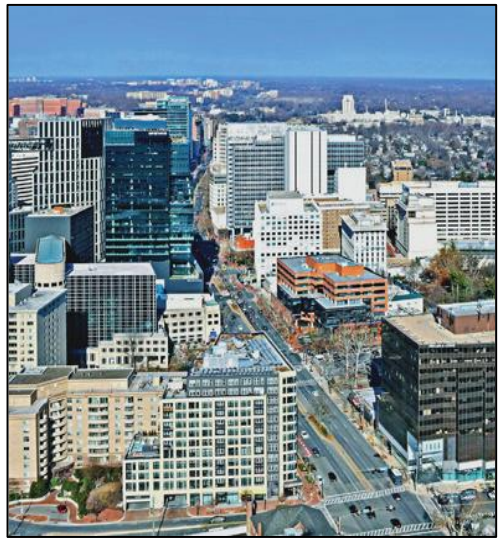
PDA®
Parenteral Drug Association

Glenn E. Wright
President and CEO

Member Since 1989

Serving Our Members Since 1946



PDA Global HQ
PDA Americas
Bethesda, MD USA

PDA Europe
Berlin, Germany

PDA Asia Pacific
Singapore

CHAPTER PDA® Parenteral Drug Association Midwest

25 Chapters
Around the Globe

PDA's Mission:

Advance pharma manufacturing science and regulation so members can better serve patients

Open to All Who Wish to Join

Non-Profit, Individual Membership Organization

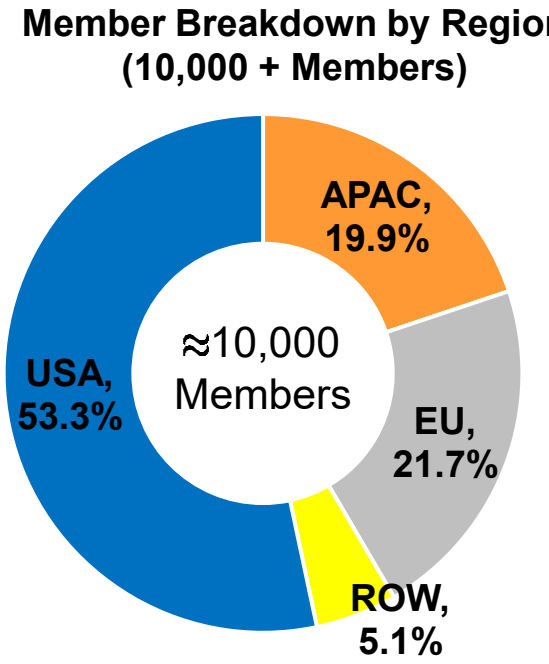
Driven and Directed by Our Members

- Members chart PDA's course through their involvement in: Chapters/ Meetings/ Task Forces/ Steering Committees/ Advisory Boards/ Board of Directors/ .....
- Members decide what PDA will work on, and the position PDA will take on topics that they identify as important

An Independent Voice of Our Members

Always Based in Science

Our Global Membership



Some of the Types of Scientists Represented in the Organization

- Analytical Chemist
- Biochemist
- Biologist
- Chemist
- Computer Scientist
- Engineer
- Microbiologist
- Pharmacist
- Pharmaceutical Scientist
- Pharmacologist
- Physician
- Statistician
- Virologist

Volunteer Progression — From the Ground Up

Long-term, experienced volunteers develop into leaders of the association

Volunteers progress with continued involvement and experience

Long-term members and industry veterans may join more experienced volunteers where appropriate for their skill level

New volunteers, Students, and Early Career members start at the ground level

* Examples of activities within each level

Board of Directors 2025

OFFICERS

Anil Sawant
Chair

Melissa Seymour
Chair-Elect

Bettine Boltres
Secretary

Emma Ramnarine
Treasurer

Susan Schniepp
Immediate Past Chair

DIRECTORS

Marcia Baroni

Lisa Bennett

Cristiana Campa

Andrew Chang

Cylia Chen-Ooi

Marc Glogovsky

Andrew Hopkins

Ivy Louis

Amy McDaniel

Morten Munk

Brigitte Reutter-Haerle

Osamu Shirokizawa

Board Of Directors Profile – Scientific and Industry Experience

Board's Combined Experience

497+ Years Industry Experience
314 Years PDA Member Experience

Types of Scientists On the Board

Analytical Chemist
Biochemist
Biologist
Biomedical Engineer
Chemical Engineer
Chemist
Forensic Scientist
Microbiologist
Pharmaceutical Scientist
Pharmacist

OFFICERS

Anil Sawant, PhD
Chair
- **Microbiologist/Biochemist**
- **35+ Years Industry Exp.**
- **PDA Member 33 Years**

Melissa Seymour, MBA
Chair-Elect
- **Biochemist**
- **30 Years Industry Exp.**
- **PDA Member 24 Years**

Bettine Boltres, PhD
Secretary
- **Biochemist**
- **16 Years Industry Exp.**
- **PDA Member 14 Years**

Emma Ramnarine, PhD
Treasurer
- **Pharmaceutical Scientist**
- **25+ Years Industry Exp.**
- **PDA Member 19 Years**

Susan J. Schniepp
Immediate Past Chair
- **Chemist**
- **40+ Years Industry Exp.**
- **PDA Member 25 Years**

DIRECTORS

Marcia Baroni. MBA
- **Microbiologist**
- **25 Years Industry Exp.**
- **PDA Member 13 Years**

Lisa Bennett, MSc
- **Forensic Scientist**
- **16 Years Industry Exp.**
- **PDA Member 9 Years**

Cristiana Campa, PhD
- **Analytical Chemist**
- **25 Years Industry Exp.**
- **PDA Member 6 Years**

Andrew Chang, PhD
- **Biochemist**
- **30+ Years Industry Exp.**
- **PDA Member 17 Years**

Cylia Chen-Ooi, MA
- **Biomedical Engineer**
- **20 Years Industry Exp.**
- **PDA Member 11 Years**

Mark Glogovsky, MS
- **Microbiologist**
- **25+ Years Industry Exp.**
- **PDA Member 26 Years**

Andrew Hopkins
- **Microbiologist**
- **40+ Years Industry Exp.**
- **PDA Member 6 Years**

Ivy Louis, MBA
- **Pharmacist**
- **35+ Years Industry Exp.**
- **PDA Member 22 Years**

Amy McDaniel, PhD
- **Microbiologist**
- **25+ Years Industry Exp.**
- **PDA Member 26 Years**

Morten Monk
- **Chemical Engineer**
- **30 Years Industry Exp.**
- **PDA Member 19 Years**

Brigitte Reutter-Haerle
- **Business Administration**
- **40 Years Industry Exp.**
- **PDA Member 20 Years**

Osamu Shirokizawa
- **Biologist**
- **40 Years Industry Exp.**
- **PDA Member 24 Years**

Chapters

Midwest Chapter
Established in 1989
Serves Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin

Chapter Officers:

Deborah Gessell-Lee, President

Jason Willett, President Elect

Lauren Specchio, Secretary

Eric Peryer, Treasurer

Chapters

- Led by PDA Members
- Are PDA's grassroots, where local PDA volunteers (members) collaborate to bring the PDA Mission close to where PDA members live and work
- Today 25 chapters across North and South America, Europe, and Asia host more than 150 events each year focused on knowledge sharing and networking
- The interest in forming new chapters continues with the formation of the latest chapter, the DACH Region chapter, in 2024. The region includes Germany, Austria, and the German speaking area of Switzerland

Some of What PDA Provides to Our Members and the Industry

- **A Place to Connect on Common Technical Topics of Interest** (Global and Local)
- **Technical Documents** (Technical Reports, Points to Consider, Consensus Standards)
- **Peer Reviewed Journal** (Journal of Pharmaceutical Science and Technology)
- **PDA Letter** (Industry Related News Articles)
- **Technical Books and Surveys**
- **Training** (At PDA's Training and Research Institute (TRI), Partner Facilities, Conferences, & On-Site)
- **Global and Regional Technical Conferences and Workshops**
- **Local Chapter Events**
- **Regulatory Commenting**
- **Technical Interest Groups**
- **Facility for Aseptic Processing Related Research** (TRI)

2025 General Highlights (as of 31 Aug)

- **19** Global Technical Conferences and Workshops
- **28** Technical Advisory Board Meetings
- **72** Courses Offered - Continuing our commitment to PDA education programing – over 23,000 industry professionals trained since 2010
- **82** Interest Group Meetings
- **96** Chapter Events
- **7** Technical Documents Completed
- **3** Books
- **15** Formal Commenting Efforts Completed – (EMA, FDA, etc.)

