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REGULATORY OVERVIEW AND COMPARISON OF PHARMACOVIGILANCE GUIDELINES IN USFDA AND EMA

Akshatha[1] and Chandan B.V.[2]*

[1]IV Pharm D, TVM College of Pharmacy, Cantonment, Airport Road, Veerashaiva College Campus, Ballari, Karnataka – 583104.

[2]Junior Regulatory Affairs Associate, Parexel International India Safety Services Private Limited, RMZ Ecoworld, Bengaluru, Karnataka – 560103.

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***Corresponding Author**
Chandan B. V.
Junior Regulatory Affairs Associate, Parexel International India Safety Services Private Limited, RMZ Ecoworld, Bengaluru, Karnataka – 560103.

ABSTRACT

Pharmacovigilance guidelines and regulations are critical components of drug safety and play a key role in ensuring the safety and efficacy of drugs on the market. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are two regulatory agencies that have established guidelines and regulations for pharmacovigilance. This review article provides a comparison of the pharmacovigilance guidelines and regulations issued by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The article examines the differences and similarities between the two agencies in terms of adverse event reporting, risk management plans, signal detection and management, periodic safety update reports, and post-authorization safety studies. The article notes that both the FDA and EMA require the reporting of serious adverse events within a 15- day timeline, but the FDA has a 90-day timeline for the reporting of non-serious events while the EMA allows for up to 90 days for both serious and non-serious events. The article suggests that this difference may impact the ability to detect potential safety issues early. The article also highlights differences in requirements for periodic safety update reports (PSURs) and periodic benefit-risk evaluation reports (PBRERs). The EMA requires PSURs for all authorized medicines in the European Union, while the FDA does not require PSURs but instead requires PBRERs for some medicines. The article suggests that this difference in requirements may reflect differences in the approach to risk management between the agencies. Overall, the review article provides a concise overview and comparison of pharmacovigilance guidelines and

regulations issued by the FDA and EMA. The article highlights important differences and similarities between the two agencies, which could impact the development and marketing of new drugs in both the USand Europe.

Introduction and History of Pharmacovigilance

Pharmacovigilance is the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems. The history of pharmacovigilance can betraced back to the mid-20th century.

In the 1950s, the sedative thalidomide was prescribed to pregnant women as a treatment for morning sickness, which resulted in a high number of birth defects. This incident led to the establishment of the first pharmacovigilance program in the world in the UK in 1964. The program was established to monitor and report adverse drug reactions (ADRs) and ensure patient safety.[1]

In 1968, the World Health Organization (WHO) established the International Drug Monitoring Program to facilitate the exchange of information on ADRs between member countries. This program was instrumental in the development of the International Classification of Diseases for ADRs andthe Adverse Reaction Terminology.[1]

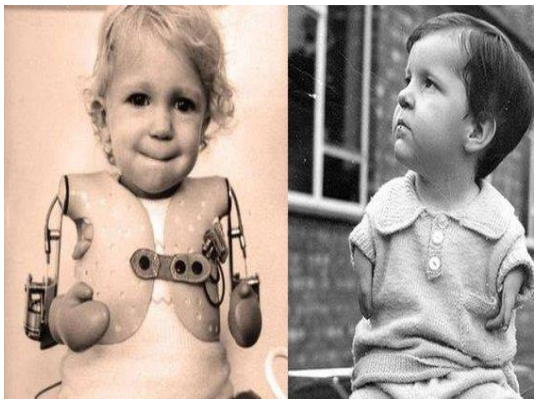


Fig. 1: Child Victims of Thalidomide Tragedy 1950.[2]

In the 1970s and 1980s, the focus of pharmacovigilance shifted from spontaneous reporting of ADRs to the systematic evaluation of drug safety through clinical trials and observational studies. The US FDA established the Adverse Event Reporting System (AERS) in 1998 to collect and analyze ADR reports frommanufacturers, healthcare providers, and consumers.

