GMP Related updates and Hot topics

- *PDA Israel*
- *February 2025*

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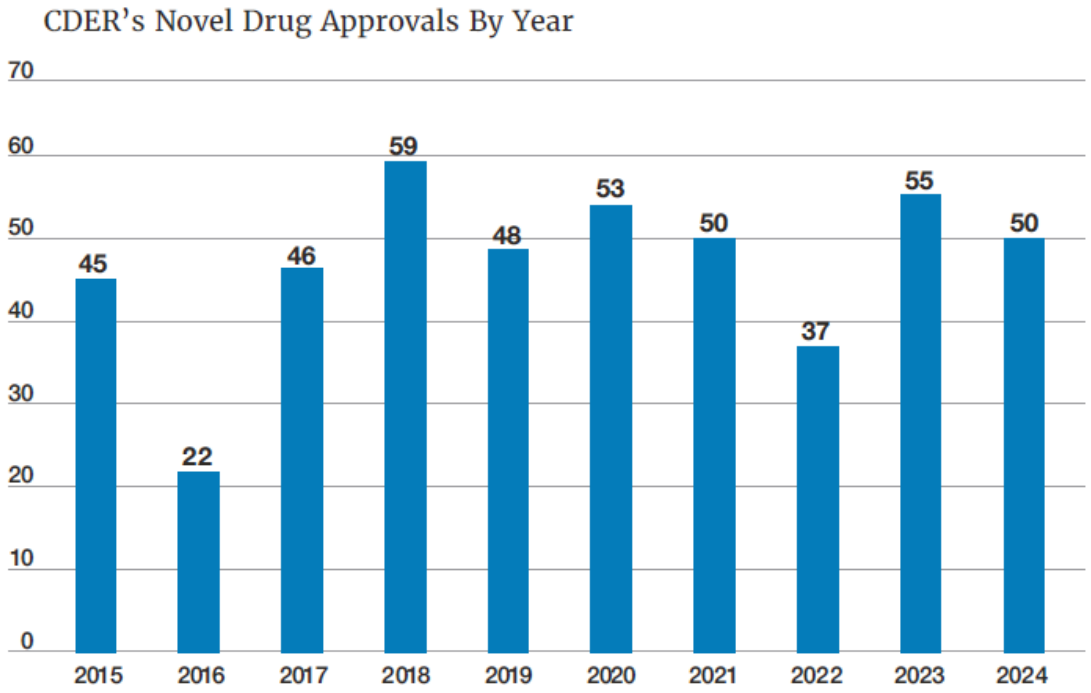
Advancing Health Through Innovation:

FDA New Drug Therapy Approvals 2024

FDA New Drug Therapy Approvals 2024

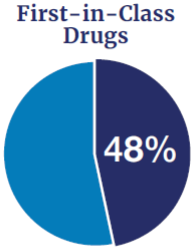
CDER's Annual Novel Drug Approvals: 2015 – 2024

The 10-year graph below shows that from 2015 through 2024, CDER has averaged about 47 novel drug approvals per year.



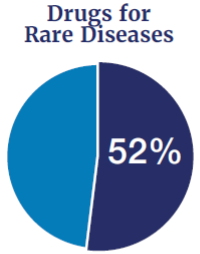
FDA New Drug Therapy Approvals 2024

(48%) in 2024 as first-in-class. These drugs produce a novel pharmacologic effect, the impact or influence that a drug has on the body or a specific biological target, in a disease.



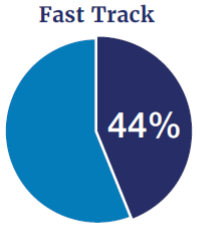
CDER identified 24 out of the 50 novel drugs (48%) approved in 2024 as first-in-class.

26 of CDER's 50 novel drug approvals (52%), were approved to treat rare or "orphan" diseases (diseases that affect fewer than 200,000 people in the U.S.). Patients with rare diseases often have few or no drugs available to treat their conditions.



Over half (52%) of the drugs CDER approved in 2024 received orphan drug designation.