Pharma Trends - Looking Towards the Future

Discussion Points

- Update - Small Peptides with a Big Impact
- AI Advancing
- EU Annex 1 Implementation Update - PUPSIT
- Training for the Operator of the Future
- US FDA Complete Response Letters
- Globalization to Regionalization (if time allows)

Update - Small Peptides with a Big Impact Their Big Role in Treating Obesity and …

https://www.worldobesity.org/news/economic-impact-of-overweight-and-obesity-to-surpass-4-trillion-by-2035

https://www.statnews.com/2023/03/02/obesity-costs-4-trillion-2035/

GLP-1 Market Expected to be >150B (USD) by 2030

World Obesity Foundation forecasting by 2035:

- >50% of global population (over 4 billion people) will be overweight or obese
- Child obesity could more than double
- Global Economic impact could be over 4 trillion dollars (USD)

For the individual, being obese has some significant impacts:

- Increased risks of dying at a younger age from cancer and many other causes; including heart disease, stroke, diabetes, kidney disease, and liver diseases
- Increase in other medical conditions related to obesity
- Reduced life expectancy
- Reduced activity level and a significant social stigmatism

New polypeptides may dramatically shift the obesity forecast and is transforming the lives of patients

- GLP-1 (Glucagon like Peptide 1) Agonist
- GIP (Gastric Inhibitory Polypeptide) Agonist

Injectable GLP 1 Agonist

Natural Occurring

GLP-1 (Glucagon-like Peptide 1)

1-2 Min (Half-life)

~94% homologues

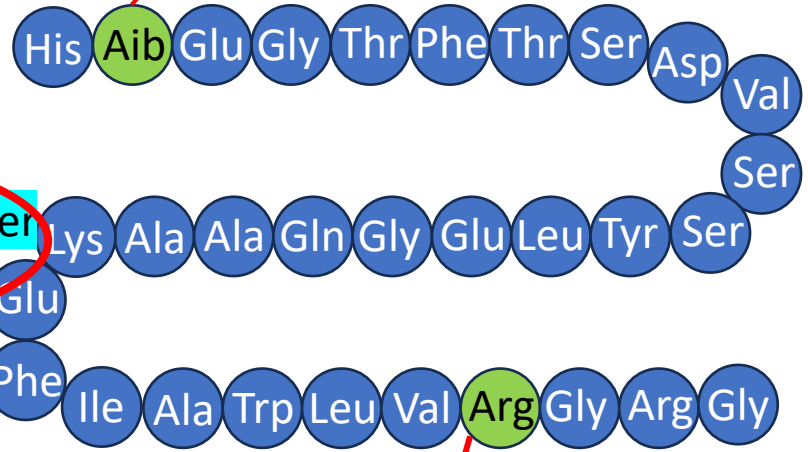
Both are GLP-1 Agonist

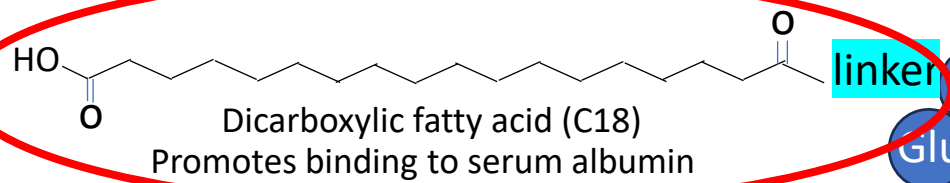
Activating the GLP-1 Receptor

Semaglutide

165 Hour Half-Life)

α-aminoisobutyric acid replaces alanine to resist DPP-4 (Dipeptidyl peptidase 4) cleavage





Dicarboxylic fatty acid (C18)
Promotes binding to serum albumin

Arginine replaces Lysine to prevent incorrect binding of the Dicarboxylic fatty acid (C18)

Injectable GIP / GLP-1 Agonist

Natural Occurring

(Gastric Inhibitory Polypeptide)

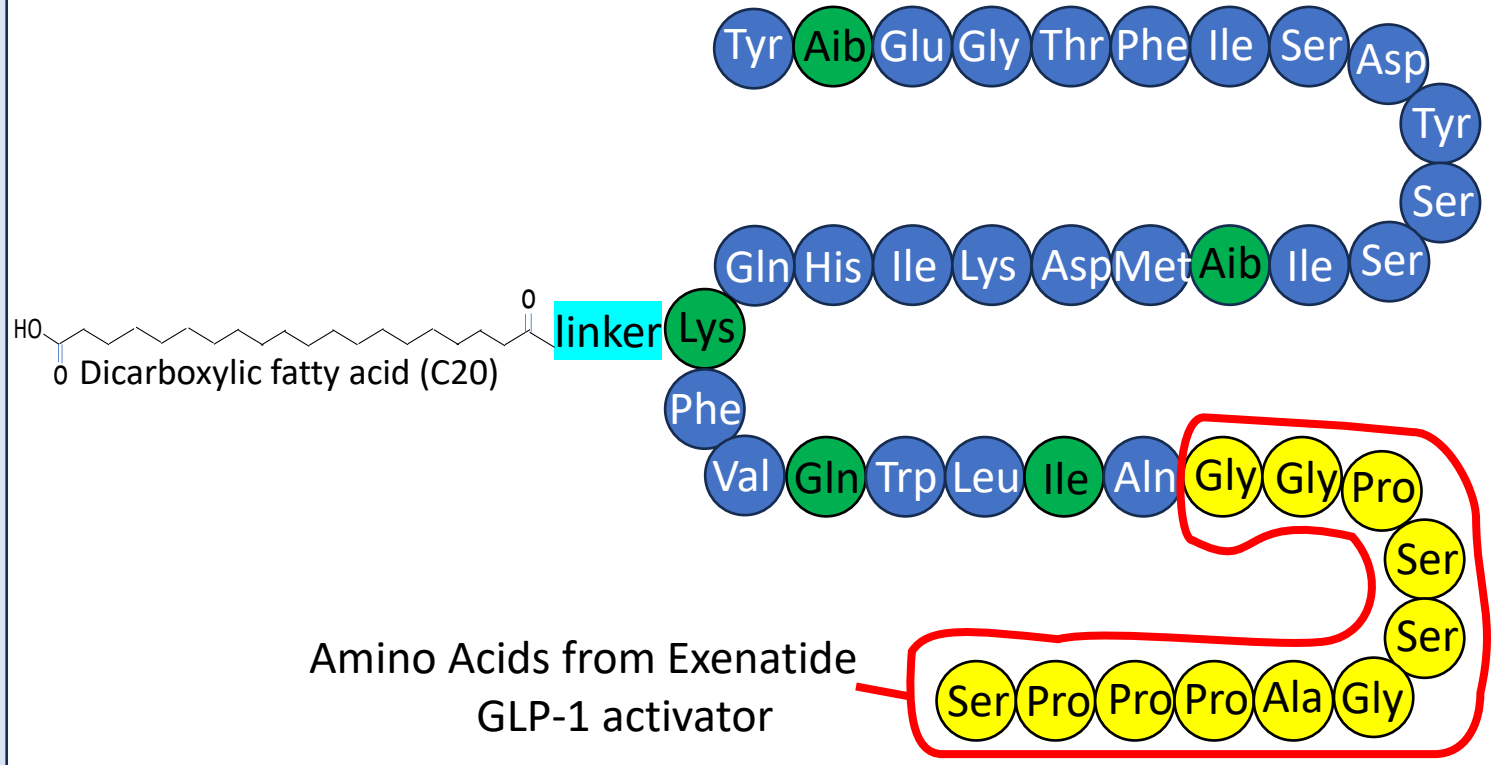
1-2 min (Half-life)

GIP Agonist activating the GIP Receptor

Trizepatide

120 h (Half-life)

GIP-1 and GLP Agonist activating the GIP ang GLP-1 Receptors



Over 40 companies are currently working on GLP-1 products (large number of orals)

Work ongoing on triagonist: targeting (GLP-1/GIP/GCG Receptors)

Overall, What does this mean for the larger pharma industry?

