Speaker Biographies:

Jack Cook, Ph.D. is a Vice President in the Clinical Pharmacology Department of the Global Product Development unit at Pfizer, Inc. Dr. Cook holds adjunct faculty positions at the Universities of Michigan and Florida Colleges of Pharmacy. He received B.S. degrees in Applied Mathematics and Pharmacy from Ferris State College, and his Ph.D. in Pharmaceutics from the University of Michigan. He has authored/co-authored over 70 peer-reviewed publications. He served as an industrial representative for the United States Food and Drug Administration's Pharmaceutical Science and Clinical Pharmacology Advisory Committees from 2012 to 2019. He is a fellow of the AAPS. His current interests include improving therapy by optimizing drug delivery and the use of modeling and simulation to make rational decisions in the development of drugs.

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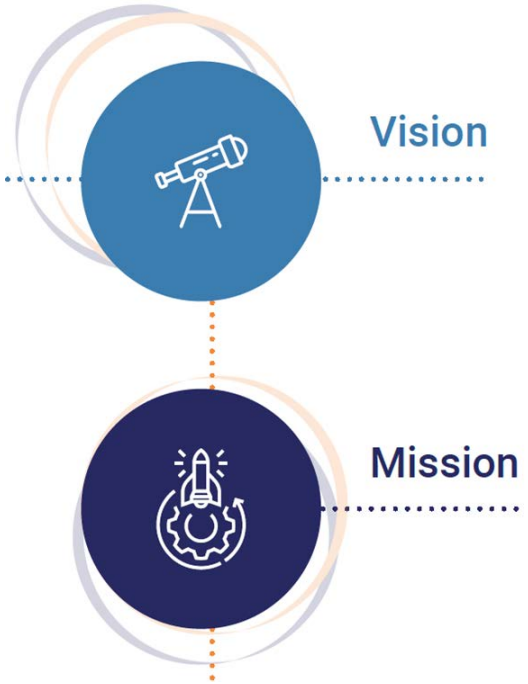
INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

Experiences with the FDA's MIDD Paired-Meeting Pilot Program

Jack Cook (Pfizer) and Gerald Galluppi (Sunovion)

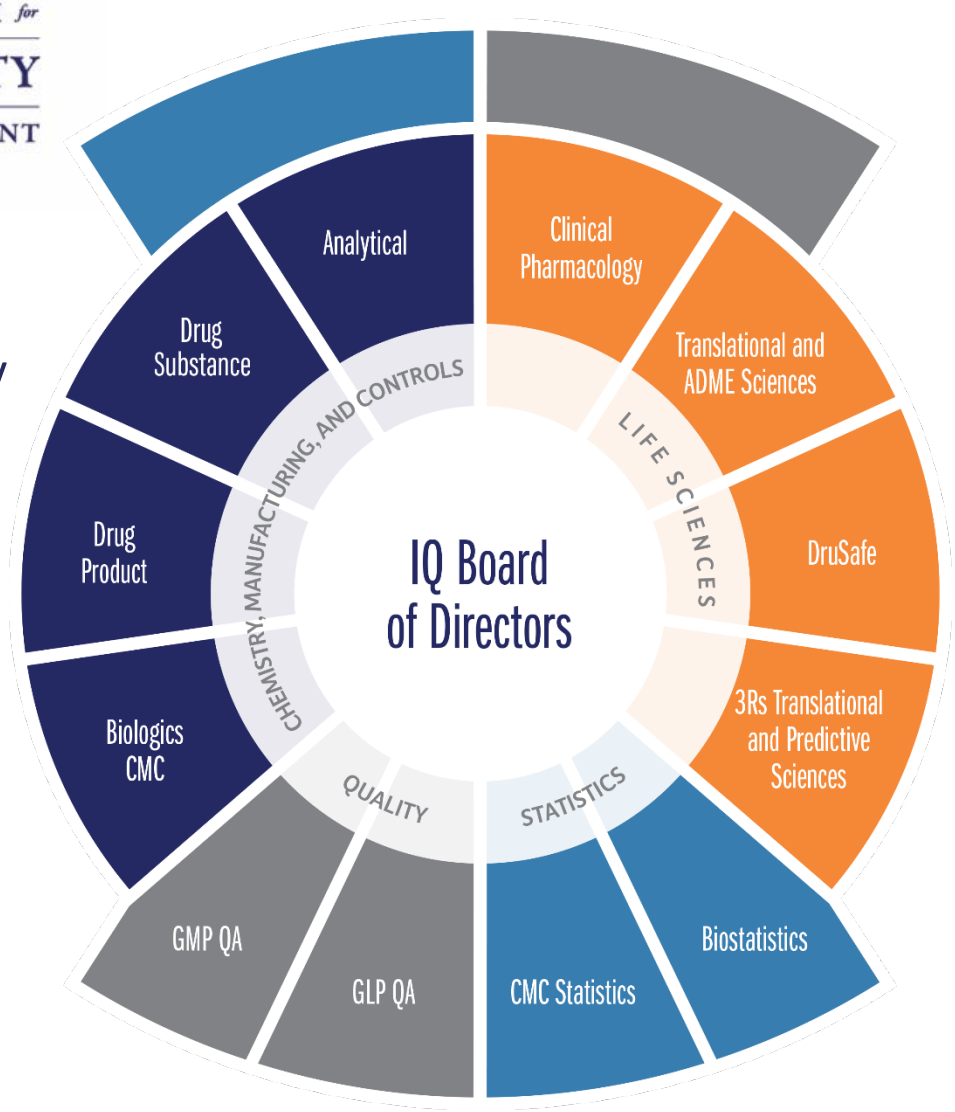
INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium) was established in 2010 as a technically-focused, not-for-profit organization comprised of nearly 40 pharmaceutical and biotechnology companies.



