

NEW DRUGS REGULATORY PROGRAM MODERNIZATION:

IMPLEMENTATION OF THE INTEGRATED ASSESSMENT OF MARKETING APPLICATIONS

A VIRTUAL PUBLIC WORKSHOP

OCTOBER 30, 2020 | 9:00 AM – 3:00 PM | VIA WEBCAST ONLY

Welcome!

- ✓ *If you are unable to hear, please adjust the volume setting on your personal computer.*
- ✓ *Submit questions using the “Q&A” feature in Zoom. All questions will be gathered and reviewed. If time permits, questions may be addressed during the workshop.*



9:00 AM	Introduction to the Integrated Assessment: Presentations from the Integrated Assessment Workstream Welcome & Introduction to the Modernization - Peter Stein, MD Rationale for Development/Core Design Features - Kerry Jo Lee, MD & Nancy Sager Implementation - Rhonda Hearn-Stewart, MD External Feedback: Synthesis & Emerging Themes - Yoni Tyberg, MS, PMP
10:15 AM	BREAK
10:30 AM	External Stakeholder Perspectives: Panel – Meeting the Needs of External Stakeholders Moderated by Sarah Connelly, MD, and John Farley, MD, MPH
12:00 PM	External Stakeholder Perspectives: Open Public Comments Moderated by Rhonda Hearn-Stewart, MD
12:30 PM	LUNCH
1:30 PM	FDA Perspective: Integrated Assessment Panel – Experience with the Integrated Assessment Moderated by Yoni Tyberg, MS, PMP
2:45 PM	Wrap-Up and Next Steps Kevin Bugin, MS, PhDc, RAC
3:00 PM	ADJOURN



Introduction to the Integrated Assessment: Presentations from the Integrated Assessment Workstream

9:00 AM – 10:15 AM



Welcome & Introduction to the Modernization

Peter Stein, MD

Director, Office of New Drugs, CDER,
US FDA

NDRP Modernization Vision is built of strategic objectives achievable through the workflows





NDRP Modernization: Rationale

Observed . . .

- Rapid and sustained growth in the volume of drug development activity
- Increased complexity of innovative therapies under development
- Greater availability of observational and other “real world” data
- Increased public engagement in FDA activity
- Persistent budget constraints
- Talent shortage

Identified Need for . . .

- Process simplification and technology-enablement
- Deeper subject matter expertise, evolution in regulatory policy and guidance, introduction of new analytical techniques, and a tighter structural alignment
- Interdisciplinary approach to drug reviews and improvements in how OND communicates regulatory decisions and their underlying rationale
- Flexibility most appropriately to leverage data sources for review and surveillance activity
- Renewed focus on how OND attracts and manages talent while fostering a world-class working environment



NDRP Modernization: Strategic Objectives

Objectives

Guiding principles for modernizing the NDRP

Scientific Leadership

Grow our scientific expertise and clarify pathways to regulatory approval.

Integrated Assessment

Critically, collaboratively and consistently assess whether information in submissions meets legal and regulatory requirements.

- We will take a new approach to document our assessments, developing a more integrated, inter-disciplinary document to foster collaboration and reduce redundant information.
- Our assessments will be rigorous, clinically relevant, focus on the key issues, and incorporate the patient perspective.

Benefit-Risk Monitoring

Systematically monitor the balance of benefits and risks of approved drugs pre- and post-approval to effectively protect the American public.

Managing Talent

Attract, develop, and retain outstanding people.

Operational Excellence

Standardize workflow, business processes, roles, and responsibilities to improve operational efficiency and enable our scientists to focus on science.

Knowledge Management

Facilitate the identification, capture, distribution and effective use of institutional knowledge.



Rationale for Development & Core Design Features

Kerry Jo Lee, MD

Associate Director for Rare Diseases (Acting),
Office of New Drugs, CDER, US FDA

Nancy Sager

Director, Division of Information Disclosure Policy
Office of Regulatory Policy, CDER, US FDA