Reported Benefits for Specific Patients

(not indicated for patients with type 1 diabetes)

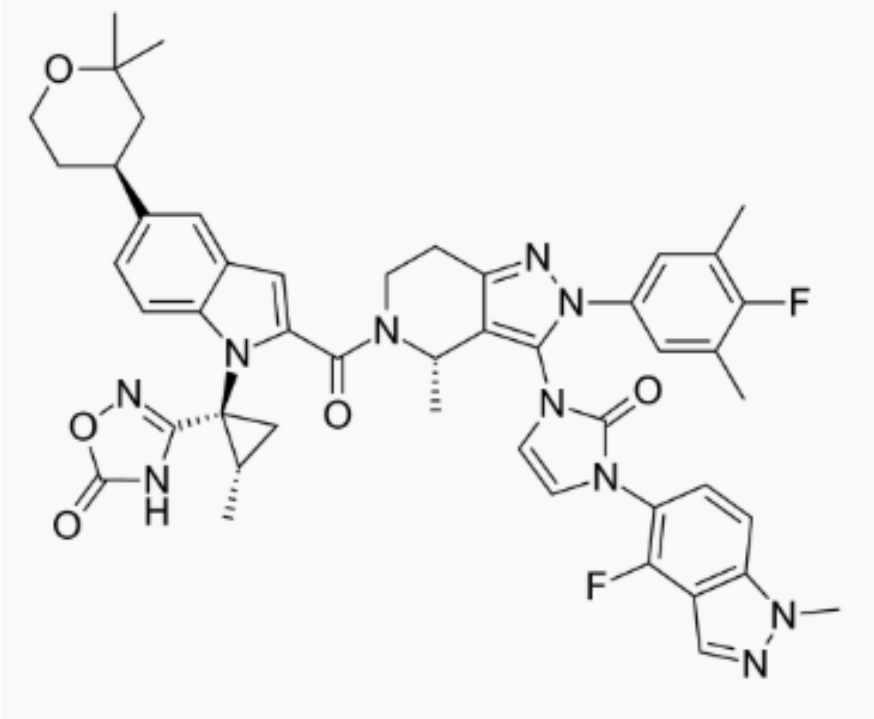
- Improves glycemic control (type 2 diabetes)
- Delays the progression of diabetes-related nephropathy (type 2 Diabetes)
- Reverses / Reduces the risk of obesity and the many related diseases

https://www.chemistryworld.com/news/the-challenge-of-developing-oral-alternatives-to-peptide-weight-loss-drugs/4021995.article

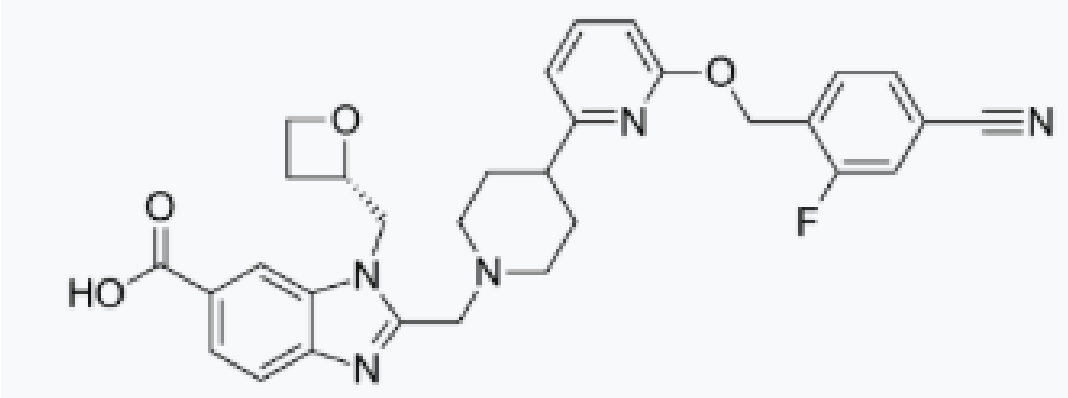
- Most of the oral GLP-1 Receptor Agonists are small molecules rather than peptides
- Toxicity in the liver has caused work on some oral drug candidates to be stopped

Oral GLP-1 Agonist

Orforglipron



Danuglipron (no longer in development)



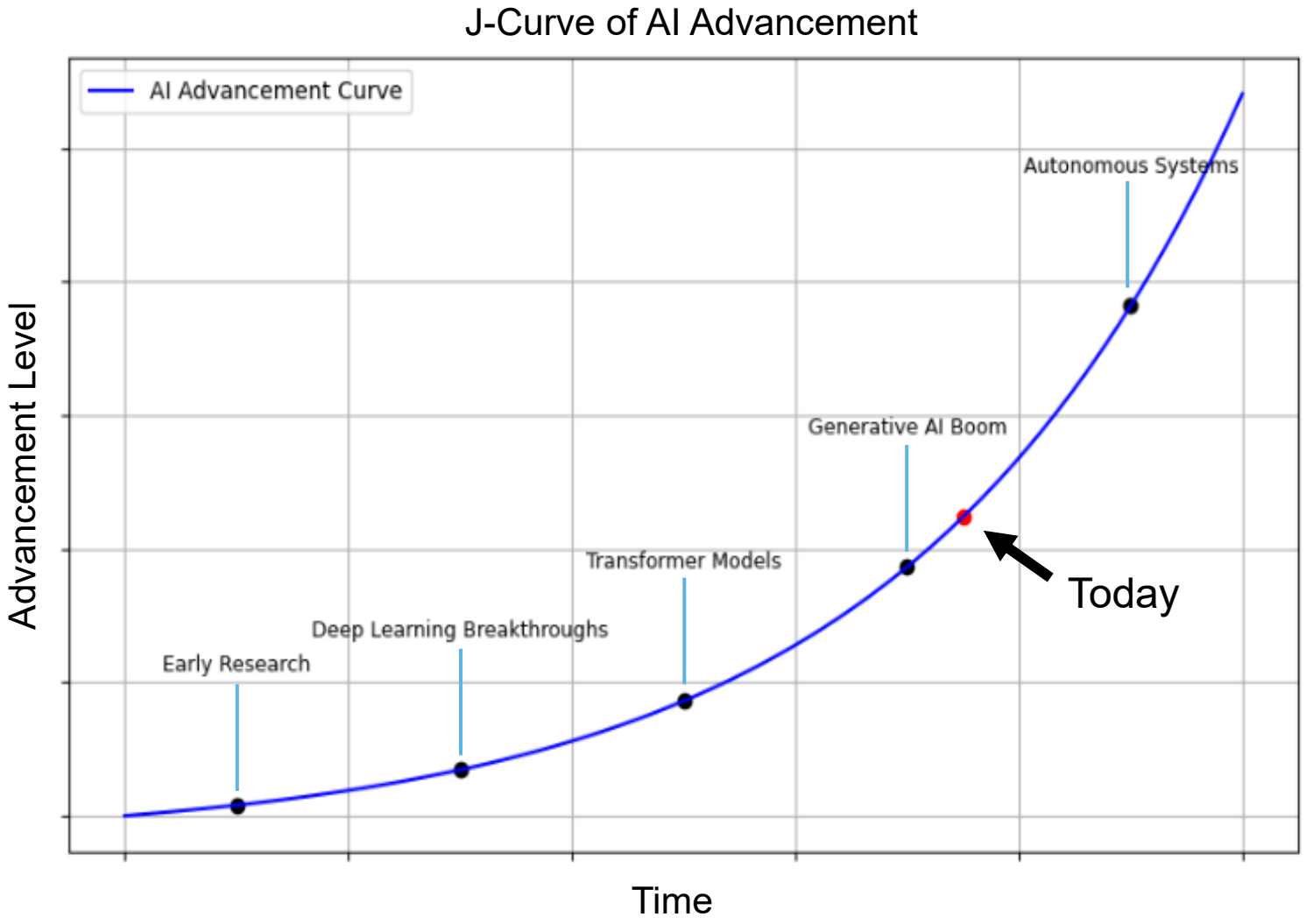
We are still, more than likely, in the early days of this race

