Workshop on FDA Implementation of the Integrated Assessment of Marketing Applications and Integrated Review Documentation

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In addition to the workshop contributors above, this summary incorporates the views, as expressed in responses to Federal Register Docket No. FDA-2020-N-1550, of the *Combination Products Coalition*; *Pharmaceutical Research and Manufacturers of America*; *Flatiron Health, Inc.*; the *National Health Council*; and the *Biotechnology Innovation Organization*.

Background and Introduction

The Office of New Drugs (OND) at the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) as part of the New Drugs Regulatory Program (NDRP) Modernization has the mission of maintaining and advancing FDA's global leadership role in ensuring that drugs and biologics are safe and effective. The NDRP modernization is necessitated by the rapid and sustained increase in drug development activity, as well as the rising complexity of the therapies under development. Added to these factors are the greater availability and utility of novel data types, including real-world evidence (RWE), and the increasing public interest in FDA's activities, together with budgetary constraints and a shortage of talent. From these factors emerged the need for a simpler and more interdisciplinary approach to the review process that makes greater use of the available talent and has the flexibility to leverage new types of data.

The NDRP modernization program comprises multiple workstreams, one being the new Integrated Assessment of Marketing Applications (IAMA). The goal of the IAMA is to critically, collaboratively, and consistently assess whether the information submitted in drug marketing applications meets the relevant legal and regulatory requirements. To this end, OND has adopted a new approach to assessments of new molecular entities (NMEs), original biologic licensing applications (BLAs), and select efficacy supplements that have a new indication and/or population—the production of a more integrated, interdisciplinary document to foster collaboration and reduce the quantity of redundant information. The IAMA process and resulting Integrated Review (IR) document has the additional goal of facilitating and clearly presenting drug assessments that remain rigorous and clinically relevant, focus on the key review issues, and incorporate the patient's perspective.

Analysis of the former drug-review process revealed that discipline-specific reviews, and subsequently Unireviews, contained much redundancy and did not facilitate interdisciplinary collaboration. It also indicated a need for greater clarity on the rationale underlying cross-disciplinary review issues. Furthermore, FDA reviewers asked for support to enable them to spend more time on critical thinking about drug safety and efficacy instead of formatting and editing the review document or other tasks, such as data mining and administrative functions. Finally, there was a need for improved knowledge management including referencing for future work. The IRT provides an approach for efficient handling, identifying, organizing, and dissemination of information within the document for easy access by staff and stakeholders.

IAMA Process

The new IAMA process, of which the IR document is an important part, addresses the challenges outlined above by promoting interdisciplinary, highly collaborative, issue-based, and scientifically rigorous assessment of drug marketing applications submitted to FDA.

Review teams are encouraged to identify and focus on key review issues early in the IAMA process, thereby promoting interdisciplinary collaboration. This enhances communication both among the members of the review team and between FDA and external stakeholders, including the company submitting the application (the Applicant).

Importantly, the IAMA process was designed from the ground up to embrace and respect differences of scientific viewpoints. The process involves early, frequent, and intensive meetings for discussion of

differences of opinion among the review-team members. Any such differences of opinion that remain unresolved at the time of the marketing application decision are captured in the IR document.

Additionally, review teams engaged in IRs of drug marketing applications are supported by two new roles—clinical data scientists (CDSs) and medical editors (MEs). Moreover, the review-team members have access to online training and to other resources to both ease the transition to the new IAMA process and enable them to spend their time on critical analysis of data.

The IAMA's focus on key review issues and promotion of collaboration and communication, as well as support from the CDS and ME, improves clarity, readability, and transparency, thereby enhancing insight, utility, and knowledge management. The end result is clear articulation of the rationale underlying the marketing application decision.

IR Template/Document

The new IR template is structured to enable an issue-based and interdisciplinary drug review. The IR template comprises three top-level sections—*Executive Summary*, *Interdisciplinary Assessment*, and *Additional Analyses and Information* (formerly *Appendices*).