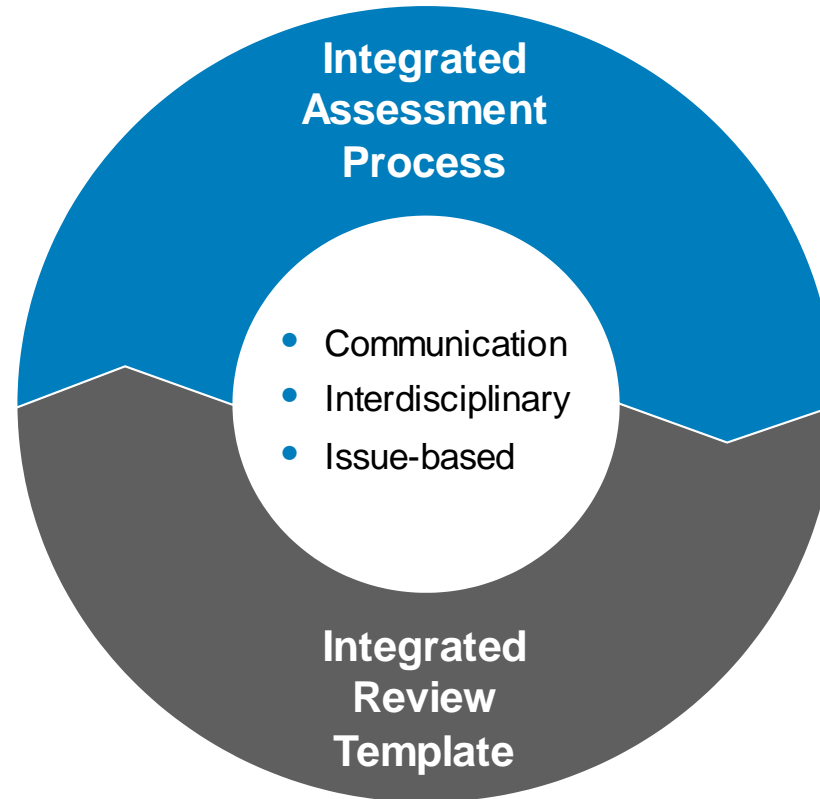


The Agency identified challenges with the prior process & template

- Discipline-specific reviews lead to redundant work and desire for additional clarity on rationale of interdisciplinary review issues
- Reviews centered by disciplines rather than interdisciplinary collaboration on review issues
- Reviewers asked for support to spend more time on critical thinking instead of editing or other programming tasks
- A need for better knowledge management



New Integrated Assessment of Marketing Applications



Key issues are generally comprised of issues that inform or characterize our **assessment of benefit and risk**.



Goals for Integrated Assessment of Marketing Applications



Team-based, scientifically rigorous review with strong **interdisciplinary collaboration**



Efficient, issue-focused assessment supported by new roles



Enhanced communication within the review team and with external stakeholders



Clear articulation of the basis for regulatory decisions



Increased support for review teams, including clinical data scientists, medical editors, on-demand resources, trainings, ambassadors and peer support, and seamless workflow management



Overview of New Components of the Integrated Assessment

Integrated Assessment Components



New **process** to enable **early identification of review issues** and **interdisciplinary collaboration**



New **template** to enable **issue-based** and **inter-disciplinary** review documentation



New roles: **Clinical Data Scientist** and **Medical Editor** to enable **more time** for critical thinking



The new Integrated Review is a three-part document

Executive
Summary



Recommended lead authors:
Signatory Authority, CDTL/clinical reviewer, and OND Division Director

Interdisciplinary
Assessment



Clinical, clinical pharmacology, clinical microbiology, pharmacology/toxicology, statistical, and virology reviewers; other subject matter experts

Appendices



Regulatory Project Manager; clinical, clinical pharmacology, clinical microbiology, pharmacology/toxicology, pharmacometrics, statistical, and virology reviewers; other subject matter experts



- Acts as a brief **summary of Regulatory Action**
- Provides **overall agency assessment, overview of the major decisions, & the rationale for these decisions**
- Includes the **Benefit-Risk Framework and assessment**, which summarizes the major benefits & risks assessed & how they were weighed against one another



- Describes **important data regarding efficacy, safety, clinical pharmacology, & pharmacotoxicology** providing a program overview, but also includes a **detailed interdisciplinary discussion** of key safety & efficacy issues critical to the regulatory decision
- **Integrated**, focused assessment **highlighting key issues** that the review team thinks are pertinent to the decision-making process



- Serves as a **repository of materials** that support or are vital to the summary document & conclusions in the Interdisciplinary Assessment
- Includes **supporting reviews** for the application from SMEs, **regulatory history & labeling summaries**, & division-specific **additional analysis**
- Addendum for work done that did not directly impact the decision-making process but may be helpful as a **reference for future work**

Key Points on the IA and Scientific Differences of Opinion



The Integrated Assessment (process and documentation) embraces and respects scientific differences of viewpoints

The process allows for the capture of and opportunity for early, frequent, and intensive meetings around differences of opinion

Meaningful differences on important aspects of the review, even if resolved, should be described in the discussion of key review issues or in other appropriate parts of the Integrated Review document

