
U.S. FOOD & DRUG ADMINISTRATION
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
BREAK: 10:15 AM – 10:30 AM
Please remember to rejoin us at 10:30 for the external stakeholder panel

External Stakeholder Perspectives: Panel – Meeting the Needs of External Stakeholders

10:30 AM – 12:00 PM

Moderated by

Sarah Connelly, MD, Clinical Team Leader (Acting), Division of Antivirals, Office of Infectious Diseases, US FDA

John Farley, MD, MPH, Director of the Office of Infectious Diseases, Office of New Drugs, US FDA

External Stakeholder Perspectives: Panel – Meeting the Needs of External Stakeholders

Moderators:

John Farley, MD, MPH & Sarah Connelly, MD

Panelists:

Naga P. Chalasani, MD, FAASLD, *American Association for the Study of Liver Diseases*

Gregory Curfman, MD, *Journal of the American Medical Association*

Jonathan Darrow, SJD, LLM, JD, MBA, *Harvard Medical School*

Kristin Dolinski, *Pharmaceutical Research & Manufacturer's of America*

Danielle Friend, PhD, *Biotechnology Innovation Organization*

Richard J. Kovacs, MD, MACC, *American College of Cardiology*

Eleanor Perfetto, PhD, MS, *National Health Council*

Joseph S. Ross, MD, MHS, *Yale-New Haven Hospital*

Richard White, *National Organization for Rare Disorders*

Naga P. Chalasani, MD, FAASLD

American Association for the Study of Liver Diseases

FDA INTEGRATED DRUG REVIEWS
Statutory Considerations

Gregory Curfman, MD
Deputy Editor, JAMA
October 30, 2020

FDA INTEGRATED DRUG REVIEWS (IDRs)
STATUTORY CONSIDERATIONS 1

CONCISE SUMMARY

Herder M, Morten CJ, Doshi P. Integrated Drug Reviews at the U.S. Food and Drug Administration -- Legal Concerns and Knowledge Lost. *JAMA Intern Med.* 2020;180(5):629-630. doi:10.1001/jamainternmed.2020.0074

CONTROLLING STATUTE

Food and Drug Administration Amendments Act of 2007 (FDAAA), 21 USC §355(l)

DO IDRs COMPORT WITH THE STATUTORY LANGUAGE?

Corollary: Is the plain text of §355(l) of the statute unambiguous?

FDA INTEGRATED DRUG REVIEWS
STATUTORY CONSIDERATIONS 2

KEY TEXTUAL LANGUAGE IN §355(l) OF FDAAA

-A summary review that documents conclusions from all reviewing disciplines about the drug, 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 of any nonconcurrence with review conclusions.

-Decision document includes a separate review or addendum to the review if disagreeing with the summary review.

-Identification by name of each officer or employee of the Food and Drug Administration who participated in the decision to approve the application

-A scientific review of an application is considered the work of the reviewer and shall not be altered by management or the reviewer once final.

FDA INTEGRATED DRUG REVIEWS
Statutory Considerations 3

CONCLUSIONS

-On the basis of the plain text, the 2007 law (FDAAA) assumed the preparation of individual scientific reviews, including disagreements, and was explicit about the need for these reviews, which are the work of the individual reviewers, to be published in an unaltered form. (Herder et al.)

-It is not obvious that the IDRs will comport with the plain text of §355(l). If the plain text is deemed unambiguous, FDA's interpretation of the text would not be granted deference.

-If the content of FDA Integrated Drug Reviews conflicts with the clear language of FDAAA, the Integrated Reviews may be subject to scrutiny.

-It is essential that the Integrated Reviews adhere closely to the spirit and the letter of the statute.

Jonathan Darrow, SJD, LLM, JD, MBA

Harvard Medical School

Individual FDA Reviewer Insights Should Be Preserved

Jonathan J. Darrow, SJD, LLM, JD, MBA

Assistant Professor of Medicine, Harvard University
Associate Professor of Law, Bentley University

Oct. 30, 2020

Federal Register notice (8/13/20)

- Represents FDA's conclusions regarding key scientific and regulatory issues while describing any differences of scientific opinion or perspective,
- Includes any dissenting data interpretations.
- includes separate reviews of reviewers who disagree with significant elements of the Executive Summary and Interdisciplinary Assessment sections or the decision of the Signatory Authority.