To be **the leading science-based organization** advancing innovative solutions to biomedical problems and enabling pharmaceutical companies to **bring quality medicines to patients**.

As a technically-focused organization of pharmaceutical and biotechnology companies**, IQ advances science and technology** to augment the capability of member companies to bring transformational solutions that **benefit patients, regulators and the broader R&D community**.



https://iqconsortium.org

Acknowledgement

This presentation was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org). IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of **advancing science and technology** to augment the capability of member companies to develop transformational that benefit patients, regulators and the broader research and development community.

The presentation is being made on behalf the members of an IQ Working Group and presents the results of the manuscript:

Industrial Perspective on the Benefits Realized from the FDA's Model-Informed Drug Development Paired Meeting Pilot Program

Galluppi GR, Brar S, Caro L, Chen Y, Frey N, Grimm H, Jackson Rudd D, Li C-C, Magee M, Mukherjee A, Nagao L, Purohit VS, Roy A, Salem AH, Sinha V, Suleiman AA, Taskar KS, Upreti VV, Weber B, Cook J.

Accepted by ***Clinical Pharmacology and Therapeutics***

FDA MIDD Paired Meeting Pilot Program

- Provide an opportunity for drug developers and FDA to discuss the application of MIDD approaches to the development and regulatory evaluation of medical products

- Provide advice about how particular MIDD approaches can be used in a specific drug development program

    - Scope – Any relevant MIDD topics with a focus on:
        - Dose selection or estimation
        - Clinical trial simulation
        - Predictive or mechanistic safety

FDA MIDD Paired Meeting Pilot Program

When applied successfully MIDD approaches can:

- Improve clinical trial efficiency – doses to be tested, patient selection, group sizes, qualified biomarkers, etc.
- Optimize drug dosing and therapeutic individualization in the absence of dedicated trials

❖ **Increase probability of regulatory success via totality of evidence approach**

The IQ Survey

- The IQ survey was directed to industrial scientists who have participated in the FDA MIDD Pilot Program

- The survey consisted of 15 questions covering:
  - Type of application, stage of development, therapeutic area
  - Benefits from participation in the program – both quantitative and qualitative