The *Executive Sum*mary provides the overall decision, rationale, benefit-risk (B-R) assessment, and high-level descriptions of key scientific differences of opinion. The *Interdisciplinary Assessment* contains discipline-specific sections, highlights key review issues for efficacy and safety while also encompassing differences in opinion among the review-team members and how those disagreements were addressed. Finally, the *Additional Analyses and Information* section is a repository of materials that support the regulatory decision, including discipline-specific assessments and detailed analyses supportive of or vital to key facts, data, or conclusions of the review and includes dissents by reviewers who disagree with significant elements of the *Executive Summary*, *Interdisciplinary Assessment*, or with the decision of the signatory authority. Importantly, the IR document includes the same level of detail in terms of data and analyses as did prior drug review documents (e.g., the Unireview, discipline-specific reviews).

Implementation of the IAMA Process

OND's goal is to use the IAMA for all NME drug and original biologic licensing marketing applications, including select efficacy supplements with a new population and/or indication as well as new clinical data. The IAMA is being implemented in several phases to facilitate feedback-based refinement and to ensure that review teams have the necessary tools, training, and resources to enable their transition to the new process.

FDA is committed to refining and adapting the IAMA process and the IRT based on the feedback received from external stakeholders in industry, government, academia, and healthcare. To that end, the Agency held a virtual workshop, *Implementation of the Integrated Assessment of Marketing Applications and Integrated Review Documentation* on October 30, 2020.

External Stakeholder Perspectives

The perspectives of external stakeholders on the NDRP modernization program's new IAMA process and the IR document were sought both at the workshop and in the form of responses to Federal Register Docket No. FDA-2020-N-1550.

Advantages of the New IAMA Process

The external stakeholders were generally supportive of the new IAMA. Specifically, the new process was considered to improve knowledge sharing, clarity over the rationale underlying regulatory decisions (particularly the B-R table), decrease costs and increase efficiency, and promote communication both among members of review teams and between FDA and applicants.

There was widespread support for the enhanced inclusion and use of patient-experience data (PED), and for the two new roles of CDS and ME. Additionally, the IR document was regarded as accessible, easy to navigate, structured to enable location of the contents of interest, and as eliminating much of the redundancy that was a feature of discipline-specific reviews and Unireviews. Finally, it was thought that by describing clearly the rationale underlying regulatory decisions, the IR document will provide enhanced insight to international regulatory agencies that refer to FDA's findings.

Concerns and Areas for Improvement

The concerns and areas for further improvement expressed by the external stakeholders can be organized into three major themes: *transparency and independence*, *patient perspective/data*, and *clinical utility/other*.

Transparency and Independence

Transparency

Transparency regarding the processes and methods used by FDA to reach regulatory decisions is critical for the drug development ecosystem and enhances predictability by granting insight into FDA thinking, thereby facilitating the development of novel drugs.

The external stakeholders stated that the IR should be but one of several documents available, with appropriate redactions, to the Applicant, the general public, and other stakeholders. The identification of key review issues, maintaining the level of detail by limiting deletions to redundant information repeated across discipline-specific reviews, and preserving the insights of individual reviewers were cited as critical considerations. FDA was encouraged to establish mechanisms of ensuring that all material information is captured in IR documents, while protecting all confidential commercial information and trade secrets.

Furthermore, FDA was recommended to make available to the general public review documentation for supplementary, as well as original, drug marketing applications.

To promote the development of novel drugs, it was proposed that the redacted information in IR documents be provided to the Applicant. It was noted that some IR documents have redactions in unexpected sections, e.g., the summary of clinical studies. The external stakeholders expressed that information related to a drug's safety or efficacy should not be protected in this way.

Rather than include merely excerpts considered relevant by FDA, it was suggested that the 2018 policy change be reversed and enhanced summaries of administrative correspondence (with appropriate redactions), including presubmission correspondence, and meeting minutes again be included in action packages. Rationale provided indicated that information is vital for drug development because it grants insight into FDA's thinking. This is particularly important for areas in which available guidance is sparse, for instance, the use of RWE in drug marketing applications.

The external stakeholders emphasized the importance of preserving dissenting opinions and scientific disagreements. This view is shared by FDA. In the new IAMA process, signatory authorities aim to normalize scientific disagreements within the review team and to empower the individual reviewer to ensure that their voice is both heard and documented.