- Preserve reviewer comments about:
  - weaknesses, skepticism, critique, characterizations, etc.
  - not just "disagreements"

Minor Points

- Ensure all pages are **text searchable**
- Ensure all pages are "**portrait**" (not "landscape")
- Provide specific info:
  - **programs**/pathways on the first page/Table:
    - e.g., fast-track, AA, breakthrough, QIDP, LPAD, 505(b)(2)
    - (not just "priority" vs. "standard")
  - WHO **ATC code** (not just pharmacologic class)
  - **IND** effective date

Use Plain-Language Efficacy

The primary efficacy endpoint was assessed in the Randomized Cohort. The study
to show superior antiviral activity of FTR compared to placebo when combined v
regimen over a period of 8 days. At least 140 subjects were planned to be randon
or placebo. Log_{10} HIV-1 RNA change from Day 1 to Day 8 was calculated using

Table 15. HIV-1 RNA (log_{10} copies/mL) Results for Randomized Cohort—ITT-E Population, BRIGHTE Trial

Study Visit and Imputation Used (If Any)	FTR 600 mg BID (N=201)					Placebo (N=69)				
	n	Mean	SE	Upper 95% CL	Lower 95% CL	n	Mean	SE	Lower 95% CL	Upper 95% CL
Screening	201	4.533	0.06	4.41	4.65	68	4.656	0.112	4.43	4.88
Baseline (Day 1)	201	4.437	0.069	4.3	4.57	69	4.38	0.142	4.1	4.66
Day 8	195	3.646	0.074	3.5	3.79	65	4.161	0.147	3.87	4.45
Day 8 (LOCF)	201	3.643	0.073	3.5	3.79	69	4.222	0.143	3.94	4.51
Day 8-Day 1 (LOCF)	201	-0.794	0.051	-0.89	-0.69	69	-0.158	0.075	-0.31	-0.01

Source: Statistics Reviewer's analysis
Abbreviations: BID, twice daily; CL, plasma clearance; FTR, fostemsavir; ITT-E, intent-to-treat, exposed; LOCF, last observation

- Help readers understand what this means:
  - How much longer will patients live?
  - How much better will patients feel (or function)?

Kristin Dolinski

Pharmaceutical Research & Manufacturer's of America

Danielle Friend, Ph.D
Senior Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

Implementation of the Integrated Assessment of Marketing Applications and Integrated Review Documentation

October 30, 2020

Bio Biotechnology Industry Organization

Richard J. Kovacs, MD, MACC

American College of Cardiology

Who we are

- 56,000 member, worldwide professional society.
- The trusted source for guidance on all aspects of cardiovascular care in the U.S. (90% of all practicing cardiologists) – including guidelines, expert consensus pathways, and patient facing information.
- A partner to FDA through the ACC National Cardiovascular Data Registries.

AMERICAN COLLEGE of CARDIOLOGY

What we stand for, and how we are changing in 2020 and beyond.

- In support of
  - Advancing regulatory science
  - Modernizing the drug safety system
  - Incorporating patients and their input into the total product lifecycle

- Multidisciplinary
  - Cardio-oncology
  - Cardio-diabetes
  - Cardio-obstetrics

AMERICAN COLLEGE of CARDIOLOGY

ACC Comments Regarding Integrated Assessment

Alignment

- Familiarity with interdisciplinary review of QT
- Reflects the new collaborative nature of cardiology
- Supports ACC goals regarding science, safety and patient voice

Potential Concerns

- Groupthink
  - designated “contrarian”?
- Accurately reflecting the input of advisory committees?
- Consistency across time for repurposed drugs: fenfluramine

AMERICAN COLLEGE of CARDIOLOGY

Integrated Assessment of Marketing Applications Virtual Workshop

External Stakeholder Perspectives:
Panel – Meeting the needs of External Stakeholders