CDER granted fast track status to 22 of the 50 novel drugs (44%) in 2024. Fast track speeds development and review of new drugs and biologics by increasing the level of communication between FDA and drug developers and by enabling CDER to review portions of a drug application on a rolling basis.



CDER designated 22 of the 50 novel drugs (44%) as fast track.

EMA- AUTHORISATION OF NEW MEDICINES

EMA- AUTHORISATION OF NEW MEDICINES

Key figures[1] on the European Medicines Agency's (EMA) recommendations for the authorisation of new medicines in 2024:

114

POSITIVE OPINIONS

5

NEGATIVE OPINIONS

8

WITHDRAWN APPLICATIONS[3]

Among the positive opinions:

46 New active substances

6 PRIME

15 Orphan medicines[2]

1 Advanced therapy medicinal product (ATMP)

28 Biosimilars

17 Generics

3 Accelerated assessments

8 Conditional marketing approvals

4 Approval under exceptional circumstances

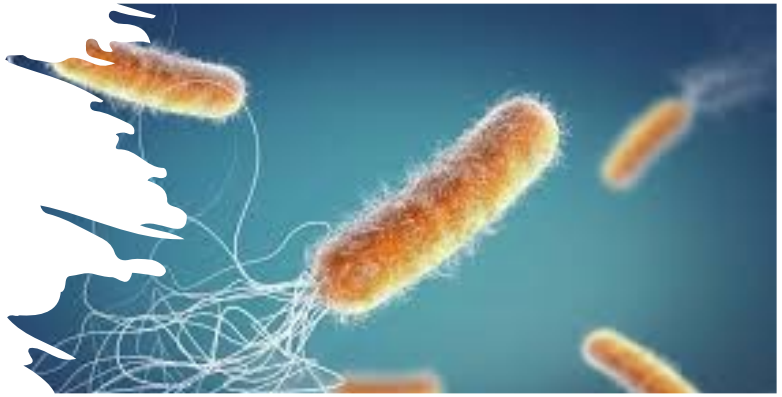
EMA -MEDICINES FOR RARE DISEASES

The EU framework for orphan medicines aims to encourage the development and marketing of medicines for patients with rare diseases by providing incentives for developers. The assessment of orphan medicines is conducted by the Committee for Medical Products for Human Use (CHMP) using the generally applicable evaluation standards.

In addition, orphan designations are reviewed by EMA's Committee for Orphan Medicinal Products (COMP) at the time of approval to determine whether the information available to date allows maintaining the medicine's orphan status and granting the medicine ten years of market exclusivity. In 2024, **15 medicines** had their orphan designation confirmed by the end of the year.

PDA
Parenteral Drug Association

OTC- Contaminated Eye Drops and Eye Ointments



Another death, more cases of vision loss linked to contaminated eye drops, CDC reports

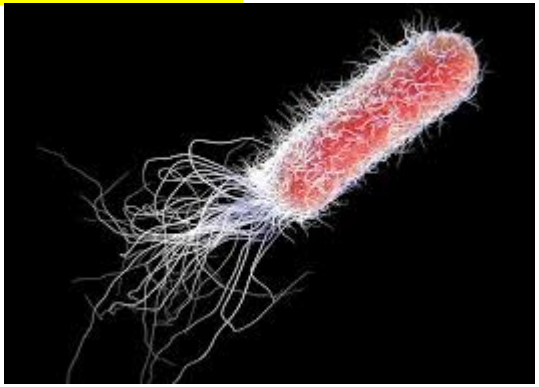
Four deaths and 14 cases of vision loss in total have now been reported among more than 80 infections of a rare strain of drug-resistant ***Pseudomonas aeruginosa*** that had never been identified in the United States prior to this outbreak. The CDC has also reported four cases of surgically removed eyeballs.

sterility testing of EzriCare

As part of this investigation, FDA collected finished product samples of Artificial Tears batches that were manufactured for EzriCare LLC by Global Pharma Healthcare Private Limited, and we sent the samples for sterility testing at FDA laboratories. Our analysis of intact (unopened) units found that 14 batches of EzriCare LLC's Artificial Tears were non-sterile.