The AI Curve and the Pharma Industry

AI development and adoption will only accelerate from here

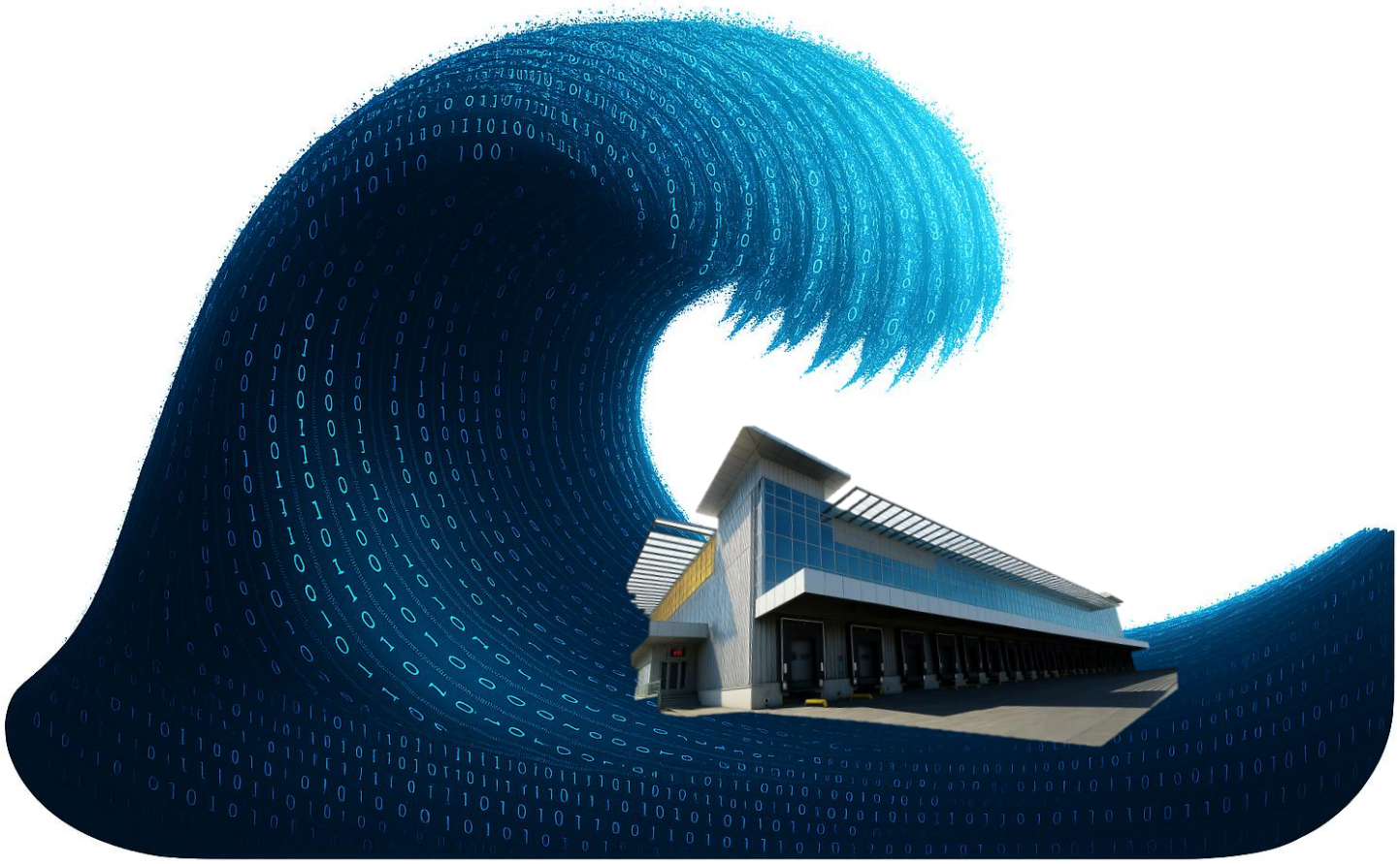
Significant Drivers:

- Mass data availability
- Exponential growth in computing power and infrastructure
- Improved algorithms and frameworks
- Cloud computing
- Funding



What does all of this mean for the Pharma industry?

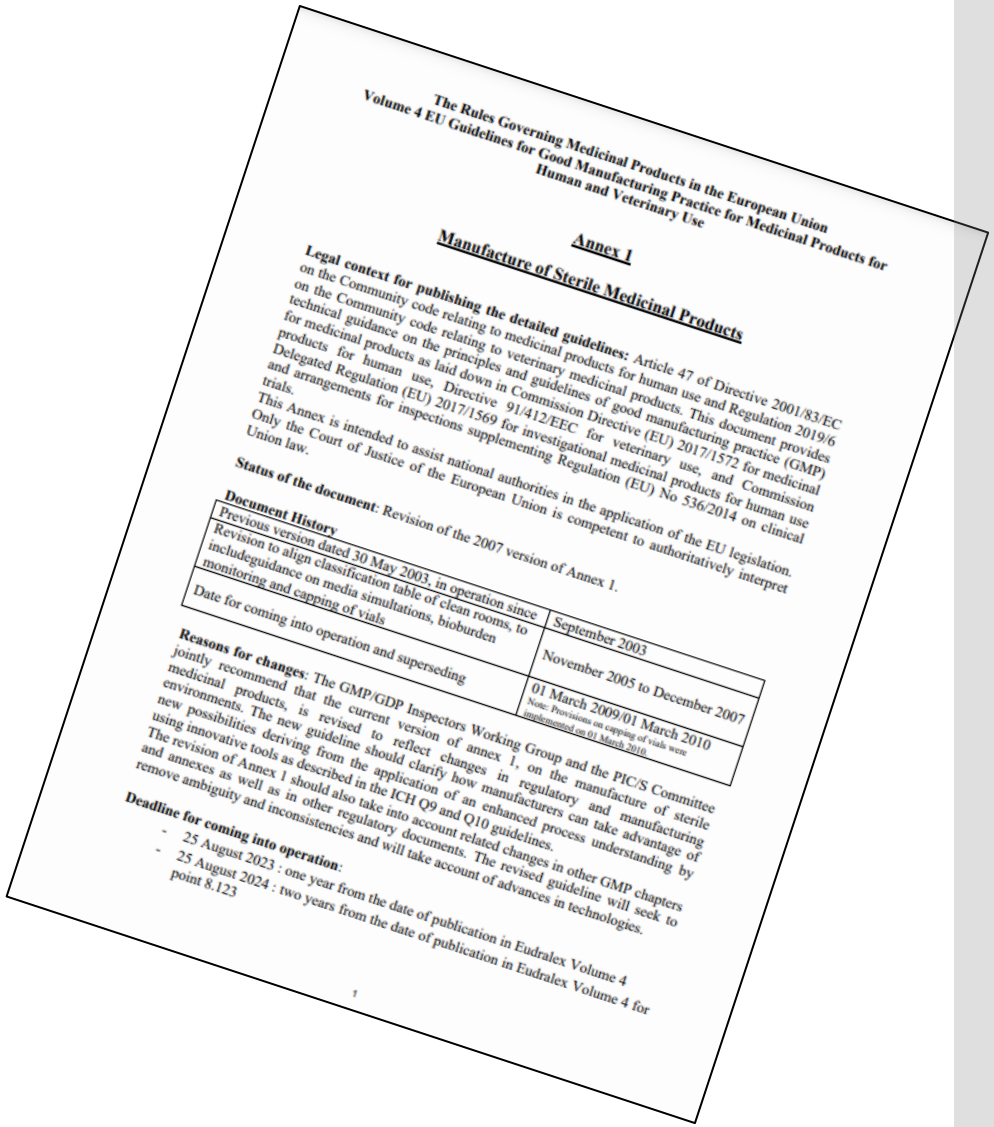
- **More Transformation!**
- An extreme wave of AI analysis, prediction, design and control is set to hit Pharma manufacturing
- Powered by the application of tools such as Vibe Coding and the many other advances
- What required months and weeks will now take days and hours. More insight, better control, increase predictability
- The patient stands to benefit significantly
- Can regulatory agencies and guidance keep up with the changes coming. Most likely not! It's to fast and the tools to important, no mater the area it is being applied to



Vibe coding - where the user describes a desired outcome in their natural language, and the AI handles the implementation details

AI as a review/inspectional/audit tool is increasing in its value

- Directionally regulators and companies are embracing its use
- Starting to see its application – with some success
- Just as with use in manufacturing its use will increase rapidly as AI advances
- Think about provide access to large manufacturing data sets to inspectors/audits that are using AI tool
- The ability to identify anomalies, problem areas and events, to identify fraud will increase significantly



The Rules Governing Medicinal Products in the European Union
Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

Annex 1

Manufacture of Sterile Medicinal Products

Legal context for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation 2019/6 on the Community code relating to veterinary medicinal products. This document provides technical guidance on the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Commission Directive (EU) 2017/1572 for medicinal products for human use, Directive 91/412/EEC for veterinary use, and Commission Delegated Regulation (EU) 2017/1569 for investigational medicinal products for human use and arrangements for inspections supplementing Regulation (EU) No 536/2014 on clinical trials.

