics like immunotoxicity);
- Training in translational science;
- Training on industrial practices including food processing, GMPs (Good Manufacturing Practices), and HACCP (hazard analysis and critical control points) procedures; and
- Training in communications.

A number of interviewees mentioned DABT certification in terms of training, as well as job satisfaction and retention. They felt that DABT certification should be supported (via training and travel funds) and encouraged by the Centers.

Another training area that was addressed by a number of interviewees, especially within CFSAN, was training on how to do the job of regulatory review: "We don't generally share our personal search techniques or any details of how we do the daily work. There is not much in the way of SOPs, a manual for new hires, or anything like this." SOPs seemed to be more readily available at CVM, where they were identified as a program strength. Interviewees also suggested cross-training (via presentations or details) with different groups and offices within the Centers including:

- Cross-training for toxicologists with chemists to learn how they determine exposure;
- Cross-training for OARSA with OFAS to learn how the review process is done and the related regulations and guidance, so that research scientists can figure out what can be done to support the reviewers and how to develop good projects; and
- Cross-training for regulatory personnel with the laboratory.

Several interviewees commented that details needed to be of sufficient duration to be valuable (e.g., "They can't come in short-term and learn: they need to be committed to a long-term assignment with specific objectives within a specific timeline"). In conjunction with these suggestions were requests for training to provide an overview of the entire FVMP. One

interviewee commented, "I know only what I am involved in. I know the scope of what FDA regulates, but not the specifics of what and how it is done within other groups and offices."

Interviewees also included attendance at meetings and conferences and allowing scientists to present their work as part of the training picture. One interviewee recommended that scientists be encouraged to actually participate in the meetings (submit abstracts) and to present their findings when they return. Several interviewees suggested programs to allow people to go on details or sabbaticals to academia or other agencies (e.g., for revisiting laboratory techniques and methods). Another suggestion was mentoring for new hires.

In conjunction with training, a number of interviewees mentioned the Staff Colleges. Most interviewees commented favorably on the Staff College and noted that it was especially good for business and personal development training, was "good for the basics, but not for cutting edge science" and was "not specific to the work we do." But other interviewees noted that many employees seem unaware that the Staff College is also available to support science courses either by identifying available courses or helping to design or develop them. One interviewee mentioned collaboration with the Staff College to develop a course in genetic epidemiology that was offered at CFSAN. A recommendation was made to establish joint Staff Colleges with other centers (e.g., CDER) and to increase class sizes so that more training could be offered by this route.

When asked what **outside entities the Centers could partner with for more training opportunities**, suggestions included other centers and programs under HHS, other agencies, academia, scientific societies and associations, industry groups, and non-profit organizations. We note that in response to this question, a number of interviewees also recommended expanding in-house training rather than going outside.

Outside entities to partner with for training	
Other Centers and Programs: • CFSAN/CVM • CDER • NTP • NCTR • FDA SRL (Southeast Regional Laboratory) **Other Agencies:** • CDC for statistics • USDA for statistics, USDA Graduate School • EPA for risk assessment • NIH and NIEHS • OPM (Eastern Management Development Center, Shepherdstown, WV) **Academia:** • University of Maryland for course work on nanotechnology, materials science, new equipment and techniques • JIFSAN (Joint Institute for Food Safety and Applied Nutrition) for risk assessment • UMBC (University of Maryland, Baltimore County)	**Scientific Societies and Associations:** • AAPS (American Association of Pharmaceutical Scientists) • ACS (American Chemical Society) for current trends in equipment and research, toxicology for chemists, risk assessment • ACT (American College of Toxicology) • ASQ (American Society for Quality) • AVMA (American Veterinary Medical Association) • SOT (Society of Toxicology) • SRA (Society for Risk Assessment) • STP (Society of Toxicologic Pathology) **Non-profit organizations**: • The Hamner Institute • ILSI • TERA (Toxicology Excellence for Risk Assessment) • Various food safety institutes • Various food law institutes

Outside entities to partner with for training	
• Johns Hopkins • Harvard School of Public Health • Purdue University for botanicals **Industry Groups:** • IFT (Institute for Food Technologies) • Various equipment manufacturers for workshops on operating equipment, improving techniques • Various food processing facilities for on-site visits (e.g., Hershey, poultry plant, paper recycling) • Various testing laboratories for training on methods and techniques	

When asked **how can we better ensure professional development needs are being met to ensure development and retention of qualified scientists**, ~31% of responses included increasing emphasis on training, ~20% included increasing opportunities for advancement, ~17% included increasing recognition of contributions, ~16% included increasing attendance at meetings and conferences, ~7% included increasing incentives or money, and ~6% included conducting regular surveys of employees or exit interviews.