Microbiological isolates from the non-sterile samples were further characterized using whole genome sequencing and compared to isolates in a national database.[2] *Pseudomonas aeruginosa* isolates from three different batches of intact Artificial Tears samples collected by FDA were found to be close genetic matches to more than 85 clinical isolates associated with the outbreak

Figure 2: Examples of positive growth in Steritest™ EZ canisters



Global Pharma Healthcare –FDA inspection

In April, the FDA said in an inspection report that the Global Pharma Healthcare facility in India did not follow proper protocol to prevent contamination of its products.

The FDA visited the facility for an 11-day inspection that started in mid-February, 2½ weeks after the company recalled EzriCare Artificial Tears due to possible contamination.

The inspection of the Global Pharma facility resulted in 11 observations by the FDA, including a “manufacturing process that lacked assurance of product sterility,” specifically for batches of product that were manufactured between December 2020 and April 2022 and shipped to the US.

Warning letter
Drug Recall
Drug Production Suspended
We acknowledge your commitment to suspend production of drugs for the U.S. market.

BrassicaPharma

FOR IMMEDIATE RELEASE – 12 February, 2024 – Thane, Maharashtra, India, BrassicaPharma Pvt. Ltd. is voluntarily recalling Eye Ointment products listed in the table below with expiration date ranging from February 2024 to September 2025. The products are being recalled due to lack of sterility assurance at the facility noted during an inspection conducted by the Food and Drug Administration (FDA).

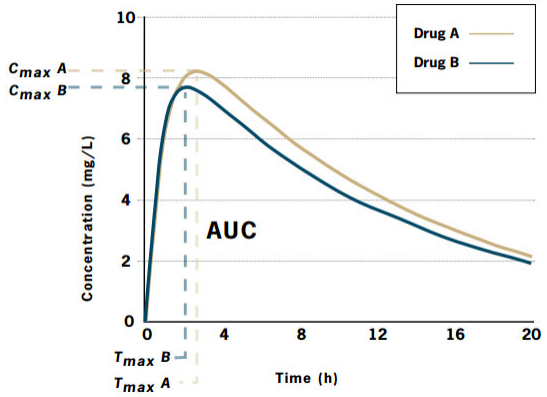
Risk Statement: For those patients who use these products, there is a potential risk of eye infections or related harm. These products are intended to be sterile. Ophthalmic drug products pose a potential heightened risk of harm to users because drugs applied to the eyes bypass some of the body's natural defenses.

To date, Brassica Pharma Pvt. Ltd. has not received any reports of adverse events up to 16th February 2024 related to this recall.

Synapse Labs Pvt.

Synapse Labs Pvt. Ltd: re-examination confirms suspension of medicines over flawed studies

On 21 March 2024, EMA's human medicines committee (CHMP) confirmed its recommendation to suspend or not grant the marketing authorisations of a number of generic medicines tested by Synapse Labs Pvt. Ltd, a contract research organisation (CRO) located in Pune, India. This confirmation concludes the re-examination requested by the applicants and marketing authorisation holders for some of the medicines concerned.



Synapse Labs Pvt.

- The CHMP adopted its initial recommendation in December 2023, after a good clinical practice (GCP) inspection, which showed irregularities in study data and inadequacies in study documentation and in the computer systems and procedures to manage study data. This raised serious concerns about the data from bioequivalence studies conducted at the CRO.

- For the majority of the medicines tested by Synapse Labs on behalf of EU companies, the CHMP concluded that supporting data were lacking or insufficient to show bioequivalence and therefore recommended suspending the marketing authorisations of these medicines.

- The CHMP's recommendation was sent to the European Commission, which issued a legally binding decision on 24 May 2024.

Synapse Labs Pvt.

- To reach its conclusion for the over 400 medicines tested by Synapse Labs on behalf of EU companies, EMA's human medicines committee (CHMP) looked at all available information, including bioequivalence data potentially available from other sources. A list of the medicines concerned is available on the EMA website.

Synapse Labs Pvt.

- To lift the suspension, companies must provide alternative data demonstrating bioequivalence. Medicines for which ongoing marketing authorization applications rely only on data from Synapse Labs will not be granted EU authorization.