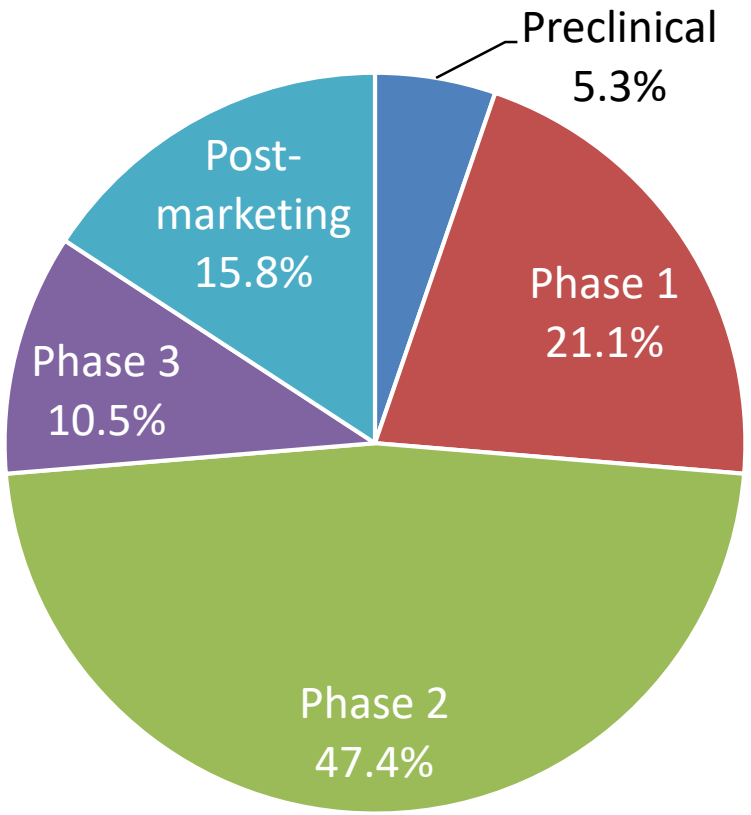
- IQ Secretariat received 19 survey responses, or about two-thirds of participants to date, and retained anonymity of respondents (per FDA: through 1Q2021 there have been 34 requests and 30 meetings granted)

Program Characteristics: Therapeutic Areas

Therapeutic Area	Number
Oncology	5
Rheumatology	3
Immunology	2
Infectious Disease	2
Hematology	1
Heme Oncology	1
Metabolic Disease	1
Neurology	1
Psychiatry	1
Pulmonary	1
Respiratory	1

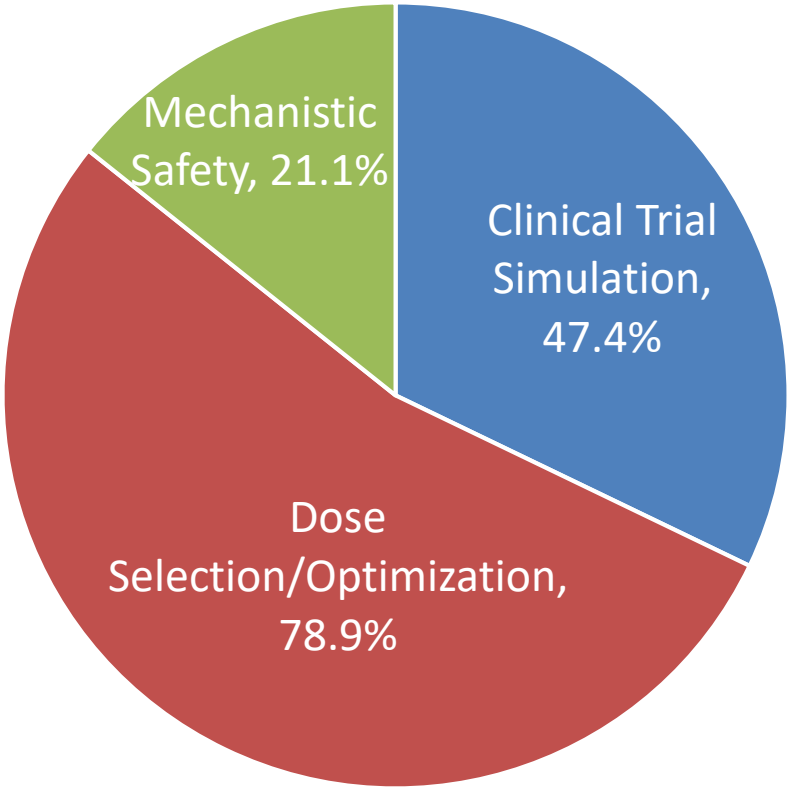
- 19 Programs across 11 different therapeutic areas shows broad applicability of program
- Oncology is most common therapeutic area