FDA has committed to include dissenting opinions in the IR document. However, this may not be sufficient to document, for instance, a reviewer's skepticism over an applicant's explanation for missing data or statement of efficacy. Such would not be considered a dissent and so would not be documented. These, together with key review issues raised at the B-R scoping meeting, or potentially even earlier at the pre-NDA (new drug application) meeting, should be included in the IR document.

The IAMA process aims to avoid the concept of groupthink, with the underlying rationale that scientific disagreements are useful for determining, for instance, the breadth of the indication of a drug. To this end, it was suggested that a review team include one or more *designated contrarians* (colloquially, 'devil's advocates'), whose role would be to argue against the team's viewpoints and decisions. Their dissents could be formalized in a summary statement in the *Additional Analyses and Information* section of the IR document.

FDA was encouraged to include details sufficient to enable understanding of the basis of scientific disagreements by ensuring that the issues and decision points are outlined in the *Additional Analyses and Information* section of the IR document. Furthermore, the corresponding conclusions should be stated clearly and succinctly.

The need for a means of preventing any documented scientific disagreements from being taken out of context by a nonspecialist audience was recognized.

The external stakeholders expressed a desire for full transparency from FDA on all matters related to the regulatory decision-making process, including the rationale underlying the decision. In particular, the data used in the determination of whether the standard for substantial evidence of effectiveness has been met should be stated clearly and in a consistent location in the IR document, thus enhancing knowledge management.

The identification of review issues as early as possible in the review process is beneficial because it brings them to the attention of the signatory authority. The external stakeholders requested that issues raised be documented in Section II (*Interdisciplinary Assessment*) of the IR and described in detail in Section III (*Additional Analyses and Information*). Those issues could then be communicated to the Applicant at the midcycle meeting, which is scheduled early in the review process, providing context to FDA's questions, and further promoting transparency over the basis for the regulatory decision.

There was a desire for greater transparency over matters related to labeling and postmarketing requirements, including whether new tools and/or technologies were used to inform the decisions. If possible, the rationale for the contents of crucial elements of the package insert should be described in the IR. Also, information requests from FDA to applicants should state the reason for the request, the FDA division or center from which the request originated, the Applicant's response to the request, feedback from the consulting reviewer, and how the request was resolved.

Regarding the efficiency and effectiveness of the new IAMA process, there was interest in knowing whether it has enhanced the communication between FDA and applicants. For example, has it reduced the number of questions received from applicants during the drug review process?

The external stakeholders also inquired as to the effectiveness of the IAMA process in terms of workflow and workforce management and promoting collaboration. Moreover, have the new roles of CDS and ME increased efficiency and enhanced the usability of the IR document? Also, after the new IAMA process has expanded to other divisions, will all IRs receive such support? If not, how will CDS and ME support be allocated? Additionally, there was interest in any new processes or information technology systems that FDA has created or reengineered to support the IAMA initiative.

Retention of Relevant Information

The external stakeholders stated that the information and insights captured in reviews of drug marketing applications are critical for several sectors of the public health and research community. These include clinical research; public health research; regulatory science research; health policy research and other policy research; and the development of patient and clinician decision-making tools for use of medical products. For this reason, the external stakeholders expressed a desire that all pertinent information be retained in drug reviews and, if possible, that FDA establish mechanisms to ensure that this is so.

FDA was encouraged to retain information formerly included in drug reviews. For instance, former discipline-specific review memos providing useful information (e.g., information related to why a request was made and why FDA found the response acceptable) that are no longer included in the IR document should be restored. Also, the memos should be publicly available.

The totality of the evidence used by reviewers used to support the approval decision—including documentation of decision-making processes and agreements across the development process as well as consultations internally or with outside experts—is critical for drug development and there was interest in it being made available to stakeholders. For example, the drug development community has benefited from the availability of internal FDA consultative reviews by the Division of Epidemiology in the Office of Surveillance and Epidemiology of RWE in marketing applications for oncology drugs.

It was recommended that FDA retain, in publicly available documents, details on the design of individual studies; the use of new drug development tools, data sources, and technologies; and how FDA applied such data to regulatory decision-making.