Differences of opinion that remain at the time of the marketing application decision can be documented as a full review of the issue in a separate write-up that resides in the Appendices



Avenues for expression of scientific disagreement & Equal Voice:

Process

- ✓ **Interdisciplinary meetings** provide a forum for early, frequent, & thorough discussions of key issues & **sharing, addressing, & discussing differences in viewpoints**

Documentation

- ✓ **Executive Summary** includes high-level description of key **scientific differences of opinion** & final decision by the signatory authority; summarizes any major **differences of opinion** & documentation for each reviewer/discipline and the rationale for the resultant regulatory action
- ✓ **Interdisciplinary Assessment** includes **discussions of differences in opinion** regarding key review issues on the review team and how scientific disagreement was addressed
- ✓ **Appendices** includes **separate reviews** written by reviewers who disagree with significant elements of the Executive Summary and Interdisciplinary Assessment sections or the marketing application decision of the signatory authority



Review Issues Section

- I. Issue
- II. Background
- III. Assessment
- IV. Conclusion

If a difference of opinion is related to a significant element of the planned action (e.g. labeling, post marketing actions, overall decision on marketing application), a separate, detailed review should additionally accompany the review document in the Appendices

- A. **Clinical Review Team Perspective**
- B. **Non-Clinical Review Team Perspective**
- C. **Signatory Perspective** (identifies which perspective the signatory aligns with & why)

New roles and well-defined responsibilities allow each review team member to focus on analysis and critical thinking



New & enhanced roles include . . .

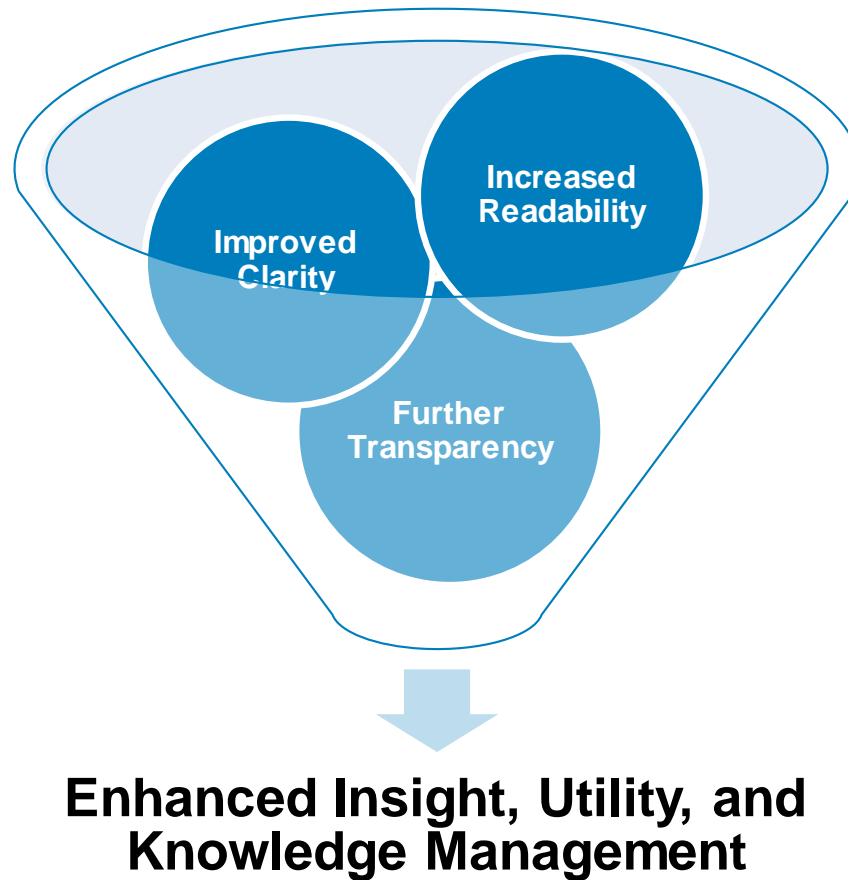


- **Medical Editor (ME):** Formats and edits the Integrated Review document so reviewers can focus on critical thinking.
- **Clinical Data Scientist (CDS):** Provides key safety tables and figures needed early in the review and, in collaboration with clinical reviewers, executes the Safety Data Analysis Plan to improve the efficiency and quality of the clinical review.
- **Enhanced Clinical and Regulatory Partnership:** Cross Discipline Team Leaders and Regulatory Project Managers utilize their respective expertise to work closely and lead the interdisciplinary review process together.