Program Characteristics: Development Stage



- Programs spanned all development cycles, again showing broad applicability
- Phase 2 was most common

Program Characteristics: Meeting Topic

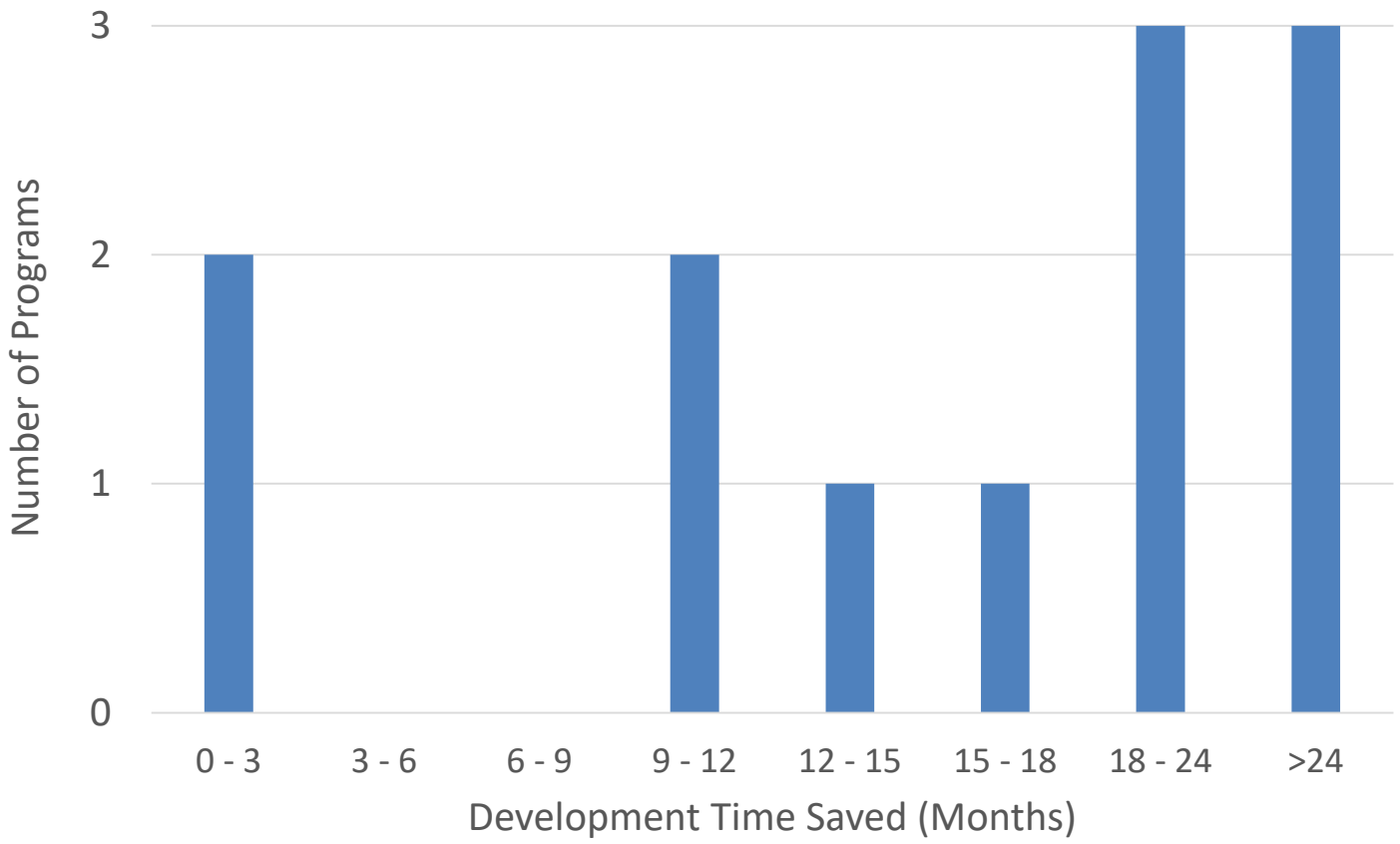


- Dose selection and optimization was most common topic

Responses allowed multiple meeting topics

Quantitative Benefits

Benefit: Development Time Savings



- Many programs projected to have development savings as a result of the meeting
- Other responses included:
  - 3-6 months potential time savings but not realized as internal strategy changed
  - Too soon to provide estimation, but will be ≥ 6 months (1), or ≥ 12 months (1)
  - Too soon to provide estimation (2)
  - Pathway for approval that **otherwise would not be pursued** (infinite time savings)
  - Approximately 2 years

How Time Savings Are Expected to be Achieved

- **Accelerated timelines** to reach a go/no-go decision supported by simulated outcomes (6)
- **Obviating the need for a clinical trial** in favor of a simulated outcome (e.g. PBPK extrapolation from adults to pediatrics) (6)
- **Reduced group sizes** leading to faster trial recruitment and completion (3)
- **Obtaining approval based on a single pivotal trial plus totality of evidence** supported by modeling and simulation (3)
- Not applicable (2)
- Expected saving should mainly come from the **accelerated timelines** to reach a go/no-go decision supported by simulated outcomes (1)
- **Obtained early feedback** on feasibility of MIDD development path (1)
- Pathway for approval that **otherwise would not be explored** (1)
- **Saved 2 mo. time** with respect to alternative regulatory interaction (1)

(Number of responses) More than one response per program was possible

Benefit: Development Cost Savings

Million USD	N
0 - 1	1
1 - 10	2
10 - 30	2
30 - 70	3

- Many programs noted significant savings of developmental costs
- 11 responses of not applicable