This Annex is intended to assist national authorities in the application of the EU legislation. Only the Court of Justice of the European Union is competent to authoritatively interpret Union law.

Status of the document: Revision of the 2007 version of Annex 1.

Document History

Previous version dated 30 May 2003, in operation since	September 2003
Revision to align classification table of clean rooms, to include guidance on media simultations, bioburden monitoring and capping of vials	November 2005 to December 2007
Date for coming into operation and superseding	01 March 2009/01 March 2010 Note: Provisions on capping of vials were implemented on 01 March 2010

Reasons for changes: The GMP/GDP Inspectors Working Group and the PIC/S Committee jointly recommend that the current version of annex 1, on the manufacture of sterile medicinal products, is revised to reflect changes in regulatory and manufacturing environments. The new guideline should clarify how manufacturers can take advantage of new possibilities deriving from the application of an enhanced process understanding by using innovative tools as described in the ICH Q9 and Q10 guidelines.
The revision of Annex 1 should also take into account related changes in other GMP chapters and annexes as well as in other regulatory documents. The revised guideline will seek to remove ambiguity and inconsistencies and will take account of advances in technologies.

Deadline for coming into operation:

- 25 August 2023 : one year from the date of publication in Eudralex Volume 4
- 25 August 2024 : two years from the date of publication in Eudralex Volume 4 for point 8.123

1

EU GMP Annex 1 Implementation Update

PUPSIT

Pre-Use Post Sterilization Integrity Test Benchmarking Survey

- PDA Survey Conducted Q1 2025
- Blinded (anonymous) Survey
- **Sites** responding – 146
- Publication Expected this Month

Geographical Data – Site Location

Question
What geographic region is your company's manufacturing site, for which this survey is being completed, located? (Select one)
Respondents: 128 Sites

Geographic Region	Responses	Percent
Europe	50	39.1%
Asia/Pacific (APAC)	36	28.1%
North America	28	21.8%
Africa	7	5.5%
South America	7	5.5%

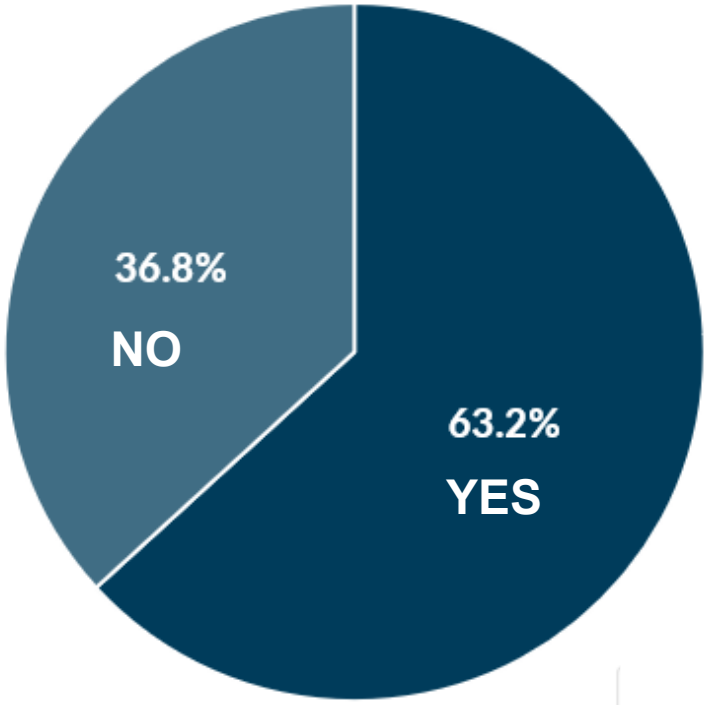
Geographical Data – Product Distribution

Question:
What geographic region(s) does your company's manufacturing site, for which this survey is being completed, provide product to? (Select all that apply)
Respondents: 128 Sites

Geographic Region	Responses	Percent
Europe	72	29.6%
Asia/Pacific (APAC)	63	25.9%
North America	57	23.5%
South America	27	11.1%
Africa	24	9.9%

Implementation

Question
Have you implemented PUPSIT into your filling processes?
Respondents: 106 Sites



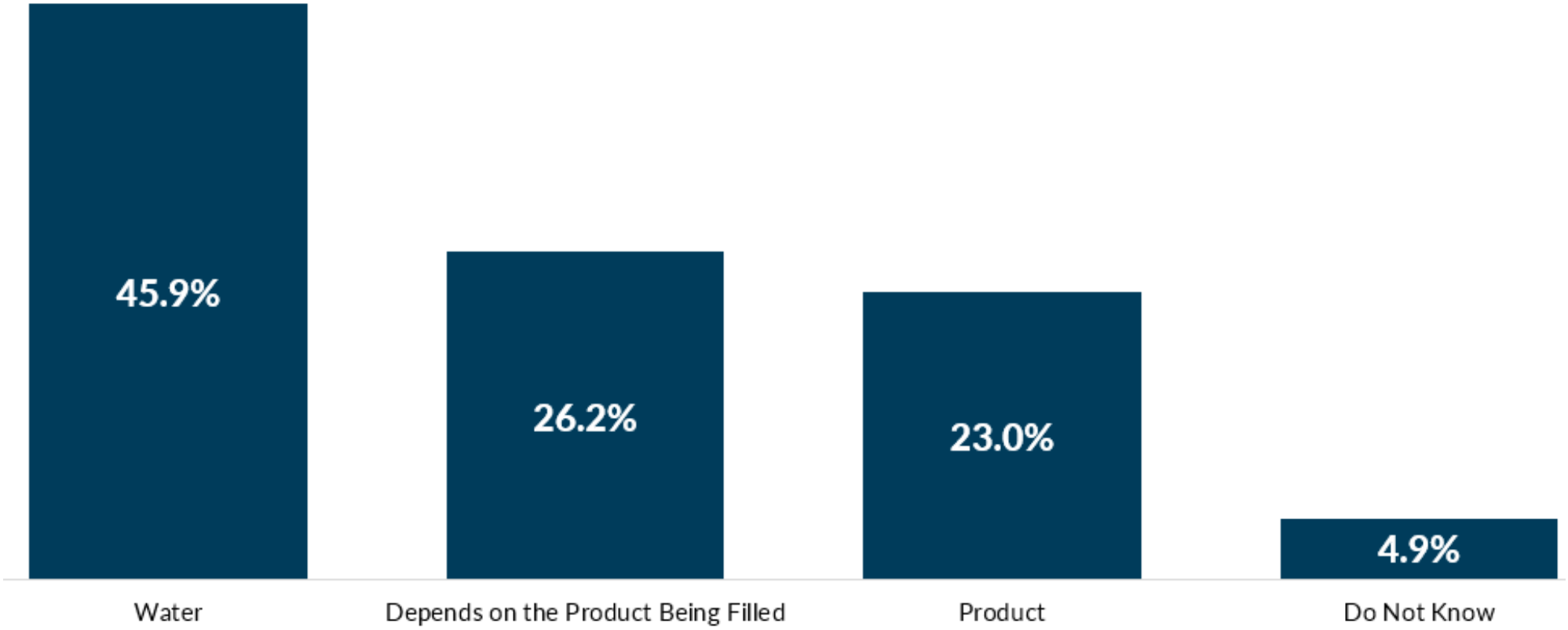
Implementation

Question
If you have not implemented PUPSIT. Will PUPSIT be implemented into the aseptic filling lines (processes) at the site that utilize a sterilizing filter for drug product sterilization in the future?
Respondents: 37 Sites