The appendices of Unireviews contained critical information, the level of detail of which, as well as any independent analyses, was requested to be maintained. Also, the external stakeholders asked that data moved to the *Additional Analyses and Information* section of IR documents as well as other information (including, for the Applicant only, redacted material) remain publicly available without the need for a Freedom of Information Act (FOIA) request. (Note that information in the *Additional Analyses and Information* section of the IR document is publicly available.) Also, with no requirement for a FOIA request, applicants should have access to chemistry, manufacturing, and controls–related content redacted to protect intellectual property.

The external stakeholders requested that FDA add to IR documents information on several aspects of clinical trials and the review process. FDA was encouraged to describe in detail the design of clinical and

nonclinical trials and its approach to analyzing the data from those trials. Furthermore, FDA should reference information on novel tools and technologies used in drug development and review them in dedicated sections of the IR document. There was a desire for access to information (possibly by provision of references) on study design and innovative tools and approaches (e.g., biomarkers, RWE, digital health tools, models, and simulations) used in clinical trials, protocols, and clinical study reports not in the IR document. Moreover, the external stakeholders encouraged FDA to describe how such data were leveraged for regulatory decision-making or if they were included in the labeling.

FDA was encouraged to consider including information on exclusivity (e.g., orphan drug designation, NME, and pediatric exclusivity), review designation, and priority review vouchers, as well as on key discussions and special attributes of the application. Because of its utility for understanding the FDA decision-making process, documentation from previous approvals of a drug would make a useful addition to the IR document. Finally, inclusion in the IR document of key information on topics of discussion by the review team that did not become review issues would be welcomed by the drug development community.

The format in which data are available was a topic of interest. It was stressed that pertinent information should be made available in an electronic format other than Portable Document Format, and which is both downloadable and amenable to searching for contents of interest. This would facilitate knowledge sharing within FDA and with a wide range of external stakeholders, as well as review of similar issues across applications. The eXtensible Markup Language format was suggested for this purpose.

There was some concern over the deletion or reduction in the importance/prominence of review components. Some of the external stakeholders stated that the Clinical Study Report summary in the IR document is short and lacks tables and figures, and the Review of Relevant Individual Trials has lost detail and nuance (particularly related to the efficacy and safety data from individual trials). These concerns notwithstanding, Table 3 in the IRT document lists pertinent information on the clinical studies included in the review (Figure 1).

Figure 1. Example Summary of Clinical Trials Table from the IRT Document

Table 1. Clinical Trials Submitted[1] in Support of Efficacy and Safety Determinations for [Drug]

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized[3]	No. of Centers and Countries
Study X NCT #	Patients with moderate to severe disease as defined by XX baseline or clinical characteristics	DB, R, PC, PG, MC	Drug X mg BID (N=X), XX weeks Drug Y mg BID (N=X), protocol-specified dose adjustment permitted; XX weeks. Placebo (N=X), XX weeks Duration:	Primary: clinical response[2] at week XX, as defined by XX. Secondary: clinical response at week X, as defined by XX.	YYY; ZZZ	X centers in Y countries
Study Y NCT #	Patients completing X weeks treatment or withdrawn due to treatment failure in Study X; or non-responders after completion in studies X and Y	OL, LTE	Part 1: Drug X mg (N=X) Drug Y mg (N=X) Drug Z mg (N=X) Part 2: Drug X 25 mg (N=X) Active control Y mg (N=X) All taken orally BID with Drug Z X mg Duration:	Long-term durability of efficacy and long-term safety	YYY; ZZZ	X centers in Y countries

Source: FDA analysis vs. Applicant's source.

Abbreviations: BID, twice daily; DB, double-blind; LTE, long-term extension study; MC, multicenter; NCT, National Clinical Trial; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized

[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

[2] Clinical response is defined by [ ].

[3] If no randomization, then replace with "actual enrolled."