How Development Costs Are Expected to be Achieved

- Smaller (reduced) trials (4)
- **Simulated outcomes replacing the need for clinical trials** (e.g. PBPK in place of drug-drug interactions, reduced organ impairment studies) (4)
- **Did not use resources to test the wrong dose levels**; getting to the right dose faster (4)
- **Evaluating PK/PD on less costly but validated biomarkers** to demonstrate proof of efficacy and choosing the best doses to test in subsequent trials (2)
- Not applicable (5)

Other Responses:

- It is too soon to know the cost saving but they are expected to come mainly from **not using resources to test the wrong dose levels** – getting to the right dose, faster
- Note while cost savings were not achieved, it **allowed for a path to potential new indication**
- There may be some **savings on material**, even without running trial
- It's hard to translate the time savings into dollar amount, Decision is priceless but hard to quantify.
- **Waiver of additional clinical trials** would be the reason if the cost saving were achieved
- Assumes successful trial

(Number of responses) More than one response per program was possible

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Benefits that Change Drug Development

Greater understanding and alignment

Note some responses have been edited for brevity

Survey: Questions on Alignment & Learnings

- Please describe **internal alignment within your company** that was achieved in relation to participation in an MIDD pilot program meeting
- Please describe **alignment achieved with FDA** through MIDD pilot program meeting participation
- Please describe **learnings and clarifications** afforded by MIDD pilot program meeting participation
- Please provide **any comments or outcomes** about the MIDD Pilot program that were **not captured above**

Benefit: Internal Alignment (17 Responses)

Participation in the pilot program changes company culture to one that is more accepting of MIDD