PUPSIT to be Implemented	Responses	Percent
Yes	24	64.9%
No	13	35.1%

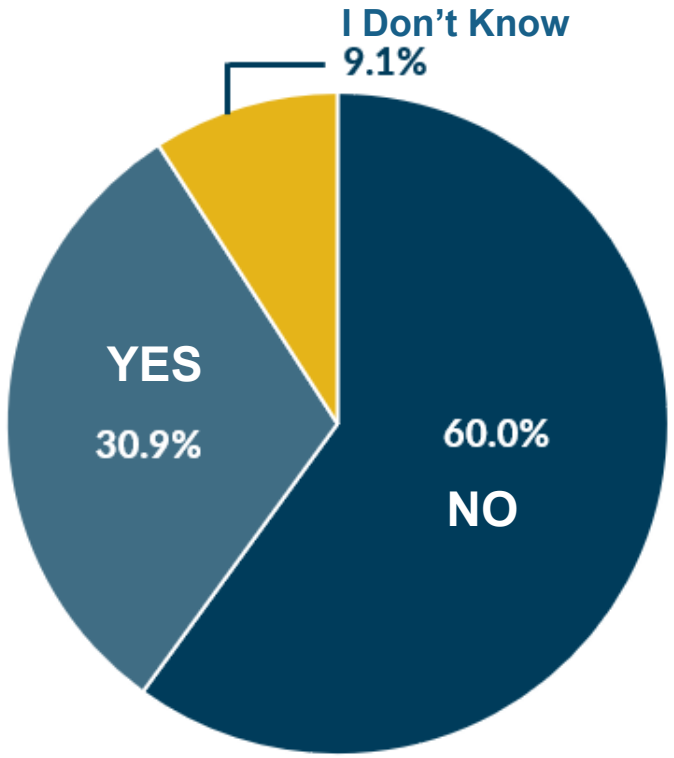
PUPSIT Execution

Question
For PUPSIT, what filter wetting agent is used?
Respondents: 61 Sites



PUPSIT Execution

Question
Have there been any PUPSIT failure?
Respondents: 55 Sites



PUPSIT Execution

Question

Follow-up question: What were the root causes of the PUPSIT failures?

- Assembly, PUPSIT assembly scheme
- Connection or equipment piping connections
- Damage to filter
- Equipment set up issue
- Failed tests due to insufficient wetting, but not failures of the filtration system
- Filter not enough wet, product dried, filter broken during wetting 1 bar
- Filter with integrity test close to the limit and failing the product integrity test
- Insufficient filter membrane wetting followed by leaks in purchased tubing assemblies are the most common cause
- Incomplete wetting
- Improper filter installation of filter damage.
- Improper wetting. Drying of filter
- Mostly for after filtering process, the criteria for filter that retained product are not same as the original filter with water (surfactant).
- Wetting issues primarily.
- Wetting with water is insufficient. We checked with IPA and found filter is integrity. But, we can not used that filter anymore.
- Wrong Recipe, wrong handling by operators.

PUPSIT Execution

Question
Has there been microbial contamination(s) on the filter's filtrate side that was potentially related to PUPSIT?
Respondents: 47 Sites

Microbial Contamination(s)	Responses	Percent
No	38	80.8%
Do Not Know	6	12.8%
Yes	3	6.4%

PUPSIT's Impact on Design Complexity (After Implementation)

Question
After implementing PUPSIT, in your opinion did the filter assembly design complexity (filter assembly and associated piping, valves, and control system) on the filtrate (sterile) side of the sterilizing filter stayed the same, was slightly more complex, or much more complex?
Respondents: 47 Sites

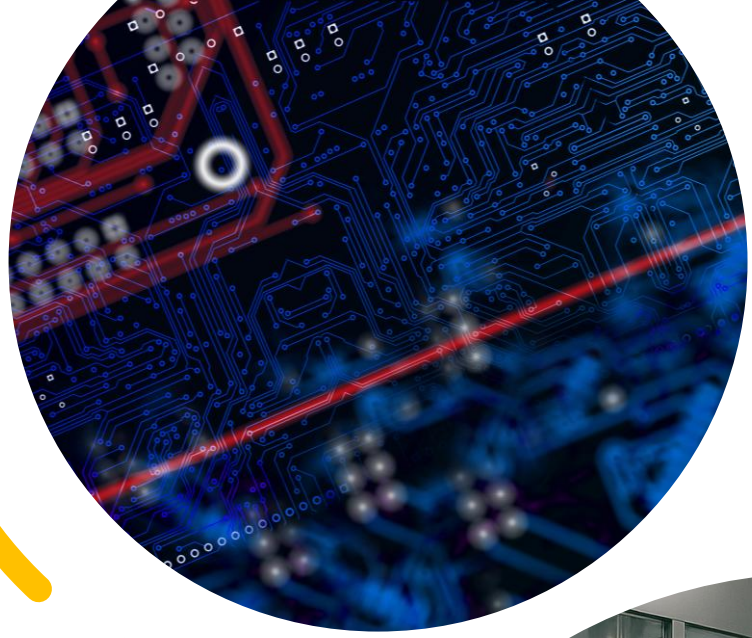
Filter Assembly Design Complexity	Responses	Percent
Slightly More Complex	21	44.7%
Much More Complex	17	36.2%
Same Complexity	9	19.1%

PUPSIT's Impact on Design Complexity (Planning to Implement)

Question
When completing any risk assessments and/or evaluations as part of evaluating PUPSIT implementation, did you find the implementation of PUPSIT increased, decreased, or had no impact to the sterility assurance risk level of the manufacturing process?
Respondents: 67 Sites

Impact to Sterility Assurance Risk Level	Responses	Percent
Increased	29	43.3%
Had No Impact	17	25.4%
Decreased	12	17.9%
Not Covered in Risk Assessment/Evaluation Performed	9	13.4%

The Operator of the Future and Training



The Operator

- As automation and the introduction of more robotic operations increases - number of operators needed expected to decrease

  <u>There will be fewer operators required</u>

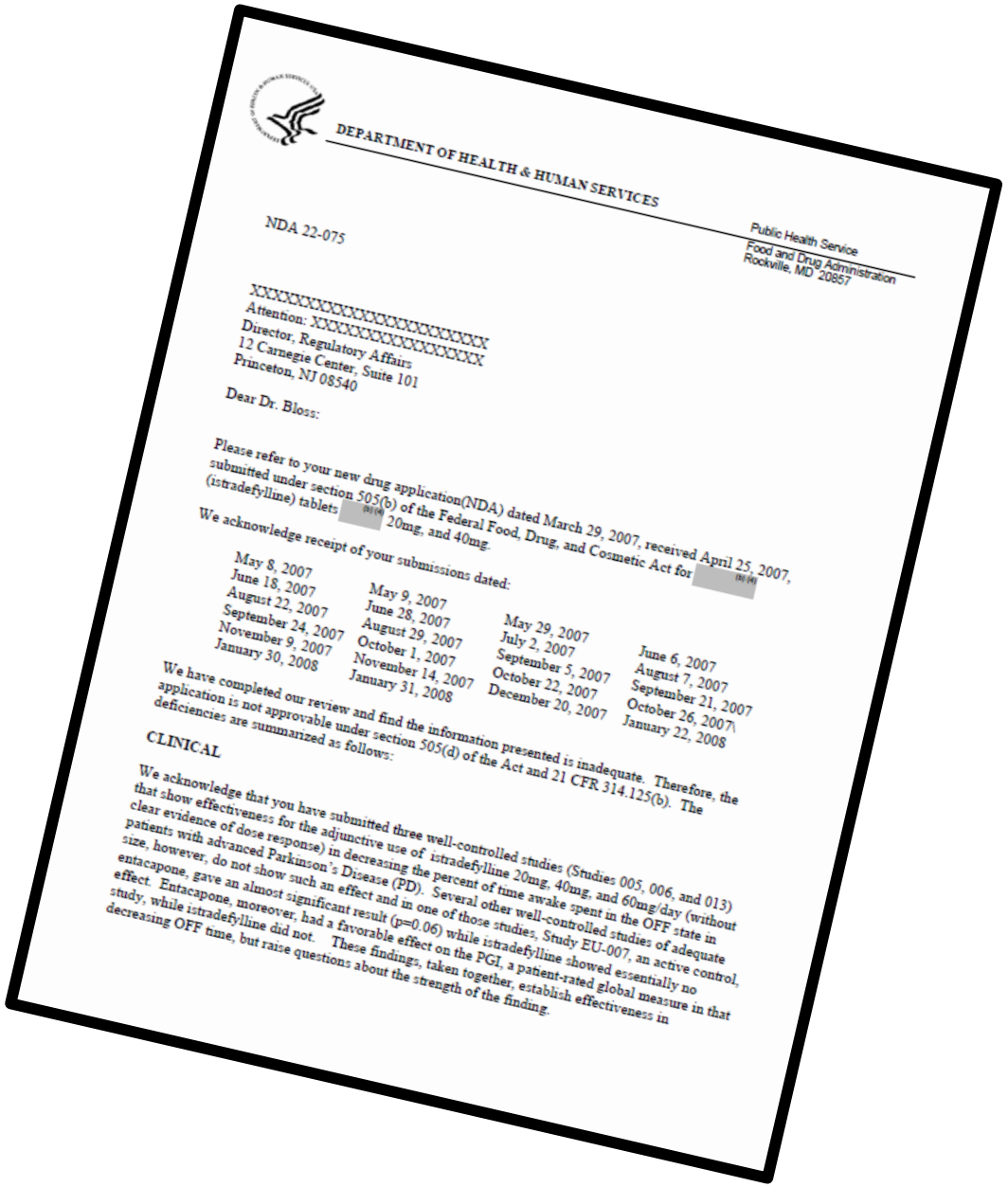
- As the overall volume of manual work decreases they will be expected to do more roles
- The skill set required for the operator will continue to change
  - Need for increasing levels of understanding in the science behind the unit operation
  - Increase in ability to quickly troubleshoot operations using the principles of QRM and the advanced AI tools provided
  - Understanding how to use and rapidly apply technology