ELEANOR M. PERFETTO, PHD, MS

INTERIM CHIEF EXECUTIVE OFFICER

NATIONAL HEALTH COUNCIL

PUTTING PATIENTS FIRST®
NATIONAL HEALTH COUNCIL
Celebrating 100 Years


National Kidney Foundation
The LAM Foundation
A BREATH OF HOPE
American Diabetes Association
National Alopecia Areata Foundation
COPD FOUNDATION
FIRST
Foundation for Ichthyosis & Related Skin Types
Educate • Inspire • Connect
EPILEPSY FOUNDATION
PANCREATIC CANCER ACTION NETWORK
American Heart Association
Celiac Disease FOUNDATION
celiac.org
FH FOUNDATION
ALPHA-1 FOUNDATION
THE TREVOR PROJECT
American Kidney Fund
GBS|CIDP Foundation International
National Eczema Association
Help Us Solve The Cruel Mystery
LUPUS FOUNDATION OF AMERICA
MHA Mental Health America
AMERICAN LIVER FOUNDATION
Your Liver. Your Life.
Huntington's Disease Society of America
PKD FOUNDATION
Polycystic Kidney Disease
resolve
THE NATIONAL INFERTILITY ASSOCIATION
colorectal cancer alliance
alzheimer's association
FARE
Food Allergy Research & Education
aafa Asthma and Allergy Foundation of America
Children's Cardiomyopathy Foundation
amputee coalition
Arthritis Foundation
Champion of Yes
American Cancer Society
MGFA MYASTHENIA GRAVIS FOUNDATION OF AMERICA, INC.
PUTTING PATIENTS FIRST
NATIONAL HEALTH COUNCIL
THE MARFAN FOUNDATION
Know the signs. Fight for victory
Tourette Association of America
IDF Immune Deficiency Foundation
American Foundation for Suicide Prevention
BEYOND CELIAC
awareness • advocacy • action
OSTEOGENESIS IMPERFECTA FOUNDATION
Unbreakable Spirit
WomenHeart
The National Coalition for Women with Heart Disease
cure SMA
Spina Bifida Association of America
NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders
EVERYLIFE FOUNDATION FOR RARE DISEASES
GO2 FOUNDATION FOR LUNG CANCER
NATIONAL OSTEOPOROSIS FOUNDATION
MS National Multiple Sclerosis Society
Prevent Blindness
Our Vision Is Vision
ABDA
American Behcet's Disease Association
NATIONAL PSORIASIS FOUNDATION
American Autoimmune Related Diseases Association, Inc.
ZERO THE END OF PROSTATE CANCER
prevent cancer FOUNDATION
ALS ASSOCIATION
Pulmonary Fibrosis FOUNDATION
LUNG CANCER ALLIANCE
Barth Syndrome Foundation
National Blood Clot Alliance
Stop The Clot
Mended Hearts
AMERICAN LUNG ASSOCIATION.
Fighting for Air
THE MYOSITIS ASSOCIATION
nfed
Supporting you. Supporting each other.
NATIONAL FOUNDATION FOR ECTODERMAL DYSPLASIAS
Hydrocephalus Association
Solve ME/CFS Initiative
Parent Project Muscular Dystrophy
LEADING THE FIGHT TO END DUCHENNE
NORD
National Organization for Rare Disorders
Sjögren's FOUNDATION

We support, of course…

- A coordinated review
- Improved communications among review teams
- Streamlined review of drugs and biologics
- A central place for anyone to look for information

NATIONAL HEALTH COUNCIL
Celebrating 100 Years

We'd like to ensure…

- Assessments include a specific section on how patient-experience data was considered. (Transparency)
- Risk/benefit analyses include a discussion of how the patient experience influenced the Agency's decision. (Transparency)
- A user-friendly version, a nontechnical abstract or document in layman's terms, is available to patients. (Transparency, Clarity and Readability)

PUTTING PATIENTS FIRST®
NATIONAL HEALTH COUNCIL
Celebrating 100 Years

4. Patient Experience Data

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Thank you!

Eleanor M. Perfetto, PhD, MS
Interim Chief Executive Officer
National Health Council
eperfetto@nhcouncil.org

Integrated Assessment of Marketing Applications FDA Virtual Workshop

October 30, 2020

Joseph S. Ross, MD, MHS **@jsross119**
Section of General Internal Medicine, School of Medicine
Center for Outcomes Research and Evaluation, Yale-New Haven Hospital

Important Scientific Uses for the Information Available in FDA Action Packages

- Clinical research, such as conducting systematic reviews and meta-analyses
- Public health research, such as characterizing selective publication and outcome reporting
- Regulatory science research, such as characterizing review times, evidentiary standards, patient representation and postmarket requirements
- Health policy research, such as impact of FDAAA registration and results reporting requirement and legislation creating special regulatory programs
- Health policy research, such as characterizing regulatory uncertainty or debate within FDA or between FDA and advisory committees
- Developing patient and clinician decision-making tools for medical product use

Source: Public comment on FDA-2019-N-2012-0010 available at https://www.regulations.gov/document?D=FDA-2019-N-2012-0010.

Integrated Review Documentation: Current Advantages

- Clear representation of FDA's conclusions
- Clear overview of the major decisions made during the review process
- Revised 'benefit-risk assessment' is substantially more clear
- Appreciate 'table of patient experience data'

Integrated Review Documentation: Current Disadvantages

- Only two exemplar integrated reviews provided as templates, so my assessment may not be fully informed
- However, seemingly missing was critical information from the medical review documents (or perhaps I am simply having difficulty locating this information):
  - 'Table of Clinical Studies': only 2 for one, other non-searchable – all use of images should be avoided
  - 'Review of Relevant Individual Trials Used to Support Efficacy': lost nuance and detail
  - Detailed safety information from individual trials
  - ClinicalTrials.gov registration numbers not used/linked
  - Advisory committee meeting links?
- Less clarity regarding disagreements within FDA, including whether postmarketing requirements should be imposed

NORD®
National Organization for Rare Disorders

Integrated Assessment of Marketing Applications Virtual Workshop: NORD Perspective

Rick White, Policy Analyst, NORD

Alone we are rare. Together we are strong.®

NORD, an independent nonprofit, is leading the fight to improve the lives of **rare disease patients and families.**

We do this by supporting patients and organizations, accelerating research, providing education, disseminating information and driving public policy.