- National authorities will decide if any of the medicines recommended for suspension are of critical importance in their countries and make final decisions on whether to suspend their use or allow them to remain available while new data are generated.

Notification to Pharmaceutical Companies: Clinical and Bioanalytical Studies Conducted by Synapse Labs Pvt. Ltd. are Unacceptable

Drug Safety and Availability

Drug Alerts and Statements

Information about Nitrosamine Impurities in Medications

[06/18/2024] FDA is notifying sponsors of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) that clinical and bioanalytical studies conducted by Synapse Labs Pvt. Ltd. (Synapse)—a contract research organization (CRO) based in Pune, India—are not acceptable because of data integrity concerns. Studies conducted by Synapse must be repeated.

During analyses of study data generated at Synapse and submitted in several applications, FDA identified significant unexplained anomalies in the data that indicate the data were falsified. FDA issued an initial general correspondence letter (GCL) to Synapse

Synapse Labs Pvt.

FDA has been investigating **postmarketing safety reports** for marketing applications that relied on bioavailability/bioequivalence studies conducted by Synapse for approval. To date, the agency has not identified signals related to problems with the safety or quality of the approved drugs. FDA remains vigilant and will act should we identify safety issues. Patients should not make changes to their treatment except in consultation with their health care professional.

synapse

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15 Year Exerience

780+ BA/BE Studies

Successful Track Record
Of Audits & Inspections

250+ Employees

US will not be enforcing Annex 1

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At the regulator session the next day, FDA officials were asked to address Annex 1 implementation in the US.

FDA's Richard Friedman, deputy director of the Center for Drug Evaluation and Research's Office of Manufacturing Quality said there are no plans to enforce EU's GMPs Annex 1 in the US, though FDA's existing guidance for sterile drug manufacturing is largely aligned with Annex 1.

In the meantime, regulators from the US Food and Drug Administration (FDA) said that while they will not be enforcing Annex 1, inspectors will be looking into similar areas as their counterparts in the EU.

Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice - October 2004

Annex 1, Manufacture of Sterile Medicinal Products- August 2023

US will not be enforcing Annex 1

- Friedman said each country in the Pharmaceutical Inspection Co-operation Scheme (PIC/S), of which FDA is a member, "has sovereignty and has their own national laws and guidances" and are not obligated to comply with Annex 1. Instead, these laws and guidances are only supposed to be harmonized with Annex 1.

  FDA officials also said that for similar reasons, they will not be enforcing PUPSIT, yet said that PUPSIT was largely aligned with FDA's existing guidance.

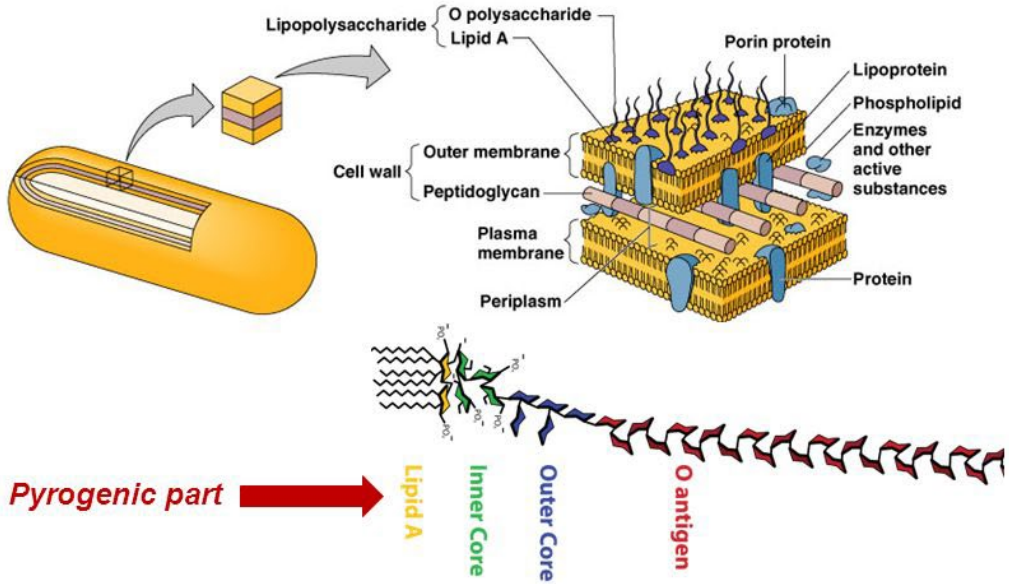

Atlantic horseshoe crab (*Limulus polyphemus*).