Selected Responses:

- **Some line functions within the sponsor were skeptical** with the novel approach. The alignment with the FDA gained **significant traction and acceptability of the proposal**.
- Gave increased **confidence in using** the approach **for other programs**
- Internal alignment as pilot program generated **more internal awareness and support** for accelerating and streamlining drug development projects with MIDD approaches
- Increase internal confidence and **acceptance of modeling approaches** - The internal cross-functional efforts to prepare for an MIDD meeting formalize the use of MIDD strategies **across multiple programs**
- Positive Agency feedback gave confidence in acceptability of strategies **across functional teams**
- Well received internally. **Led to use by other teams**

More than one response per program was possible

Benefit: Alignment with FDA (16 Responses)

Paired-Meeting allows sponsor and agency to come to agreement on strategy and details

- At a level not typically achieved with other types of regulatory meetings

Selected Responses:

- Study design, population , MIDD approaches for proof of concept, dose selection.
- E-R analysis and dose selection
- Agreement on model-based dose selection for a pivotal Phase 3 study using dose not previously studied
- PK/PD model to bridge formulations from Phase 2 to Phase 3
- Model-based dose selection and model-based assessment of product benefit/risk profile
- Content needed to support the submission.
- Model-based dose selection to maximize drug benefit and reduce safety risks
- Model-based label change.

Benefit: Learnings and Clarity (17 Responses)

Meeting often results in clear expectations, understanding of agency's rational and additional insight from the agency

Selected Responses:

- FDA provided **valuable feedback** on data needed for eventual approval
- **Clear insight** into the agency's technical expectations for MIDD and approach to decision making. Technical discussion with respective agency SME's (Statistics, Clinical Pharmacology and Pharmacometrics) was unprecedented.
- **Timely, direct and actionable advice.** While company proposal was not accepted, clarity was achieved regarding possible paths forward
- **Became aware** of the role of drug-excipient complexation on the interpretation of CYP3A DDI. MIDD approach can explain confounding DDI results without conducting additional dedicated study
- **Gained an understanding** on the acceptability of certain parts of the MIDD approach (technical feasibility) and the issues which required further alignment within FDA (between OCP and other functions).

Additional Comments

Potential for future work with sponsors and the agency

Selected Responses:

- Overall acceptability of proposed MIDD approach. Showed feasibility of using prior exposure-response information for **designing pragmatic clinical trials and labeling**
- **Opportunity to think creatively** about how modeling can be used to bridge "gaps" in clinical data
- Discussed **future scientific exchange opportunity**, e.g. work with the FDA and the broader scientific community to build consensus in the pharmaceutical industry on the approach for the use of endogenous biomarkers in the development of future NMEs
- Discussed potential scope of **interest for future scientific platform strategy exchange**

Conclusions

Companies experience with the pilot program has been **strongly favorable**.

Demonstrated or expected **savings in resources**

Achieved **alignment with the FDA** on developmental strategies

Gained **clarity** on important aspects of programs and product characteristics.