Positive Aspects

- Accessibility
  - Organization
  - Well defined sections
- Features
  - Benefit/Risk
  - Endpoints
  - Regulatory History
  - Patient Experience Information
  - FDA Insight
- Incredible potential to communicate FDA's thinking to patients about their experiences.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	III.16.5: Health Outcomes Endpoints
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Suggestions for Improvement

- More examples
- Increase value for patients
  - More robust PED section
  - Connect PED to regulatory decision making
  - Qualitatively assess data provided by sponsor
- Formatting
  - Hyperlinks to enable smoother navigation
- Expand Designation Info
  - Provide more information on factors related to designation

NORD® National Organization for Rare Disorders

rarediseases.org

Alone we are rare. Together we are strong.®

rarediseases.org

Q & A

External Stakeholder Perspectives: Open Public Comments

12:00 PM – 12:30 PM

Combination Products Coalition

Integrated Assessment of Marketing Applications Virtual Workshop

October 30, 2020

CPC Representative:
Jason Lipman, Director, Global Regulatory Affairs, Devices and Combination Products, Sanofi

Combination Products Coalition

CPC Priorities

- **Integrated review memo program addresses critical combination product and device constituent part review topics**
  - **Clinical data**
  - **Human factors studies**
  - **Design verification/validation activities**
  - **Bridging-related information, etc.**
- **Continued access to all valued and currently publicly available documentation following a drug/biologic approval, including, but not limited to:**
  - **Discipline-specific review memos**
  - **Pre-submission correspondence**
  - **Inquiries and responses**
  - **Inspection report summaries or decisions to defer inspections**

Combination Products Coalition

Advantages of Current Detailed Review Memos

- Clarifies current FDA expectations for required content and testing as applied to product-specific cases – provides details that go beyond issued FDA Guidance documents and International Standards
- Allows Industry to provide complete submissions that will better address known FDA concerns for specific types of delivery devices
- Current review memo structure and traditional organization facilitates location of information [e.g., “Other Reviews” for CDRH and Division of Medication Error and Prevention Analysis (DMEPA) consulting reviews]

Combination Products Coalition

Advantages of Proposed Interdisciplinary Assessment

- Eliminates duplication of content
- Makes location of information easier (e.g., benefit risk assessments)

Combination Products Coalition

Areas for Improvement

- Providing review memos for all supplements for new/modified delivery devices
- Specific section for CP and device-related content including:
  - Summaries of CP-related pre-submission correspondence
  - CP-related Information Requests
    - reason for the request
    - who originated the request
    - sponsor response, consulting reviewer feedback and resolution
  - Summaries of CP bridging/leveraging along with determination of (non)-acceptability
  - Summaries of CP clinical requirements/submitted clinical data or why not necessary
    - Incl. PK comparability studies, real-life patient handling studies
  - Summaries of HF requirements/submitted HF data or why not necessary
  - Summaries of delivery device requirements, EPRs, Dver/Dval activities, CDRH and DMEPA review checklists, release testing, quality systems, manufacturing, labeling requirements, etc.

Combination Products Coalition

Thank you

GILEAD
Creating Possible

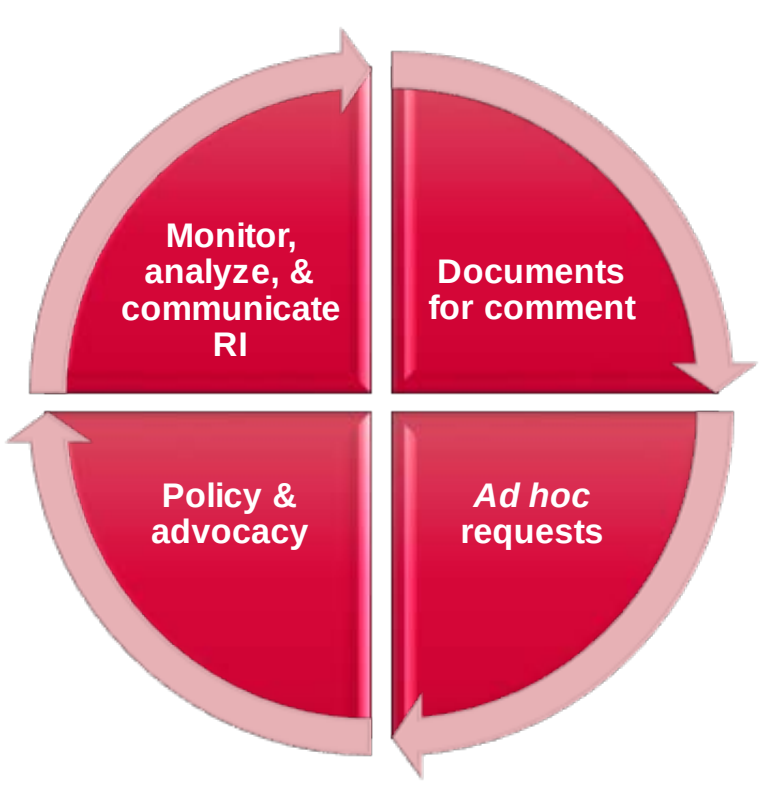
FDA Virtual Workshop: Integrated Review Documentation