Regarding **increasing emphasis on training**, interviewees were concerned about the availability of funds for training, limits on travel outside the area, and obtaining approval to attend training: "People have to feel when they come here that learning is ongoing." Several suggested making training part of an individual's job responsibilities (e.g., a requirement for a certain number of hours/year as part of the PMAP, or a requirement to demonstrate that you have done re-training or continuing training within a 5-year period) and including training attendance in performance evaluations. In this way, they felt that people would be more likely to make attending training a priority, and that training would be more likely to be approved by supervisors. One interviewee commented, "We need to implement training that actually helps people with career development and gives them opportunities to use their expertise. The managers need to be willing to let go of resources to allow people to go out [for training] instead of thinking of it as losing a resource." One suggestion that addressed both training and the need to recognize the contributions of staff members was to allow new hires with expertise in new areas to give presentations in their areas of expertise.

Increasing opportunities for advancement was felt to be an important means of improving employee retention. One interviewee stated that working at CFSAN was good for development as a regulatory specialist but was not good for development as a scientist. Interviewees commented on:

- Limited opportunities for advancement above a GS 13: job openings do not come available very often, "you need to be an expert to qualify for advancement but are encouraged to be a generalist";
- Differing professional development opportunities for different areas of expertise;
- Different promotion/retention policies and different retirement benefits across the Agency (e.g., a peer review requirement for CVM but not for CFSAN and CDER, whether retention bonuses are offered or not); and

- The impact of supervisors on job satisfaction and opportunities for advancement: "with a good supervisor, you feel as if you can advance and you are being acknowledged."

Interviewees recommended establishing a long-term plan to be ready for advancement, including identifying career goals, planning attendance at meetings, identifying training, and establishing a re-qualification checklist. To address the issue of supervisory impact on advancement, interviewees suggested a formalized system of documenting personnel issues that could be passed upwards or a means by which scientists could access managers outside their immediate line of command.

A number of interviewees commented on the peer review process for promotion. The peer review process was variously reported to be: a deterrent to promotion due to the need to demonstrate expertise via research and publications prepared in addition to work obligations; a way for employees to chart their own path for promotion through self-nomination without having to go through management; a means of preventing the promotion of "preferred" employees by management without sufficient qualifications; and a means of establishing true expertise via the outside recognition that is the usual criteria for promotion to GS 14 or above.

Increasing recognition of contributions was mentioned by both staff and management as being important in retention of employees and as an area where improvements are needed to increase morale. Interviewees commented on the lack of acknowledgement of scientific expertise, as well as the lack of acknowledgement of contributions on the job:

> *You are not even encouraged to go to meetings in areas on which you are an expert; therefore, you receive no recognition as a scientist.*
>
> *It makes it really hard to get excited about your work when you don't see where you fit in to the big picture, or you don't know if your work is important or how it could help somebody else or how somebody else uses your data or could use your data.*
>
> *FDA needs to see scientists as scientists, not just as reviewers. Over time if they are not encouraged, good scientists will not stay.*

Interviewees felt that improving recognition would help resolve other issues by motivating personnel to seek additional training and attend meetings when they felt their contributions were valued. Suggestions for improving recognition included: increasing identification and inclusion of the individual; increasing internal support for competence; increasing encouragement; acknowledging contributions; working through mistakes; reducing criticism; asking people for their opinions; identifying when they're having difficulties with an assignment; letting them know where they fit within program offices and needs; encouraging more involvement in regulatory decisions; allowing participation in interesting topics/issues; showing appreciation for their knowledge, skills, and work; offering training in new areas or expanding training in areas of expertise; and emphasizing professional development.