A pyrogen is a foreign substance that causes a fever (temperature elevation) in an animal's body. Typically, pyrogenic substances include endotoxin

Endotoxin

Pyrogens

- **Lipopolysaccharide is a component of Gr (-ve) bacteria cell wall**

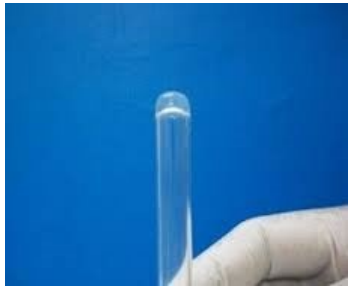


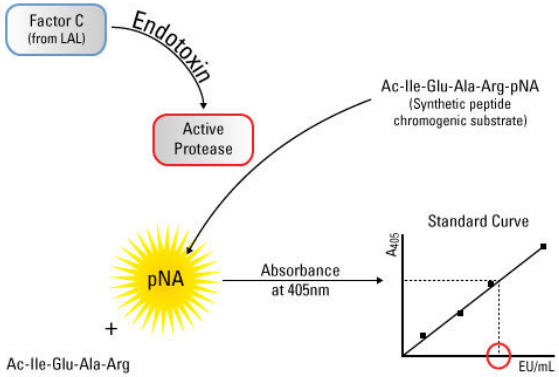
LAL test / Bacterial Endotoxins Test (BET)

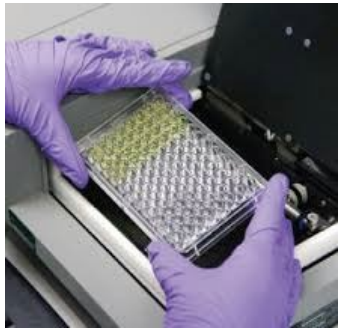
The Bacterial Endotoxins Test (BET) is a test to detect or quantify endotoxins from Gram-negative bacteria using amoebocyte lysate from the horseshoe crab (Limulus)

There are three techniques for this test:

1. The gel-clot technique, which is based on gel formation.
2. The turbidimetric technique, based on the development of turbidity after cleavage of an endogenous substrate
3. The chromogenic technique, based on the development of color after cleavage of a synthetic peptide-chromogen complex.







PDA
Parenteral Drug Association

Aug 19 2024

The Road to Regulatory Approval for Recombinant Cascade Reagents: USP Approves Chapter <86>

As announced by the US Pharmacopeia (USP) on Friday, July 26th, 2024, The USP Microbiology Expert Committee has **finalized and approved the inclusion of Chapter <86>,** Bacterial Endotoxins Test Using Recombinant Reagents. This significant development permits the use of non-animal-derived reagents for **bacterial endotoxin testing (BET)**, including **recombinant cascade (rCR)** and recombinant Factor C (rFC) reagents. Publication for early adoption will be released in November 2024 and will become official in May 2025. This timeline allows our partners to plan for the implementation of these innovative testing methods.

Alternative test systems for testing for endotoxins had already found their way into other pharmacopoeias some time ago, e.g. into the Ph.Eur. general chapter 2.6.32. Test for bacterial endotoxins using recombinant factor C. These methods have also been included in the water monographs since 2023.

The rFC test for the quantitative endotoxin determination has become effective as a new general chapter 2.6. 32 in the European Pharmacopoeia since January 1, 2021

Now the United States Pharmacopoeia (USP) is following suit. In August 2023, the new chapter <86> Bacterial Endotoxins Test Using Recombinant Reagents was announced with a link to the draft of the corresponding document and the corresponding opportunity to comment.

since 2023.