Emily Huddle
Senior Manager Global Regulatory Policy & Intelligence
Gilead Sciences

FDA Topics/Questions

1. We are interested in preserving for stakeholders what they find most useful in FDA reviews.
   a) Comparing the integrated Review to previous reviews, is there any information you are having difficulty locating?
   b) Are you able to use the Integrated Review for the same purpose that you used previous reviews? If not, please provide specific examples.
2. We are interested in specific recommendations about any areas of the Integrated Review documentation of the Integrated Assessment that can be improved to meet the needs of stakeholders.
3. We are interested in stakeholders' views regarding the advantages and disadvantages of an interdisciplinary assessment presentation of key review issues and resulting integration of the assessments of multiple disciplines into a single Integrated Review document.

Regulatory Intelligence



"The act of gathering and analyzing publicly available regulatory information. This includes communicating the implications of that information, and monitoring the current environment to shape future regulations, guidance, policy, and legislation."

-US DIA RI WG

Regulatory precedent

Drive planning of future strategies

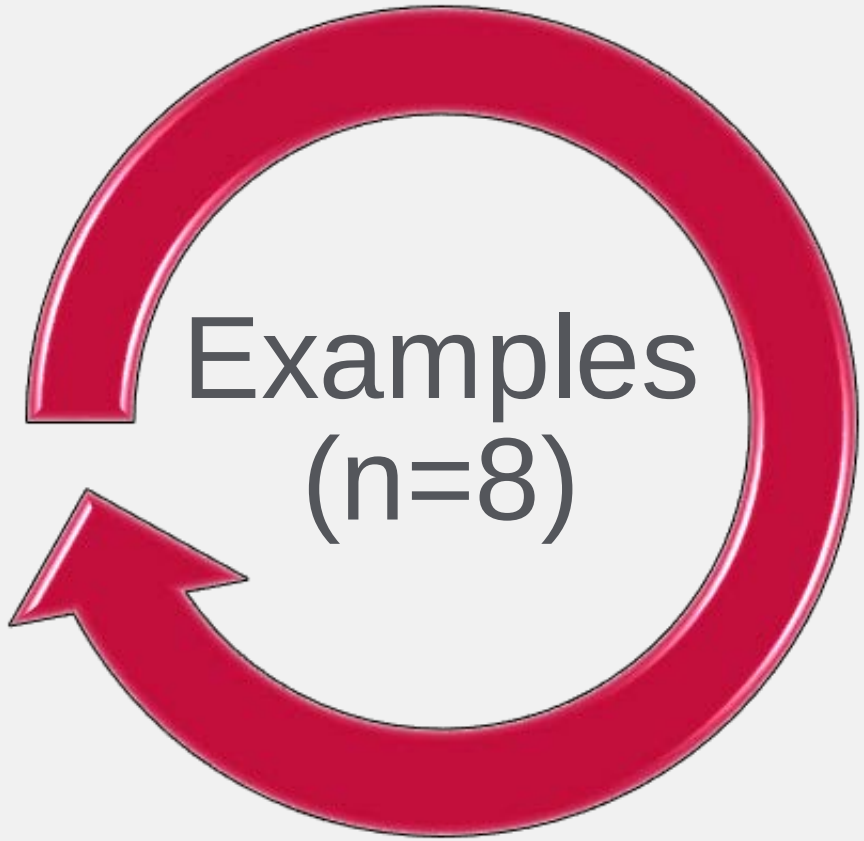
Avoidance of past failures

Drugs@FDA: FDA-Approved Drugs

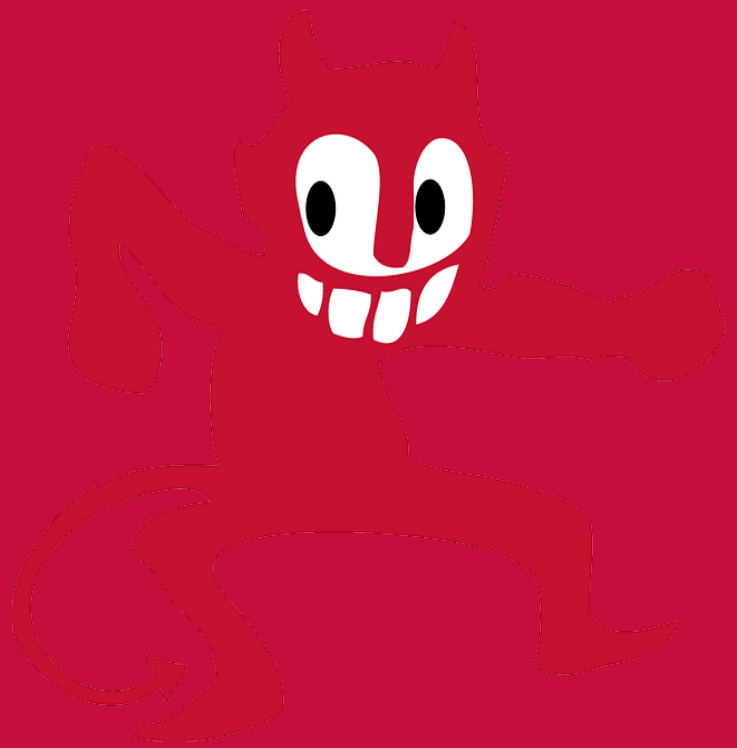
SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