Documentation

The external stakeholders had several concerns related to the formatting of IR documents. The amount of material in IR documents cut and pasted from applicant submissions should be minimized; ideally, the practice should be eliminated. Also, images of tables are unhelpful because they are not searchable, reducing usability. The text of IR documents should be searchable and plain language should be used alongside scientific language to enhance transparency. For example, alongside "$\log_{10}$ change in HIV-1 RNA level from Day 1 to Day 8," a plain-language statement describing the effect of any such change on how the patient feels or how long they are likely to survive would ensure broad and equal utility for those who study, develop, prescribe, and/or take therapies regulated by FDA. The pages in IR documents should be in portrait, not landscape, orientation. Finally, FDA should ensure that document processing does not eliminate hyperlinks, including those in the Table of Contents and cross-references to figures, tables, and sections.

There were several proposed structural changes to the IR document. The external stakeholders suggested that, to enhance clarity, the *Summary of Regulatory Action* section be renamed *Overall Conclusions and Recommendations for Regulatory Action* and that the *Approach to Review* section be renamed *FDA Approach to Clinical Review* or *Overview of Clinical Trials*. The addition of subheadings to the *Intrinsic Factors* section (e.g., hepatic impairment) would improve the ability to locate contents of interest. Also, adding a chronologically sorted table of submissions and meetings to the *Regulatory History* section, followed by a narrative of the outcomes, would be useful.

It was proposed that sections focusing on the following be added to the IR document: risk evaluation and mitigation strategies applied, marketing status of the product, reviews of information related to combination products, FDA information requests, bridging/leveraging (according to FDA's December 2019 Guidance for Industry *Bridging for Drug-Device and Biologic-Device Combination Products*) with a summary of FDA determination of acceptability, clinical requirements and required clinical data or why clinical data were unnecessary, human factors and required human factor data or why human factor data were unnecessary, reviews of all issues pertinent to approval, presubmission correspondence, and a nontechnical abstract.

There were a number of recommendations related to the issues faced by developers of combination products (CPs). Provision of full reviews on topics pertinent to CPs (e.g., the design, population, endpoints, and statistical analysis methods of CP pharmacokinetic comparability studies) would assist future CP development by enabling applicants to address FDA's concerns proactively. Moreover, there should be a specific section for CP- and device-related content, including FDA information requests. Other key information on CPs that would be useful in IR documents includes summaries of delivery device requirements, essential performance requirements for these devices and CPs, design verification and validation activities, CDRH and DMEPA review checklists, release testing, quality system-related information, manufacturing information, and labeling requirements. Finally, FDA should provide review memos for all NDA/BLA (biologics license application) supplements for new and modified delivery devices or device constituent parts, which is not always the case at present.

It also was recommended that discussion of digital recording methods used in clinical studies would be a useful addition to IRs.

Finally, if the new IAMA process is extended to cover generic products, clarification of the decision on a regulatory pathway and the sameness criteria applied for complex generic products that are CPs would be useful to developers of the latter.

Other Sources of Information

Summaries of or at least links to the minutes of advisory committee (AC) meetings should be provided in IR documents. Also, information on the outcomes of AC meetings and late-cycle discussions should be moved to the *Advisory Committee Summary* section and included in the *Administrative and Correspondence Documents* portion of the review package. The external stakeholders expressed a desire that details on the consistency of regulatory decisions over time for repurposed drugs be available. Finally, addition of links to relevant clinicaltrials.gov entries and of the PubMed identification numbers of articles published in academic or medical journals to the references section would enhance the usability of the IR document.

Patient Perspective/Data

The external stakeholders made a number of suggestions related to the inclusion of PED in the IR document. At present, the degree of inclusion and analysis of PED is inconsistent; therefore, FDA was encouraged to ensure that PED are included in the IR document and that the PED table is fully populated. Different versions of the PED table have been used across IRs, so it was proposed that FDA consider mechanisms to ensure that PED—as well as other types of nontraditional data, such as RWE—are provided in a complete and consistent format and in dedicated sections of the IR document. Furthermore, FDA should discuss comprehensively how PED were used to incorporate the patient's perspective at all stages of drug development. Importantly, such information should be conveyed in plain language to ensure the utility of IR documents for a wide range of stakeholders.