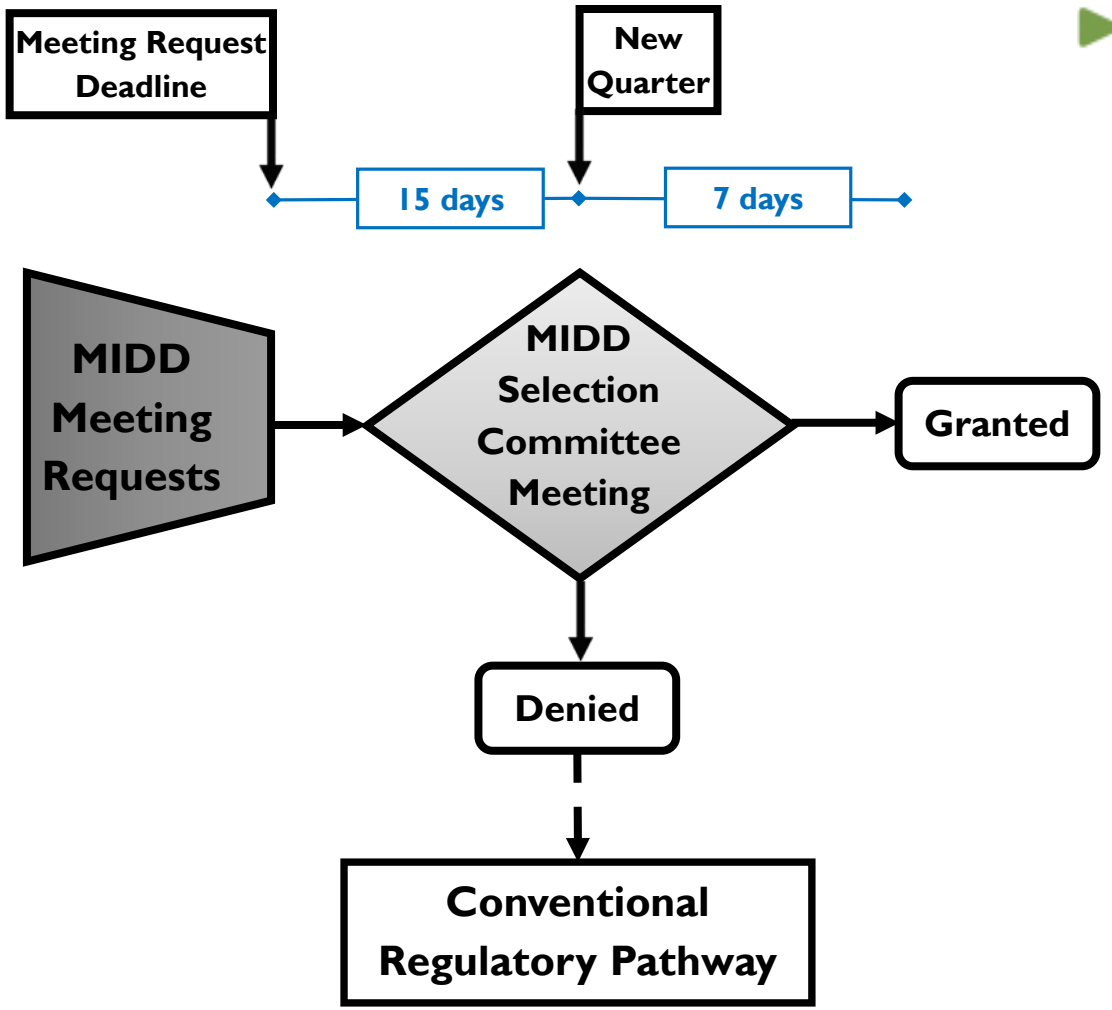
Meetings have **championed MIDD strategies within companies** and have facilitated adoption of MIDD strategies across programs within a company.

Enables **faster** and more efficient **delivery of products to patients** & medical community

Permanent adoption and expansion of the program is **strongly encouraged**

Backup slides

Selection Process*



FDA MIDD Selection Committee

- Office of Clinical Pharmacology
- Office of Biostatistics
- Office of New Drugs
- Office of Regulatory Policy

CDER

- Office of Biostatistics and Epidemiology
- Office of Tissue and Advanced Therapies
- Office of Vaccines Research and Review