Benefits of an Issue-Focused Interdisciplinary Review



Implications of an interdisciplinary review focusing on key review issues include:





Potential Key Review Issues Related to Benefit and Risk

Examples of Issues Related to Benefit

- Acceptability of the primary efficacy endpoint
- Failure of one of multiple trials
- Failure of one component of a composite or co-primary endpoint
- Concerns regarding optimal dosing
- Evidence of the contribution of components for a fixed dose or combination product
- Subpopulation factor affecting benefit

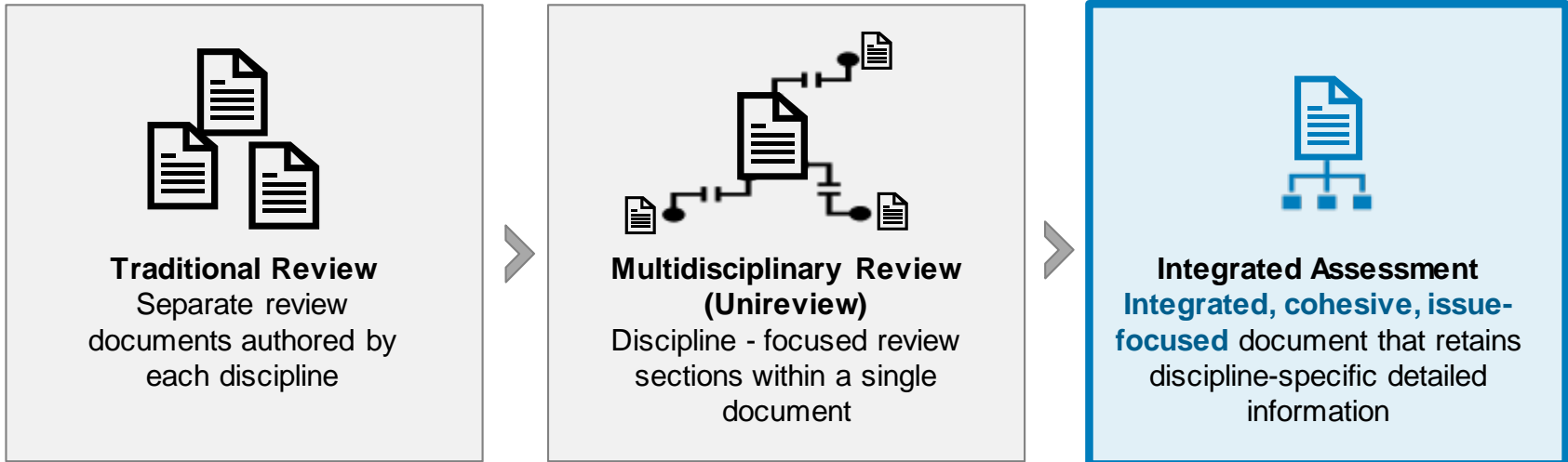
Examples of Issues Related to Risk

- Significant or serious adverse events related to administration of the drug
- Trial design that impacted the reviewer(s) assessment of causality (e.g. no placebo)
- Significant or serious adverse events related to the drug class (e.g. hypersensitivity)
- Subpopulation factor affecting risk
- Non-clinical data showing significant or serious signals that remain a concern but were not seen in clinical trials
- Considerations for the drug mechanism-of-action leading to a safety issue

Integrated Assessment moves from discipline-focused separate reviews to an integrated issue-focused document



Integrated Assessment shifts application approval decision-making to a more consistent, team-based, issue-focused process and documentation.



Challenges:

- Discipline-specific reviews, rather than issue-focused, resulted in parallel and redundant work and writing
- Redundant writing at times obscured rationale for decisions