Other proposals related to how PED are applied in the new IAMA process. To promote transparency, the external stakeholders recommended that IR documents incorporate details of the means by which PED were collected and how they influenced the regulatory decision-making process and the B-R analysis.

FDA has indicated that applicants should populate the PED table. However, some PED are not provided by applicants, e.g., the discussions at and the outcomes of *Patient-Focused Drug Development* meetings and *Voice of the Patient* meetings. Such non-applicant–derived PED are important and should be included in the IR document (even mentioning their existence would be useful) and taken into consideration in the B-R analysis and in regulatory decision-making. Additionally, use of PED of enhanced robustness would increase their value both for FDA review of products and for the patients themselves.

Regarding how the use of PED in the new IAMA process could be improved, the external stakeholders suggested that FDA encourage use of the PED form, which is populated sparsely or not at all in some IRs. Also, it was proposed that PED forms be made available for nonapproved products. Moreover, FDA was encouraged to incorporate into IR documents analyses of PED as well as a PED narrative and a description of how the PED were applied in the review. To ensure that patients' experiences and needs are reflected in the assessment, the linkage between the PED used in a review and the regulatory decision should be clearly expressed in the B-R assessment and the PED table.

A further suggestion was to outline and integrate into the review workflow the following *core* PED:

- *Description*: A brief description of the type(s) of PED, study objective, design, and methods for collection (e.g., focus group, advisory boards, listening sessions, testimonials, survey, one-on-one interviews, clinical outcome assessments, patient stakeholder meetings, and FDA-led patient stakeholder meetings), including a description of who submitted or collected the data (e.g., sponsors, patient organizations, and/or FDA).
- *Assessment considerations*: Information on how FDA considered the PED and to what extent, as well as on which aspects of the review and regulatory decision the PED informed (e.g., B-R assessment, review of the clinical study design, endpoint selection, other aspects of drug development, and labeling or other patient communications) as well as how the PED were weighted in relation to other data considered, and discussion of the decision-making process in the B-R framework or other section of the IR document.
- *Exclusion rationale*: If PED were not considered in the context of a regulatory decision, rationale for their exclusion and criteria applied by reviewers to assess their utility (e.g., PED were not representative of the patient population).

Integration of the above into the review workflow would promote consistency in how the PED table is populated and ensure inclusion of the minimum amount of information needed to render it informative and meaningful. Finally, FDA's improvements in conveying how PED data influenced its decision-making should be described clearly and in plain language.

Clinical Utility/Other

An important use of FDA drug reviews is in informing the development of clinical practice guidelines. To strengthen those guidelines, the external stakeholders recommended that the B-R analysis be written in plain, rather than technical, language. For the same reason, FDA should ensure that sufficient information is retained in IRs because not all (even pivotal) trials are published, and in many cases there are marked discrepancies between the information in the label (particularly on safety/toxicities) and that published in medical journals. Therefore, IRs are important sources of vital data. FDA was encouraged to prioritize publishing reviews from cases where new drug development tools or novel sources of data were incorporated into submissions.

The external stakeholders encouraged FDA to modify the content of the IR document to enhance its clinical utility. FDA was urged to not ignore the findings of clinical trials that are not adequate and well-controlled, because such information can be highly informative in the context of formulating and revising clinical practice guidelines. Additionally, IR documents should include comprehensive information on expedited programs and on the regulatory history of the candidate drug. The latter is compiled by external regulatory intelligence agencies to enable searching for and cross-comparison of past regulatory precedent by stakeholders in industry. Moreover, it would be useful for driving the planning of future strategies and would enable previous failures to be avoided.

Finally, the external stakeholders noted that the clinical utility of IR documents would be increased by the inclusion of sections detailing reviews of innovative tools (e.g., biomarkers or RWD) used in the development or evaluation of the candidate agent. It would also be helpful to incorporate information on trials of multiple unrelated drugs that made use of a single control group, a situation common in certain fields, such as neurology. This may not be obvious to a reader of a single journal article on one of those trials.