Ph. Eur. allows the use of recombinant factor C for control of bacterial endotoxins in water monographs

EDQM | STRASBOURG, FRANCE | 13/092023

Test for bacterial endotoxins using recombinant factor

The Importance Of The Cascade

Naturally-Sourced LAL Reagent

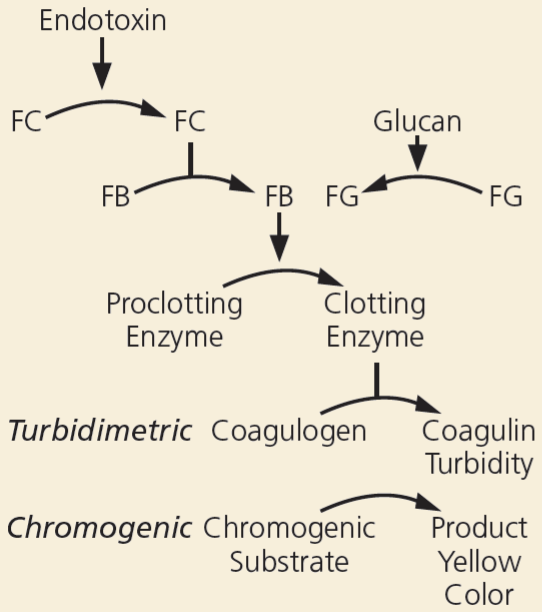


Figure 1: The LAL Cascade Mechanism
(as triggered by endotoxin and/or 1,3-β-D-glucans)

PyroSmart NextGen®

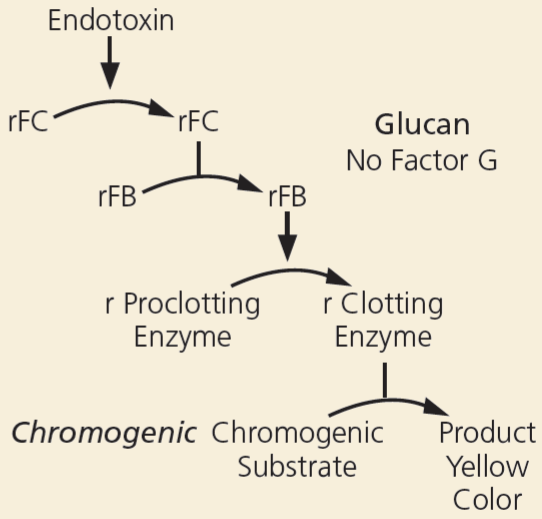


Figure 2: The Recombinant Cascade Mechanism
(as triggered by endotoxin only)

pyrogen test on rabbits

The pyrogen test on rabbits is based on the measurement of the increase in the rabbit's temperature upon being injected with a product that could contain a contaminant of the pyrogen type

EU Eliminate the Rabbit Pyrogen Test (RPT) from Its monographs

edqm European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Press release

16 July 2024, Strasbourg, France

European Pharmacopoeia bids adieu to rabbit pyrogen test in its monographs

In a landmark decision for both animal welfare and scientific advancement, the European Pharmacopoeia Commission (EPC) decided to eliminate the Rabbit Pyrogen Test (RPT) from its monographs during its 179th session in June 2024.

Pyrogens are fever-inducing contaminants that may unintentionally be present in medicines administered by injection (including vaccines, blood products, radiopharmaceuticals, antibiotics and large volume solutions for infusion). Their detection is therefore essential to ensure that medicines administered by this route are safe.

For decades, the RPT has been the traditional method of detection. The RPT involves measuring the rise in body temperature in rabbits following intravenous injection of the test substance. Despite multiple efforts to encourage medicine developers to move away from the RPT, the test is still widely used to detect pyrogens, consuming around 400 000 rabbits /year[1] worldwide.