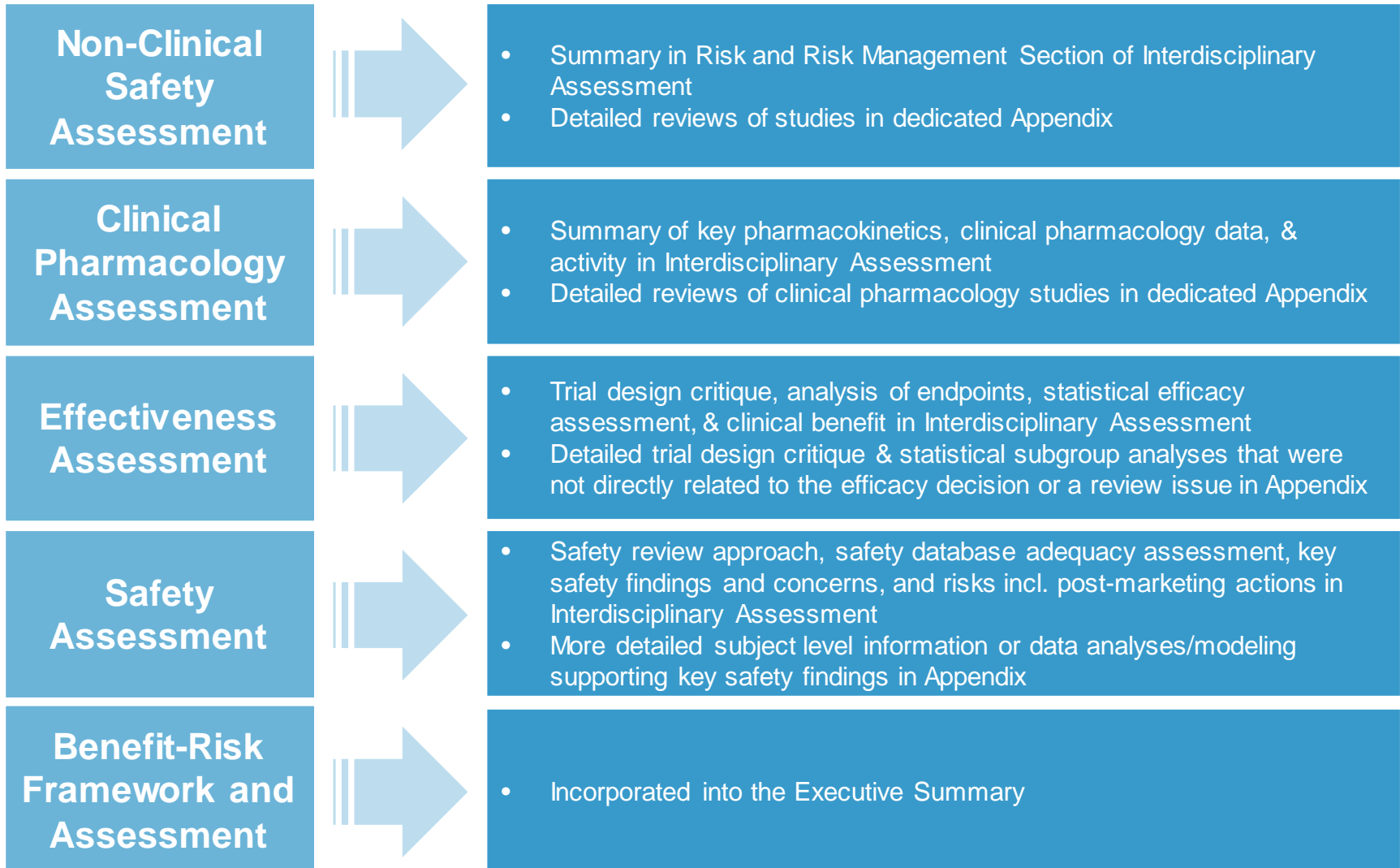
Other Type of Review: Summary Level

Relies on qualified data summaries to support approval of a supplemental application for a qualified drug use

Overall Objectives:

- Develop an integrated, interdisciplinary approach to address key review issues
- Reduce redundancy
- Improve clarity on rationale for the regulatory decision

Integrated Review documentation includes the same level of data and analyses as other review documentation



Background on the Action Package

- In approximately 2001, CDER started a proactive disclosure program to post on Drugs@FDA all action packages for original NDAs, and subsequently for original BLAs (for approvals 1/1/1998 and after)
- In 2007, the Food, Drug and Cosmetic Act was amended (FDAAA section 916) to add § 505(l)(2) to require posting of certain action packages and it also defines the contents of an action package
 - A cross-discipline team from CDER and CBER was involved in implementing FDAAA 916.
- In 2018, based on projected workload, CDER identified the need to evaluate and streamline the content of the action package.
 - the change was needed to meet the goals of timely disclosure of important drug approval information.
 - the most scientifically meaningful information and other content required by statute is prioritized and posted in a timely manner.

What is included

- Discipline/multidiscipline reviews
- Consult reviews
- Approval, Tentative Approval, Complete Response and Refuse to File letters
- Formal Dispute Resolution Request correspondences pertaining to the approval action
- Meeting minutes related to format and content of the application such as pre-NDA/BLA, BPD Type 4 and/or End of Phase 2
- Approved labeling, labels and REMS
- Division Director review and office director reviews/memos or other appropriate review signed by the Division Director or Office Director
- Officer/Employee list

What is not included

- Any checklist driven “review”
- Filing review
- Information Request (IR) emails and other emails
- Letters other than Approval, Tentative Approval, Complete Response and Refuse to File letters
- Consult requests
- Meeting minutes other than Pre-NDA/BLA related to contents and format
- Draft labeling
- Telephone consults
- Debarment and patent certifications
- Checklists/Templates (e.g., PMR/PMC development)

Content of the Action Package

Information that is not included in a posted action package may be requested via a Freedom of Information Act (FOIA) request. Instructions on how to make a FOIA request can be found on FDA.gov.