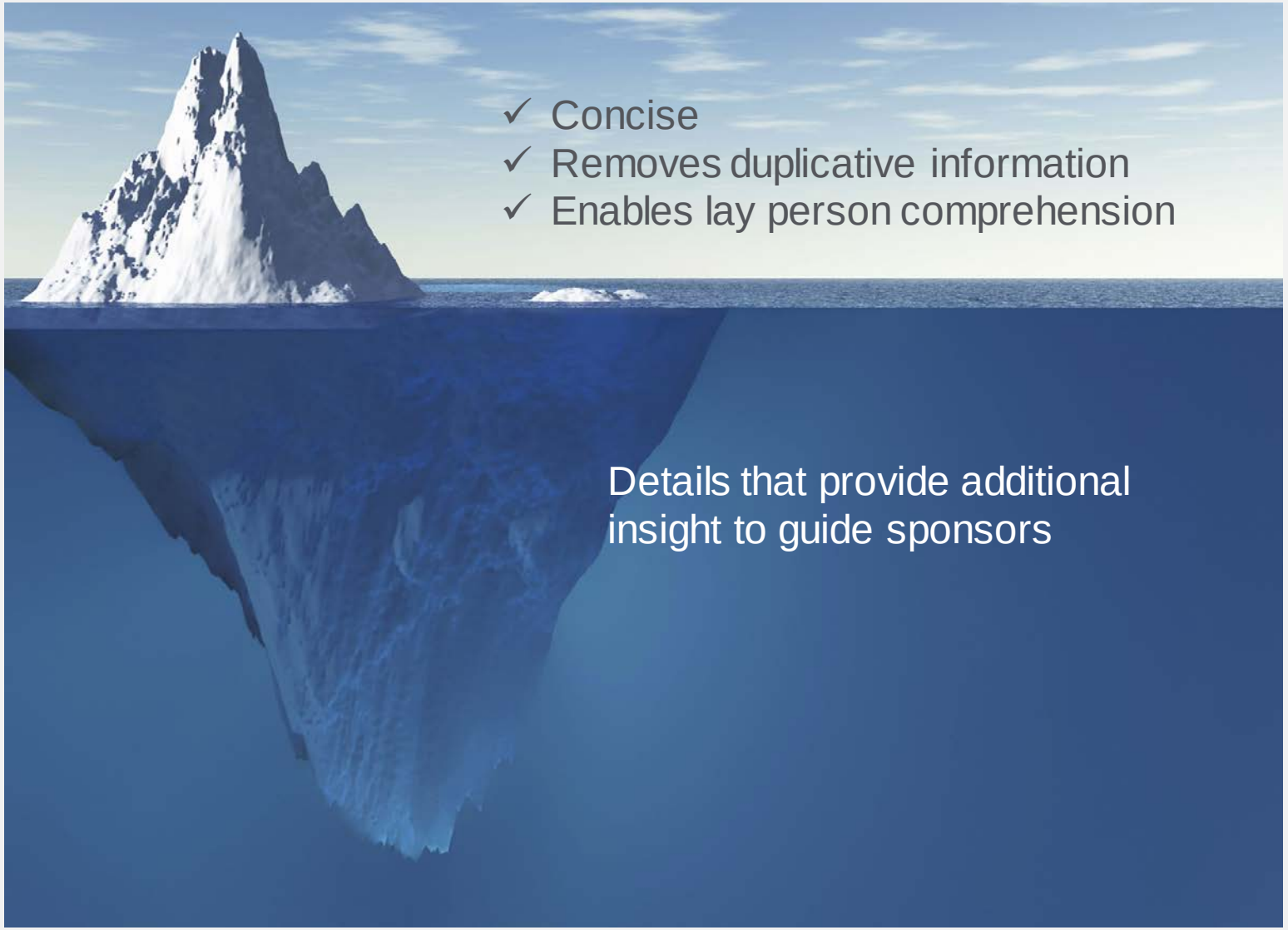
Summary Basis of Approvals

Integrated Review Examples To Date



- Original (n=6); Supplements (n=2)
- Standard (n=2); Priority (n=6)
- Antiviral (n=2); Antimicrobial (n=1); Diagnostic (n=1); Metabolic (n=3); Renal (n=1)
- Fixed-dose combination (n=2)

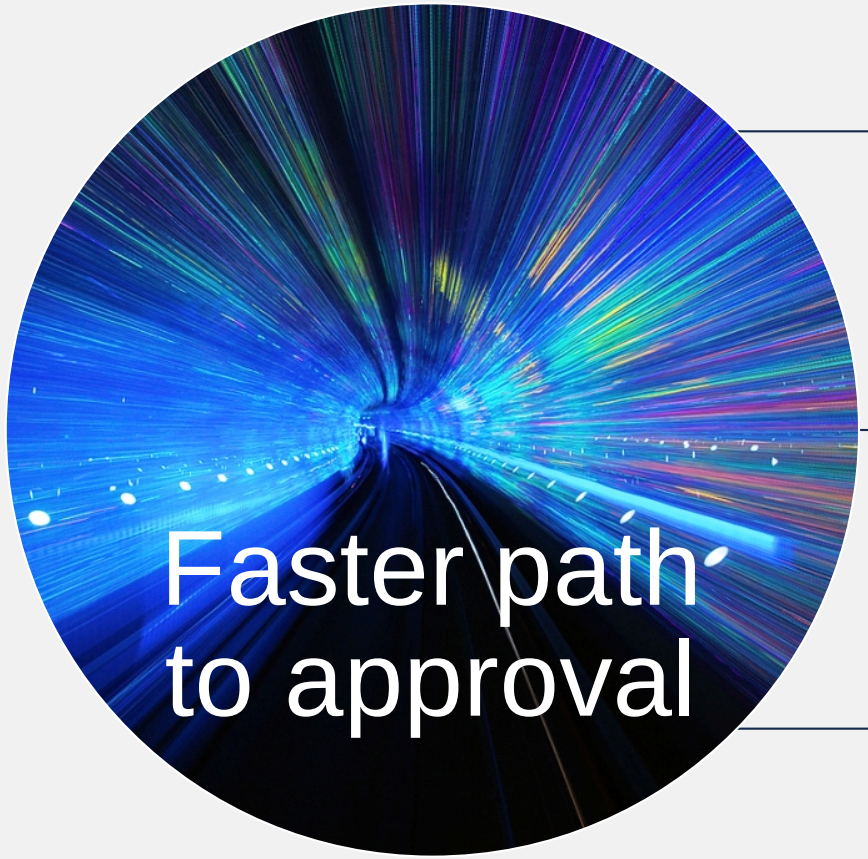




RWE- FDA did not accept use

Application No./ Product/Indication	FDA Center/TA	Designation(s)	Category/Summary
[redacted] Adult patients with locally advanced or metastatic urothelial carcinoma with FGFR2/3 mutations	CDER; Oncology products	Breakthrough therapy; Priority; Accelerated	As part of the submission, the applicant included RWD from the Flatiron-Foundation Medicine, Inc. database, which was meant to serve as a baseline for comparison of OS. According to the statistical review, "DEPI [did] not consider the study sufficiently valid for supporting regulatory decisions pertaining to drug effectiveness [since] both internal and external validity were threatened by methodological issues."
[redacted] relapsed or refractory multiple myeloma AND on June 22, 2020, accelerated approval for adult patients with relapsed or refractory diffuse large B-cell lymphoma	CDER; Hematology product	Fast track; Priority; accelerated	According to DEPI's statistical review, "the evidence generated from the RWD analysis is not adequate to provide context or comparison for the overall survival observed in the [clinical trial] patients [due to] the lack of comparability between the [clinical trial] and [real world] treatment groups." DEPI highlighted post-hoc analysis, selection bias (e.g., differential eligibility criteria for clinical trial vs. external populations, immortal time bias), confounding bias, data missingness, and limited statistical power among the shortcomings of the real world study. The resulting FDA label of excluded OS outcomes, and only referenced improvements in ORR.