The Training

- Increase training on the science of the unit operation:
  - What the unit operation is for
  - How it accomplishes its task
  - Why each step is important
- Increased training on the importance of specific environmental controls (e.g., first air, disinfection, sterilization, gowning, etc.)
- Understanding (to some level) of the automation being used, any AI controls, and how these impact the unit operations and environmental controls

(The operator becomes in essence the human analyst for the operation being performed. Higher levels of education/training are expected to be needed)

US FDA Complete Response Letters (CRLs)
An Industry Perspective



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-075

XXXXXXXXXXXXXXXXXXXXXX
Attention: XXXXXXXXXXXXXXXXX
Director, Regulatory Affairs
12 Carnegie Center, Suite 101
Princeton, NJ 08540

Dear Dr. Bloss:

Please refer to your new drug application(NDA) dated March 29, 2007, received April 25, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (istradefylline) tablets [redacted] 20mg, and 40mg.

We acknowledge receipt of your submissions dated:

May 8, 2007
June 18, 2007
August 22, 2007
September 24, 2007
November 9, 2007
January 30, 2008

May 9, 2007
June 28, 2007
August 29, 2007
October 1, 2007
November 14, 2007
January 31, 2008

May 29, 2007
July 2, 2007
September 5, 2007
October 22, 2007
December 20, 2007

June 6, 2007
August 7, 2007
September 21, 2007
October 26, 2007
January 22, 2008

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

CLINICAL

We acknowledge that you have submitted three well-controlled studies (Studies 005, 006, and 013) that show effectiveness for the adjunctive use of istradefylline 20mg, 40mg, and 60mg/day (without clear evidence of dose response) in decreasing the percent of time awake spent in the OFF state in patients with advanced Parkinson's Disease (PD). Several other well-controlled studies of adequate size, however, do not show such an effect and in one of those studies, Study EU-007, an active control, entacapone, gave an almost significant result (p=0.06) while istradefylline showed essentially no effect. Entacapone, moreover, had a favorable effect on the PGI, a patient-rated global measure in that study, while istradefylline did not. These findings, taken together, establish effectiveness in decreasing OFF time, but raise questions about the strength of the finding.

A Noble Mission Share by Both Regulators and Industry

- Protecting the public health by ensuring the safety, efficacy, and security of human drug products
- Advancing the public health by speeding innovations that:
  - Provides new medical products for unmet or undertreated medical conditions
  - Make medical products more effective, safer, available, and more affordable
- Doing all this while keeping the patient at the center of all we do

What is an FDA Complete Response Letter (CRL)

An FDA Complete Response Letter (CRL) is a letter sent by the U.S. Food and Drug Administration (FDA) to a drug sponsor when their application is not approved in its current form. The CRL details the deficiencies in the application and outlines the actions the sponsor needs to take to make the product approvable.

CRLs continue to be a challenge for industry

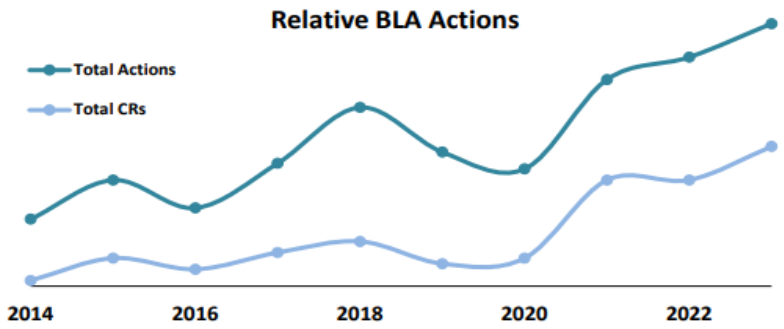
- Number of CRLs continues to be elevated
- Facility issues continue to be a significant portion of CRL issues across all CDER BLA submissions*
- New product introduction are being impacted
- Financial and perception impact on companies receiving / involved
- CRL's have for the most part not been available to the industry

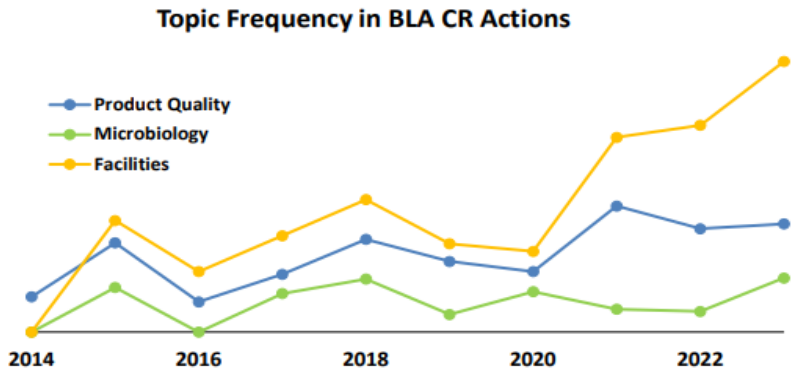
    FDA's recent decision to release CRL's and their commitment to move to real time release will be very helpful in regard to industry understand the types of challenges being seen

This is not to say that CRLs, when needed, are not appropriate. Their use in the process is an important part of ensuring public health.

* From BLA Submission, Assessment, and Facility Readiness/Inspection: CMC for Biologics & Biosimilars (https://healthpolicy.duke.edu/events/cderBLAsubmission)

Action and Topic Trends





- Total Actions on BLAs have been increasing recently, with a concurrent increase in CRs for all reasons
- Frequency analysis identified consistent trends in CR rates, with the greatest increase in facilities deficiencies
- Increase in facilities trend
  - Impact of regulatory pathway
  - Impact of multi-product considerations