<https://www.fda.gov/regulatoryinformation/foi/howtomakeafoiarequest/default.htm>



Implementation

Rhonda Hearn-Stewart, MD
Associate Director of Implementation,
Integrated Assessment of Marketing Applications,
US FDA

Our vision for implementation of Integrated Assessment of Marketing Applications

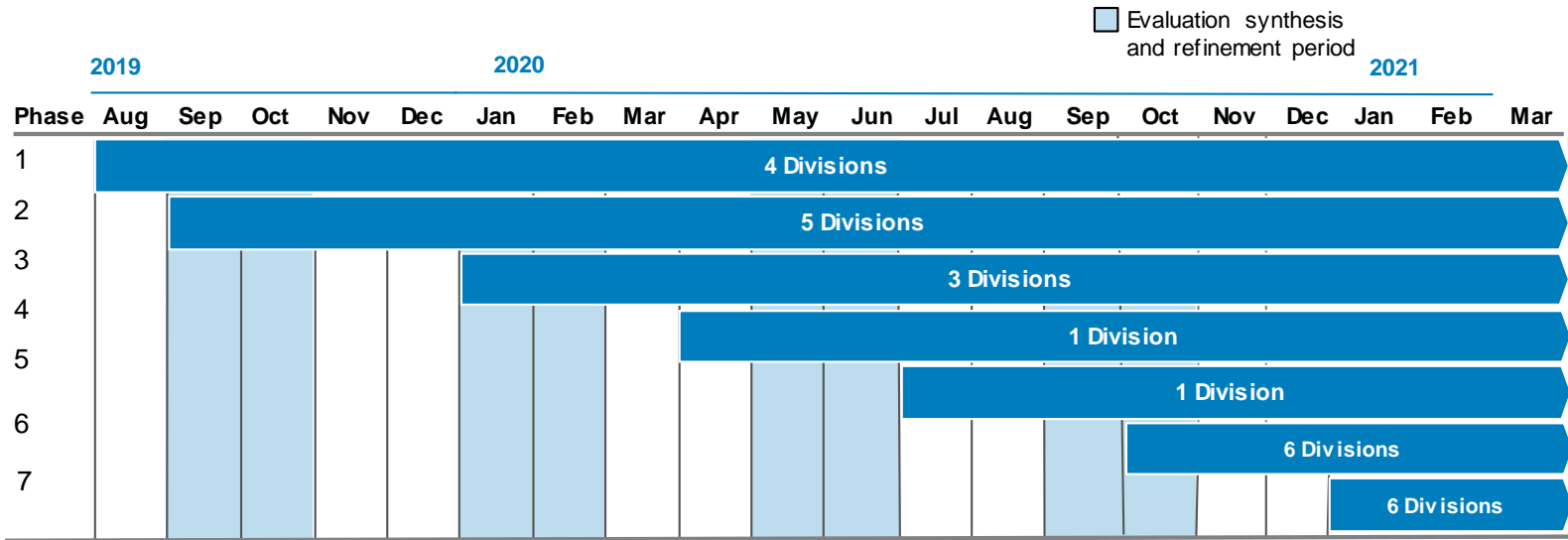


We aspire to...

- Use the Integrated Review for **all new drug marketing applications**, including supplements, in the near future
- Implement in a **phase-based manner** to enable an **iterative approach** through **evaluation, feedback, & refinement**
- **Support** successful transition of review teams through provision of ample & robust **tools, training, & resources**



Phased implementation of the Integrated Assessment



Each evaluation period consists of feedback synthesis and subsequent refinement of trainings, process, and template.

Extensive trainings, resources, and ongoing support enable successful review team transition to the new process and template



Live and self-paced trainings



Peer Ambassadors



Ongoing support and coaching by Transition Team



Quick-start Guides, Trackers, and Planners



How-to-Guides and Templates



FAQs

Phased implementation provided opportunity for feedback, evaluation, and resulting refinement of the process and template



Key feedback sources included...