Regarding **attendance at meetings and conferences**, interviewees commented on the importance of allowing scientists to maintain visibility in the scientific community by encouraging publishing and attendance at meetings and increasing opportunities to make presentations: "People go back to academia or industry to get this kind of benefit. Sometimes the quality of life benefits at FDA don't off-set this shortcoming." Regarding **increasing incentives or money**, most comments had to do with disparities between Centers, disciplines, or job descriptions, and the perception that there could be more consistency in salaries and incentives. **Regular surveys**, conducted every couple of years, and **exit interviews** were seen as a way of identifying issues within the Centers in terms of employee satisfaction and needs, free of filtering through management. Interviewees felt that past surveys were at least partly successful.

Other suggestions for ensuring development and retention of qualified scientists included: supporting virtual meetings, work from home, work from distance, and flexible hours; increasing opportunities for collaboration; allowing personnel time to do their own research or participate in collaborations in addition to work; including collaborative efforts, attending training, or publishing or reporting on new findings as a performance element in evaluations; reducing administrative duties by hiring editors for preparation of public documents; and increasing management's commitment to and support for science-based decision making. One interviewee commented, "We are not going to be able to lure people to the Federal government because of money. We will have to lure people because of the mission and work environment we provide. Most scientists want to keep up to date; if we can find a way to do that and still work here then we will be able to keep more people."

3.0. CONCLUSIONS AND RECOMMENDATIONS

As evidenced in this report, the employee interview portion of the Chemical Safety Assessment Review has yielded a wealth of valuable insight into the FVMP's current chemical safety capacity from the perspective of those involved in doing the work across different levels, offices, and disciplines. Although full consideration of all ideas, input, suggestions, and recommendations presented herein may take quite some time and will likely require additional efforts from all levels within the FVMP program, there are some over-arching recommendations that deserve to be highlighted.

When the responses are considered across all question areas, there were some recurring issues and limitations that are largely beyond the control of the Centers. These include resource issues of funding, and, to a large extent time and manpower, as well as regulatory issues affected by the current mandates and policies under which the Centers operate, including the Delaney Clause. However, the interview process also yielded many suggestions which appear to be within the means of the Centers to implement, provided appropriate support and commitment can be dedicated to them.

There are clearly no easy fixes. For example, one of the most often identified concerns during was the need for increased communication across offices and groups and within and between the Centers. This would seem to be a simple problem, easily solved by recommending that communication be increased. However, as discussed by the interviewees, the issue of

communication is complicated by obstacles including confidentiality; territoriality; lack of common ground between programs, offices, and/or divisions; lack of sufficient time; lack of management support; a cumbersome website; public perception; and more. The evidence of the difficulty in increasing communication is predominated as one of the key identified concerns across all topic areas of the interview process.

3.1. Recommendations

Based on the key findings of the chemical safety assessment personnel interviews, the following recommendations are offered for the Chemical Safety Program:

- Increase and encourage communication and dissemination of information within disciplines, across offices and groups, within and between the Centers, and with other agencies:
  - Via informal meetings, newsletters or reports, formal meetings;
  - On work assignments that are in-house, methodology, new technology, emerging issues, regulatory decisions (old and new), decision-making processes, achievements of agency personnel (publications, presentations, awards);
  - With full support and buy-in from all levels of management.
- Establish an accessible and reliable means of identifying subject area expertise within the Agency, including a system for vetting such expertise.
- Increase focus on manpower issues via improvements in the hiring process or in-house training or allowances for staff allocation of time to address:
  - Attrition due to retirement and the growing experience gap;
  - Allocation of existing staff to expand communication and collaboration, and participation in support activities that will benefit the program (e.g., cross-training, tracking emerging issues, “strike teams”, etc.);
  - The need for additional expertise in mathematics and statistics.
- Continue to build on the improving relationships between the research and regulatory science groups via increasing communication and improving alignment.
- Continue to focus on improving external transparency via:
  - Expanding direct communication with stakeholders and the external scientific community;
  - Improving the website or establishing a separate website for chemical safety;
  - Investigating alternatives such as FOI Summaries.
- Where possible, maintain or increase attendance at meetings and conferences and opportunities for publishing.

- Within CFSAN, allocate time and resources to reassessing the safety paradigm in consideration of emerging technologies, Tox21, and global regulation.

- Develop or improve SOPs and training for doing the job of regulatory scientists and in new methods and technology.

- Increase peer review of work products within divisions.