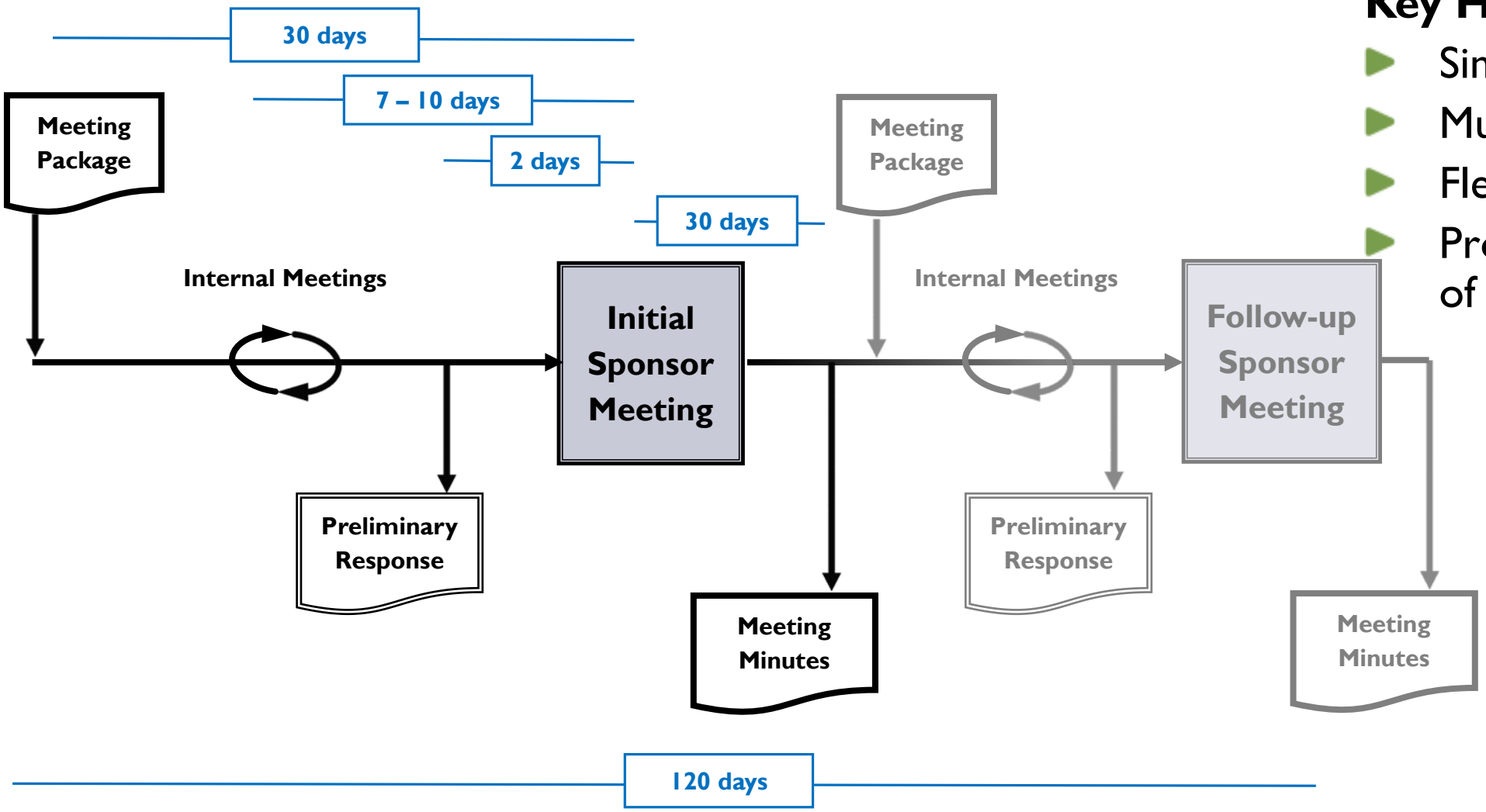
CBER

Selection Criteria

- Acceptability of the MIDD approach
- Expertise and familiarity
- Novelty of the application
- Potential impact

*Madabushi R. Mainstreaming MIDD: A Holistic and Integrative Approach. Rosa Webinar Series. Feb 2020. https://www.rosaandco.com/webinars/2020/mainstreaming-midd

MIDD Paired Meeting Process*



Key Highlights

- Similar to Type C Meetings
- Multidisciplinary
- Flexibility in follow-up
- Project managed by Office of Clinical Pharmacology

*Madabushi R. Mainstreaming MIDD: A Holistic and Integrative Approach. Rosa Webinar Series. Feb 2020. https://www.rosaandco.com/webinars/2020/mainstreaming-midd