- ✓ Surveys
- ✓ Focus Groups
- ✓ 1-on-1 interviews
- ✓ Feedback Portal and Repository
- ✓ Public Comments
- ✓ Federal Registry
- ✓ Meeting Observations
- ✓ Questions and comments from division and discipline roadshows, e-mail, in person feedback, and office hours



... and generated a diverse range of helpful feedback

- Additional learning and guidance is needed to best understand **how to most effectively collaborate**
- New roles (CDS, ME) are “incredibly helpful” in **driving efficiency**
- New process and template foster “**creative and critical thinking**” and **collaboration**
- Single integrated issue-based review format **reduces redundancy in writing**



We heard critical feedback on the template and process

Stakeholders expressed a need for additional learning and guidance regarding how to most effectively collaborate

Given the pace of the review process, team members requested additional guidance regarding writing collaboratively and collaboration.



“[M]ore guidance or more specifics on working together would be helpful.” – RPM



Action taken: Developed Effective Collaboration course. Co-leadership course for CDTL/RPM in development.

Team members requested additional guidance on deadlines for writing and reviewing co-authored sections of the Integrated Review document.



“Courses did not address the order in which reviewers should write or review the document (for sections that were written by more than one author)...” – CDTL



Action taken: Developed writing milestones and incorporated writing milestones into training resources and courses.

We also heard positive feedback on the process and template (1 of 3)



Positive feedback Description or quotation



New roles
(CDS, ME)
create
efficiency

- **91%** of all respondents surveyed agreed that the **Medical Editor (ME) was helpful**, especially with formatting and editing throughout the review.
 - “**Updating tables** and making sure the links work was a **huge undertaking**” by the Medical Editors. – Leadership
 - “Having medical editors is a huge help. **They helped me save my time, so I could focus on content.**” – Clinical Primary Reviewer
- **80%** of clinical primary reviewers agreed the **Clinical Data Scientist (CDS) was helpful** in conducting analyses.
 - “The **CDS is an expert in statistical software** and has been **incredibly helpful** in generating standard tables and additional analyses” – Clinical Primary Reviewer

We also heard positive feedback on the process and template (2 of 3)



Positive feedback Description or quotation



The process and template foster critical thinking and collaboration

- **72% of reviewers** surveyed **agreed that the new process enabled effective interdisciplinary collaboration** (with only 5% of respondents disagreeing).
 - “I've been around for many years, and this is the **most interaction I've had with clinical**, and the **most creative and critical thinking I've done**. I can see that the CDTL is also thinking more broadly and including stats more.” – Biostats Primary Reviewer
 - “They are distinctly acknowledging and supporting **integration**, so it is a **great improvement**.” – Division Director
- **83% of surveyed reviewers agreed** they had the time they needed to critically think through high-impact issues and their regulatory implications (with only 8% of respondents disagreeing).
 - The new issue-based approach **encourages “thinking about how your analyses tie into the bigger picture concurrently with your review.”** – Clinical Primary Reviewer

We also heard positive feedback on the process and template (3 of 3)



Positive feedback

Description or quotation



Writing a
single
integrated
review
reduces
redundancy

- “It’s great when people are actually writing in the shared template – it **helps the other disciplines avoid doing the same work . . .**” – RPM
- “There was **less redundancy . . .**” – Pharm/Tox Reviewer
- “I think the overall process is an improvement . . . you **do not have replications and redundancies** of disciplines.” – Office Director
- 5 of 6 office/division directors surveyed agreed the Integrated Review was structured around issues and **included only relevant information** (other director surveyed was neutral).
- 5 of 6 office/division directors surveyed also agreed that, from their perspective, **important information was not missing in the final work product** (other director surveyed was neutral).



External Feedback: Synthesis & Emerging Themes

Yoni Tyberg, MS, PMP

Acting Team Leader, Special Program Staff, US FDA



2019 and 2020 Federal Register Notice (FRN) Background

FDA requested public comment on the Integrated Review Template (IRT) in 2019 and 2020 to gather feedback on how the Integrated Review documentation can continue supporting our stakeholders' needs. Specifically, the FDA was interested in feedback across several key dimensions:

- 1 **Impact** of the new Integrated Review format on the stakeholder's understanding of the FDA's basis for making regulatory decisions
- 2 **Usability** and **accessibility** of information
- 3 **Recommendations** for improvement to meet needs of stakeholders
- 4 **Advantages** and **disadvantages** of the Integrated Review Template



Respondent Demographics

15 respondents submitted detailed letters.