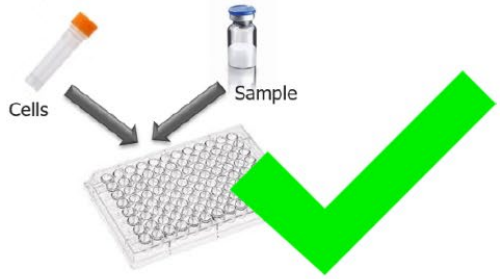
MAT- Monocyte Activation Test
RPT- Rabbit pyrogen Test

Why should I establish the MAT?

- In Ph. Eur.: Replacement of RPT
  - New Chapter 5.1.13 (*Pyrogenicity*)

- Rabbit Pyrogen Test = animal testing
- MAT = suitable *in-vitro* alternative

  - **RPT will only be allowed in rare exceptional cases in Europe**



Maria Gajewi,
Microcoat Biotechnologie GmbH

Why should I establish the MAT?

MAT is **compendial**
(European Pharmacopoeia Chapters 2.6.30 and 2.6.40)

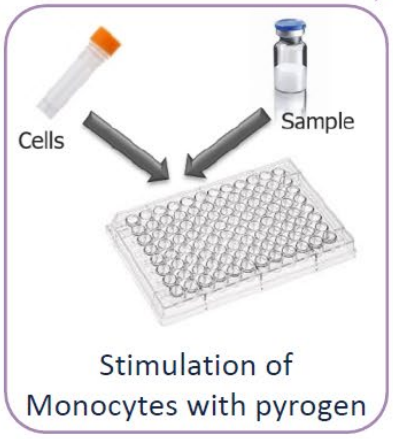
Only a product-specific verification of the method is necessary

MAT is **not compendial**

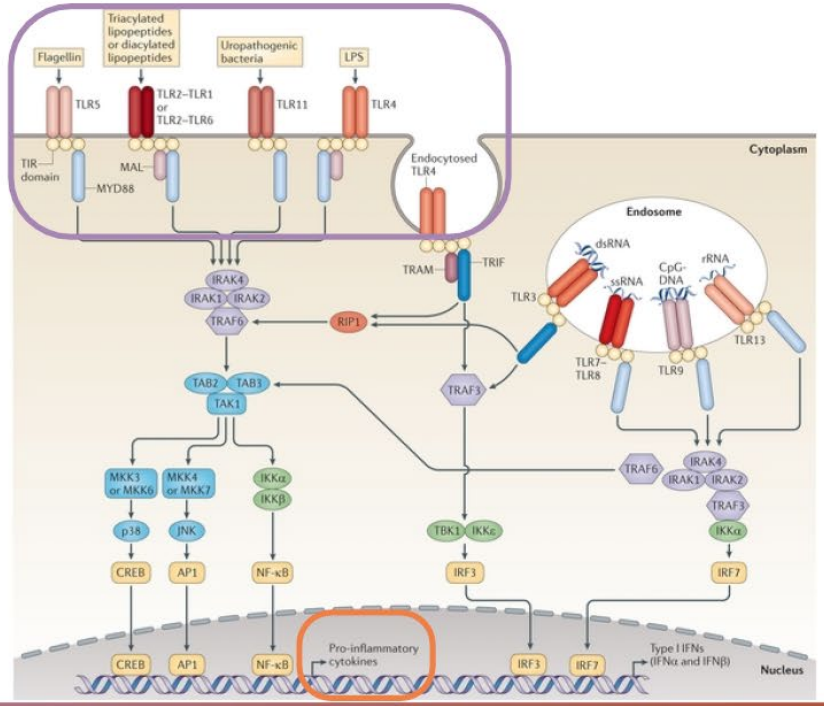
A complete validation of the method as alternative method is necessary

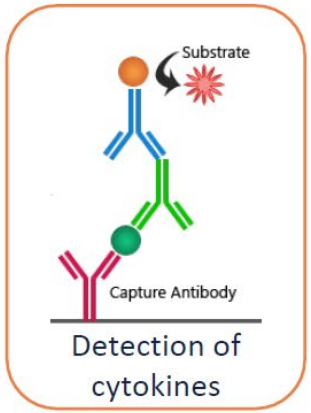
Selection of MAT system and implementation