Statutory Considerations

The new IAMA process, including the content of the IR document, must comport with the stipulations in the Food and Drug Administration Amendments Act of 2007 (2007 FDAAA). Specifically, 21 USC Section 355(l) mandates a summary review that documents conclusions of all review disciplines, noting any critical issues and disagreements with the Applicant and within the review team and how they were resolved, recommendations for action, and an explanation for any nonconcurrence with review conclusions. The decision document must include a separate review or addendum to the review if disagreeing with the summary review. Identification by name of each FDA officer or employee who participated in the decision to approve the application is mandated. Finally, scientific review of an application is considered the work of the reviewer, and once final, it cannot be altered by management or the reviewer.

To sum up, the 2007 FDAAA assumed the preparation of individual scientific reviews, including disagreements, and was explicit about the need for these reviews, which are the work of individual reviewers, to be published in an unaltered form.

The external stakeholders noted that it is not obvious that IRs will comport with the plain text of 21 USC Section 355(l). If the plain text is deemed unambiguous, FDA's interpretation of the text would not be granted deference. If the content of IRs conflicts with the clear language stipulation of FDAAA, they may be subject to scrutiny. Finally, it is essential that IRs, as a matter of law, adhere closely to the spirit and letter of the statute.

FDA Staff Perspectives

Challenges

Collaborative writing is challenging, in part because the process differs from the discipline-specific writing required for Unireviews, and as a result of the need to preserve and promote equal voice and the perspectives of individual reviewers. This can be overcome by reaching agreement on how review-team members will edit each other's work, by holding early and regular collaborative meetings attended by review-team leadership, and by participating in appropriate training and the accumulation of experience.

Benefits

The IAMA process promotes communication and collaboration among review-team members on review issues, which can therefore be identified, and labeling matters considered early in the process. Moreover, the amount of writing required is reduced, and the writing is more intentional, allowing reviewers more time for critical thinking. Additionally, the process promotes early leadership involvement in reviews.

Unireviews tended to document the *review process*, whereas IRs focus on the *review thought process*, providing stakeholders insight into the reasoning underlying regulatory decisions.

The IR template is more streamlined compared to that for Unireviews, helping with locating sections of interest, and the amount of redundant information is decreased. The IAMA also allows reviewers to focus on their respective areas of expertise and thus promotes critical thinking. Phased implementation allows feedback-based tailoring of the IAMA process over time. Finally, the new roles of CDS and ME alleviate the burden on the review team.

Paths Forward

The IAMA process should continue to be refined and adapted (such as by enhancing its searchability), and be expanded to encompass other types of applications, thus promoting consistency. Such expansion would require additional resources, including the critical support of review teams by the CDS and ME.

A modular template would assist with expansion of the IAMA to other types of applications. The utility of the IR document could be enhanced by inclusion of other types of information, such as the findings of advisory committees.

Communication with sponsors on the content of the template and on the way in which disagreements are documented would increase transparency and the level of confidence in the IAMA process. The latter could also be enhanced by communicating and celebrating successes.

It is important to strike a suitable balance between the desire for a streamlined, usable document and maintaining the high level of detail that was a feature of Unireviews. Further rejection of discipline-specific thinking would be useful; for instance, the clinical review can inform not only safety but also efficacy.

Concluding Remarks

One of the goals of the NDRP modernization is to implement issue-focused, integrative team-based approaches to assessing the safety and efficacy of drugs. The IAMA, one of many components of the NDRP modernization, aims to identify key review issues early and in an interdisciplinary way. The IR template is structured to make clear the key review issues, explain the rationale for regulatory decisions, retain differences of opinion that arose during the review process, and promote equal voice. As of the date of the public workshop, 17 CDER divisions have transitioned to the new IAMA process.

Feedback shows that the IR documents are used by a diverse set of external stakeholders. The IAMA process has been, and continues to be, refined based on that feedback as well as the experience of FDA staff. External stakeholders voiced concerns related to transparency over scientific disagreements, loss of useful information, the accessibility of IR documents, and use of PED.

FDA will continue to expand the IAMA to other divisions and to new types of marketing applications. FDA is committed to addressing the concerns of external stakeholders as expressed at the workshop and in response to the Federal Register docket, with the aim of further refining the IAMA process to ensure that the drugs and biologics approved for use in the United States are both safe and effective.

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