Respondents included:

- Scientists
- Academics
- Industry
- Patient advocacy groups
- Individuals

Summary of Comments*

Potential Concerns

- Potential of groupthink
- Potential loss of detailed data and information
- Potential loss of insight into regulatory process

Benefits

- Improves clarity of review document
- Improves usability
- Drives a more holistic assessment by reviewers

Some Respondents Voiced Potential Concerns with Future Reviews



Potential Concerns

Themes	Description	Example Quote
Potential for “ grouphink ”	Potential loss of individual review perspectives, insight into reviewers’ decision-making, and differences of opinions amongst reviewers	“Eliminating the production of such review documents by the individual disciplines could lead to dangerous grouphink and inhibit the expression of important minority views.” – Patient Advocacy
Potential loss of detailed data and information	Potential loss of comprehensive information/data (e.g., clinical and non-clinical trial design, data, and analysis)	“The comprehensive information and data contained within the FDA’s action package are a valuable and unique source of data for assessing the efficacy and harm of drugs... The [IR] will result in loss of data on published and unpublished clinical trials. ” – Scientists
Potential loss of insight into regulatory process	Potential loss of information due to lack of published documents related to FDA’s decision-making rationale	“There is a potential that integrated reviews lack ... information regarding why a specific request has been made and why FDA found the response acceptable. ” – Industry



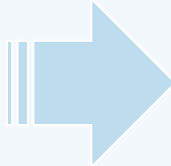
FDA is Actively Addressing Many of the Concerns Raised

Potential Concerns

Themes

FDA Actions

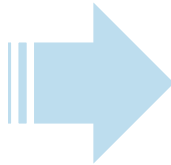
Potential for “groupthink”



FDA further defined guidelines for documentation of scientific differences of opinion within the process and template to provide clarity on avenues for discussion and documentation:

- Discussion during issue-based interdisciplinary Joint Assessment Meetings (JAMs)
- Documentation in the Executive Summary, Review Issues Section, Appendices, and discipline-specific sections within the IRT

Potential **loss of detailed data** and information



Each core discipline is still required to provide a detailed assessment of data; and additional detailed information is available in the discipline-specific appendices, which include:

- Supportive documents, assessments, and analyses
- Documents, assessments, and analyses of import to key facts, data, or conclusions of the review

Potential loss of insight into **regulatory process**



Intent behind the Integrated Review Template is to:

- Provide a standalone regulatory history section that summarizes the regulatory history of the drug product, including key regulatory decisions made throughout drug development
- Provide further insight and clarity into the regulatory process through an interdisciplinary lens



Many Respondents Expressed Benefits of the IRT

Benefits

Themes	Description	Example Quote
Improves clarity of the review document	Clearly delineates rationale for regulatory decisions; clearly outlines the benefit-risk assessment, value in executive summary	“... [use the IRT] as a comprehensive and more effective approach to providing clarity on FDA’s decisions regarding regulatory approvals ... ensure that the combination of the integrated review document and its appendices is no less comprehensive than the existing documentation...” – Industry
Improves usability	New format is easy to navigate, and the information is written in a way that should be accessible to a range of audiences	“ Usability and accessibility of the new integrated format is improved compared to the original review ... the new format begins with a succinct summary of the regulatory action and basis for the action.” – Industry
Drives a more holistic assessment by reviewers	New format provides a comprehensive summary of the input from reviewers from all relevant disciplines	“... it is helpful to have a summary of review input from all disciplines in one consolidated document rather than separated as is the approach in the current review document template.” – Patient Advocacy

FDA Continues to Evaluate and Enhance Identified Benefits

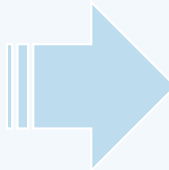


Benefits

Themes

FDA Actions

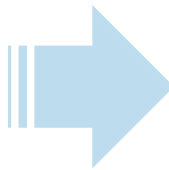
Improves **clarity** of the review document



Reviewers also agree that Integrated Review documents provide more clarity, as they focus on key review issues.

FDA intends to continue soliciting and evaluating feedback from the public to evaluate clarity of the review document.

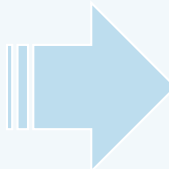
Improves **usability**



Senior FDA subject matter experts continue to evaluate completed Integrated Review documents for usability.

FDA intends to continue soliciting and evaluating feedback from the public to evaluate the usability of the Integrated Review documents.

Drives a more **holistic assessment** by reviewers



Senior FDA subject matter experts continue to evaluate completed Integrated Review documents for comprehensiveness.

FDA intends to continue soliciting and evaluating feedback from the public.

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*Please remember to rejoin us at 10:30
for the external stakeholder panel*