Pyrogen



Stimulation of Monocytes with pyrogen



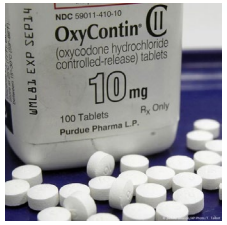


Detection of cytokines

Read-out

Overview adapted from *Nature Reviews Immunology 13, 453–460 (2013)*
Picture of ELISA antibody adapted from *IndianJMicrobiolRes 8, 10-14 (2021)*

Consulting brand McKinsey Scandal



Justice Department Announces Resolution of Criminal and Civil Investigations into McKinsey & Company's Work with Purdue Pharma L.P.; Former McKinsey Senior Partner Charged with Obstruction of Justice

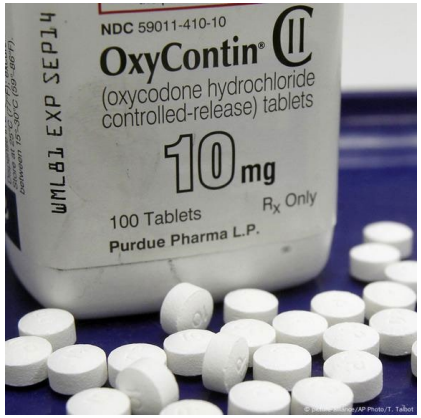
McKinsey Will Pay $650 Million, Cease Work Relating to controlled Substances, and Implement Significant New Compliance Measures

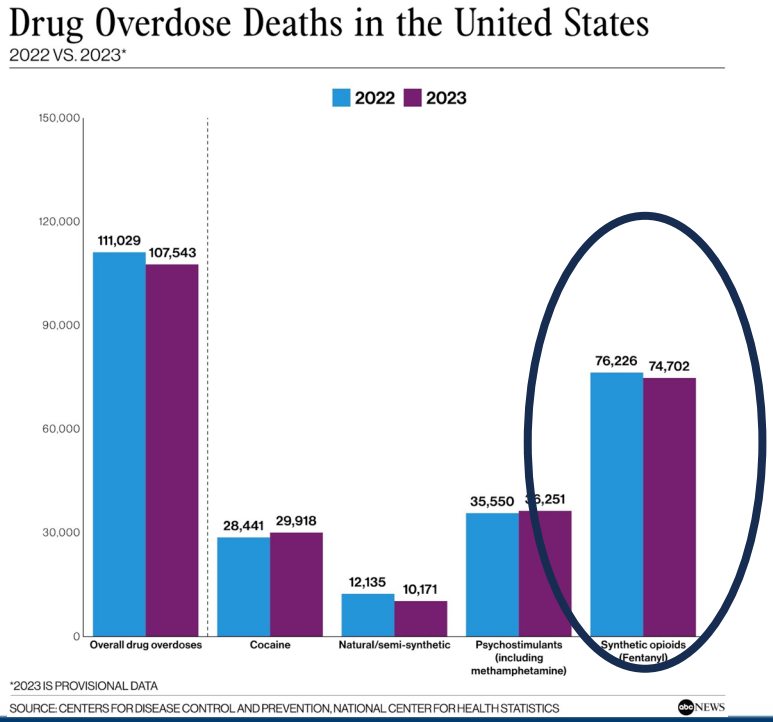
The resolution pertains to McKinsey's advice to Purdue concerning the sales and marketing of Purdue's extended-release opioid drug, OxyContin, including a 2013 engagement in which McKinsey advised on steps to "turbocharge" sales of OxyContin.

Consulting brand McKinsey Scandal

- liability under the False Claims Act for allegedly providing advice to Purdue Pharma L.P. that caused the submission of false and fraudulent claims to federal healthcare programs for medically unnecessary prescriptions of OxyContin, as well as allegedly failing to disclose to the U.S. Food and Drug Administration (FDA) conflicts of interest arising from McKinsey US's concurrent work for Purdue and the FDA.

Purdue had reached a settlement potentially worth US$8.3 billion, admitting that it "knowingly and intentionally conspired and agreed with others to aid and abet" doctors dispensing medication "without a legitimate medical purpose." Members of the Sackler family will additionally pay US$225 million and the company will close





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