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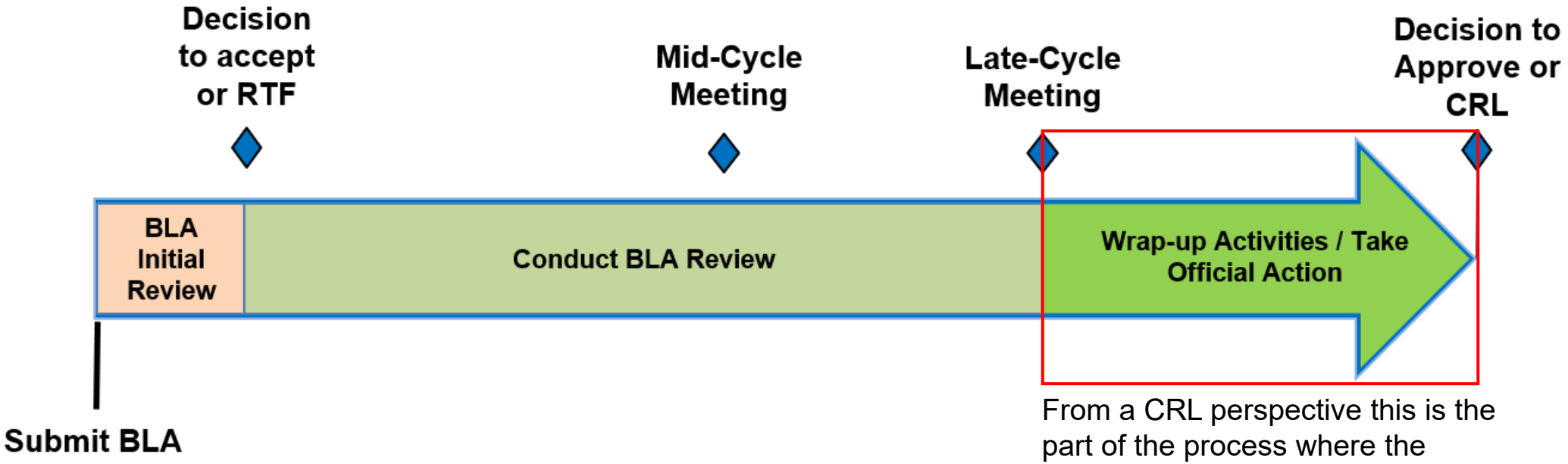
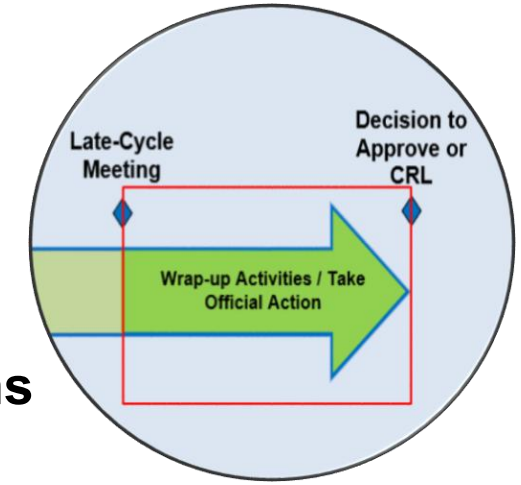
* Slide from FDA Presentation 20 Aug 2024 at the Duke-Margolis Institute for Public Health meeting: Continual Improvement of CDER BLA Submission, Assessment, and Facility Readiness/Inspection: CMC for Biologics & Biosimilars (https://healthpolicy.duke.edu/events/cderBLAsubmission)

High Level FDA Review and Approval Timeline



The FDA is required to meet the PDUFA (Prescription Drug User Fee Act) timeline and action date for a decision (to approve the application or issue a CRL)

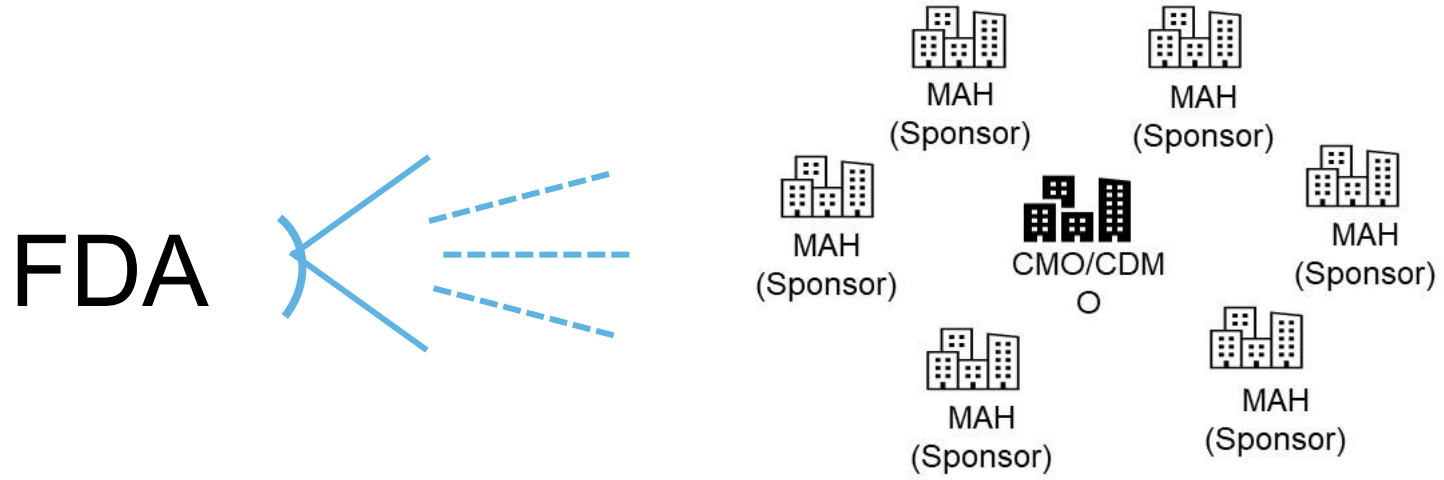
What are we hearing from industry?



- **Timing of Pre Approval Inspection (PAI)**
  Timing of the PAI is in some cases occurring very late in review cycle, insufficient time to resolve any issues or concerns prior to action date
- **Late in Review Cycle - New Request for Documents / Additional Questions**
  Arriving after Late Cycle Meeting and to close to the action date – insufficient time to resolve any issues or concerns prior to action date
- **Increasing GMP Expectations from Inspectors**
  Inspectors are challenging what had long been settled science in the pharma industry, in some cases requiring significant equipment modifications to existing equipment sets and process revalidations. Is the PAI the correct place to be setting new industry expectations?
- **Lack of Industry Visibility of Manufacturing Related CRL Issues**
  FDA has been the only group that can see across all CRLs and provide trends of concern to industry (recently announced changes welcomed)
- **The CDMO CRL Dilemma**
  Nearly half of CRs with facility deficiencies are for BLAs (CDER) with manufacturing proposed at CDMOs/CMOs*

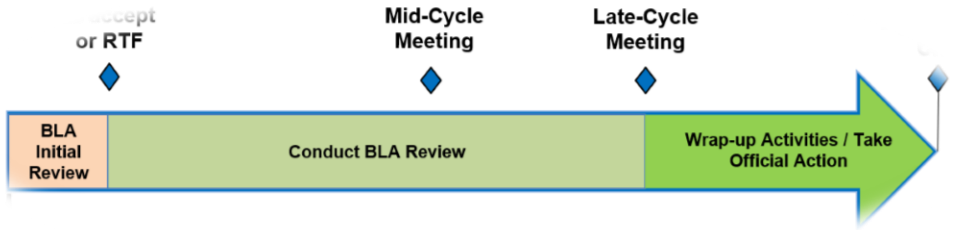
* From 20 Aug 2024 FDA Presentation at the Duke-Margolis Institute for Public Health meeting: Continual Improvement of CDER BLA Submission, Assessment, and Facility Readiness/Inspection: CMC for Biologics & Biosimilars (https://healthpolicy.duke.edu/events/cderBLAsubmission)

The CDMO CRL Dilemma



- MAH (Sponsor) receives a CRL related to a BLA for activities at a CMO/CDMO.
- Other MAHs (Sponsors) that have pending BLAs and also use the CMO/CDMO but are not aware there is a concern (based on inspection timing 483 not available)
- CMO/CDMO is not sharing based on contractual obligations
- How can the other MAHs (sponsors) know if the issues impact their BLA and if they will receive a CRL based on it? (Directionally the added transparence discussed by US FDA on CRLs may provide some help)

Final Thoughts



- CRLs will always be part of the process but should not be a surprise to the sponsor with issues being identified early for resolution if possible
- Any major concerns or issues with the submission and PAI that may impact its approval needs to be communicated no later then the Late-Cycle Meeting
- To be effective there must be sufficient FDA resources with the right expertise/training/experience for both the submission review and PAI
- Is the requirement that FDA needs to always hit the PDUFA target adding to this challenge?
- PDA is continuing to gather information on the current challenge industry is facing with CRLs and will continue to work with the industry's CQOs to raise the visibility of these challenges

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