Transparency = Predictability



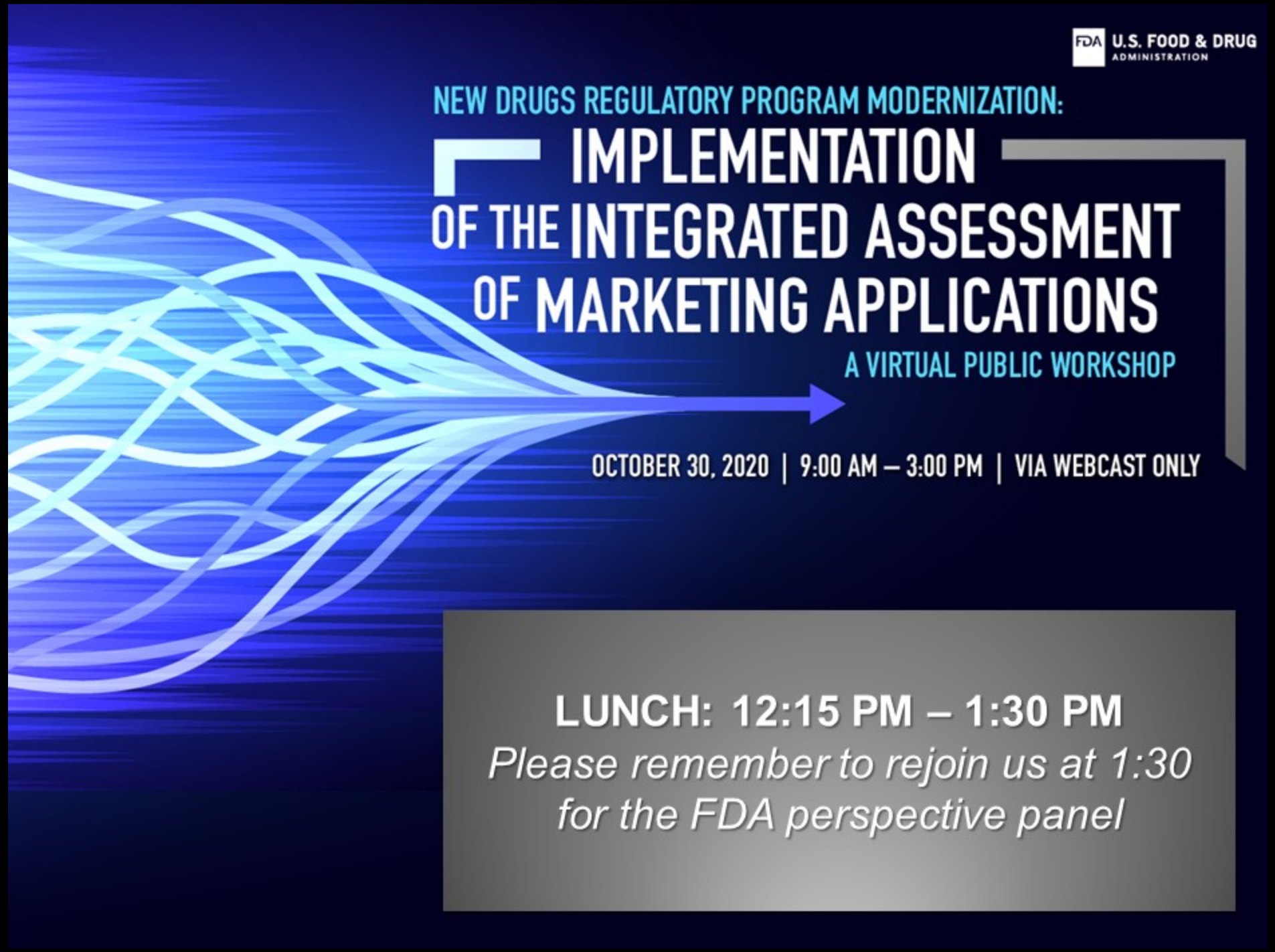
Fewer meeting requests

Current trends/insights into agency thinking

Avoid repeating past mistakes

THANK YOU

Emily Huddle
Senior Manager
Global Regulatory Policy & Intelligence
Gilead Sciences
emily.huddle@gilead.com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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
LUNCH: 12:15 PM – 1:30 PM
Please remember to rejoin us at 1:30 for the FDA perspective panel