- Improve data management:

  - Identify and organize databases available within FDA;
  - Improve data sharing between research and regulatory groups, offices, and other agencies.

- Increase willingness to consider other approaches for methods, guidances, and new technology.

- Increase identification of and access to external expertise.

- Increase outreach to industry.

- Address post-market review:

  - Its impact on workload and time commitment;
  - Whether it should be expanded (e.g., via surveillance) to address chemical safety issues.

- Address issues specific to CHAT and OCAC identified in this report.

Appendix A: List of Review Questions

Science Issues:

1. What do you see your program doing particularly well with respect to chemical safety review or research?

2. What do you see as the most obvious weakness in your program with respect to chemical safety review or research?

3. Are you aware if chemical safety risk assessment and safety evaluation methods are consistent across offices and centers? For example, are there consistent requirements for submission of raw data and data tables and if not what is the rationale for the inconsistency or inconsistencies?

4. If you are aware of differences, do you understand what the rationale is for these differences?

5. Is chemical safety research at CFSAN and CVM adequate in scope and scale and well aligned with the Centers' regulatory mission and priorities? If not, what are some examples? What suggestions do you have for changing the scope, scale and alignment?

6. Are the program's risk assessment and safety evaluation methods (a) in keeping with the current and emerging state of the art and, (b) recognized as such by the external scientific and stakeholder communities? If not, what are the shortcomings?

7. What do you see as some of the emerging issues and questions in chemical safety review? How well do we facilitate the needed developments in the science to address and answer these issues and questions?

8. How can we keep the Redbook and other guidance up to date with the pace of new science? Is there an alternative to the lengthy guidance procedure that you could suggest?

9. How can CFSAN/CVM/OF be more proactive in identifying compounds or issues of emerging safety concern (for example, contaminants, endocrine disruptors, dietary ingredients in conventional food)?

10. What internal processes are in place to ensure appropriate quality assurance and peer review on chemical safety matters? How well are we implementing these processes? What additional processes, if any, do you recommend?

Communication/Collaboration within OF/CFSAN/CVM/NCTR:

1. How effective is the coordination and collaboration across offices and centers on cross-cutting issues? If not, what are the impediments? What can be done to improve coordination and collaboration?

2. Are there sufficient opportunities for collaboration internally and externally and if not what are the gaps? What collaborations would improve/benefit the programs?

3. What toxicology research could NCTR do for CFSAN or CVM that it is not doing for either CFSAN or CVM?

With Other Programs/Agencies/Public:

1. Are those conducting chemical safety risk assessments and safety reviews obtaining the type and quality of toxicity and exposure data they need from laboratories in CFSAN, CVM, ORA, and NCTR? Do FDA scientists have access to information from databases at NTP, NHANES and other agencies/sources? What additional databases would be beneficial? What do you see as barriers to us getting this information?

2. Is there a reason for different safety assessment approaches/methodology between regulatory agencies? Could it be possible to harmonize safety assessment methodology with other agencies to avoid confusion? If so, what ideas do you have to reach this goal?

3. At what levels and in what manner does the program interact on significant chemical safety and risk assessment issues with NIEHS, CDC, EPA, USDA, other federal agencies, and international bodies? What has worked well in this regard? What improvements are needed, and how can we best achieve these improvements?

4. What is the current state of scientific transparency and engagement internally and between FDA's chemical safety scientists and programs and the external scientific community? How satisfied do you feel with the current state? What, if anything, needs to be done to improve transparency and engagement?

Expertise/Training:

1. Do CFSAN and CVM have the scope and depth of expertise they need to fulfill their chemical safety regulatory obligations and meet today's (and future) chemical safety challenges? In what areas do we have greatest expertise? Where do we most need to increase our scope and depth of expertise to improve our programs?

2. Can CFSA/CVM get adequate external expertise when needed? Why or why not?

3. To what extent should we focus on acquiring general as opposed to specialized toxicology expertise?

4. Are the staff and resources currently devoted to chemical safety reasonably deployed and efficiently used across the Foods and Veterinary Medicine Program? What ideas do you have for improving the allocation of staff and resources?

5. Are our training needs being met and if not what training types/topics would be most beneficial to the programs? Are there outside entities we could partner with for more training opportunities? How can we better ensure professional development needs are being met to ensure development and retention of qualified scientists?