In recent years, pharmacovigilance has expanded to include pharmacogenomics, personalized

medicine, and the evaluation of medical devices. The increasing use of electronic health records and social media has also led to the development of new methods for monitoring and detecting ADRs.[10]

Overall, the history of pharmacovigilance highlights the importance of monitoring drug safety and the need for continuous improvement in the methods used to identify and prevent adverse drug reactions.[3]

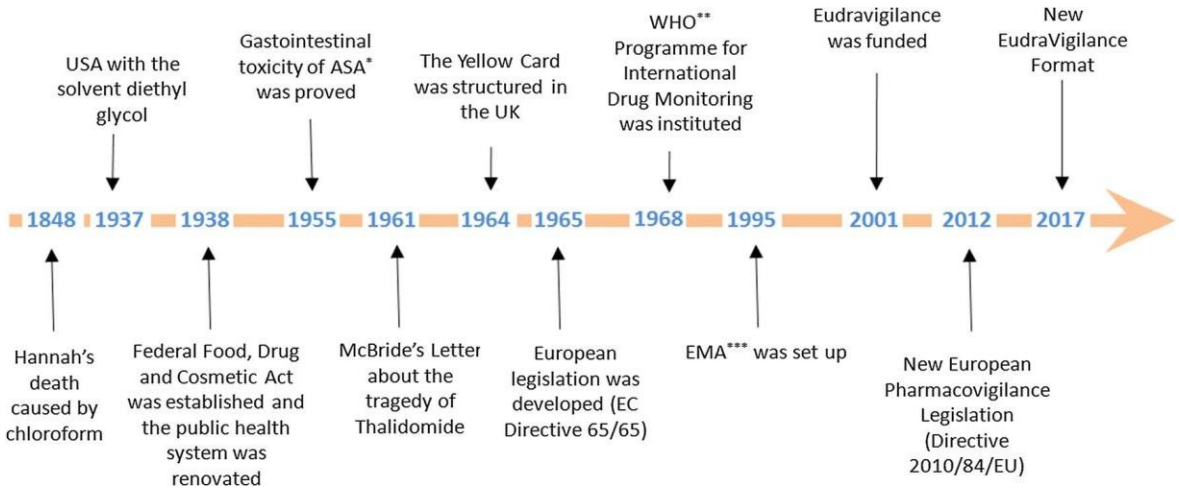
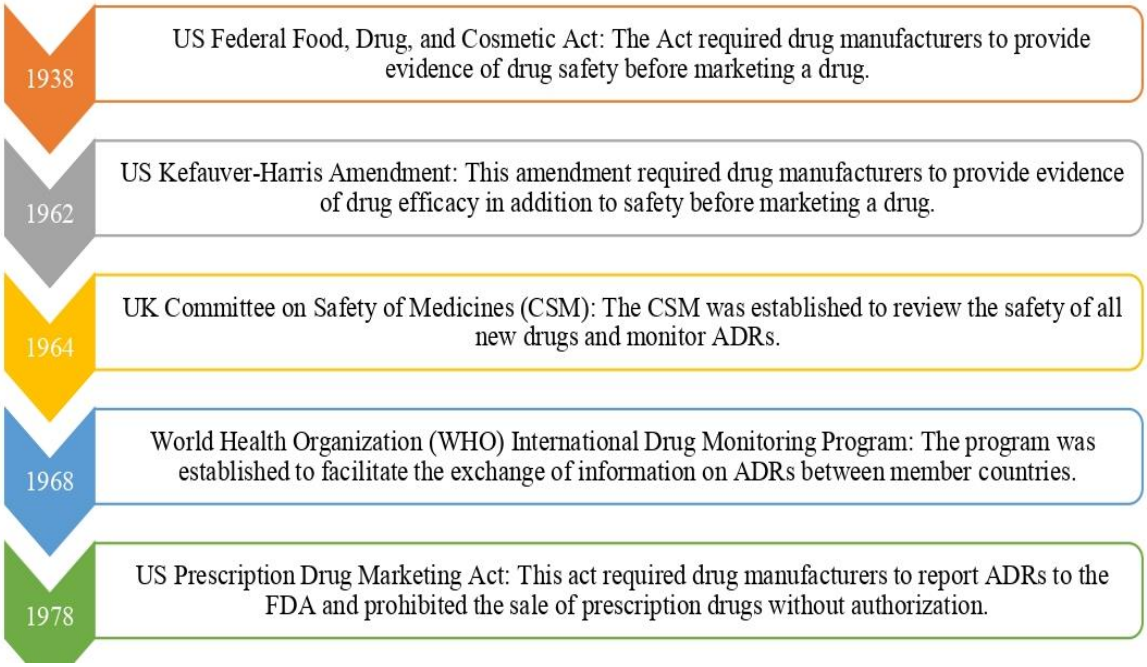


Fig. 2: Timeline of the historical evolution of Pharmacovigilance.[4]

Here are some of the key regulatory milestones in the history of pharmacovigilance



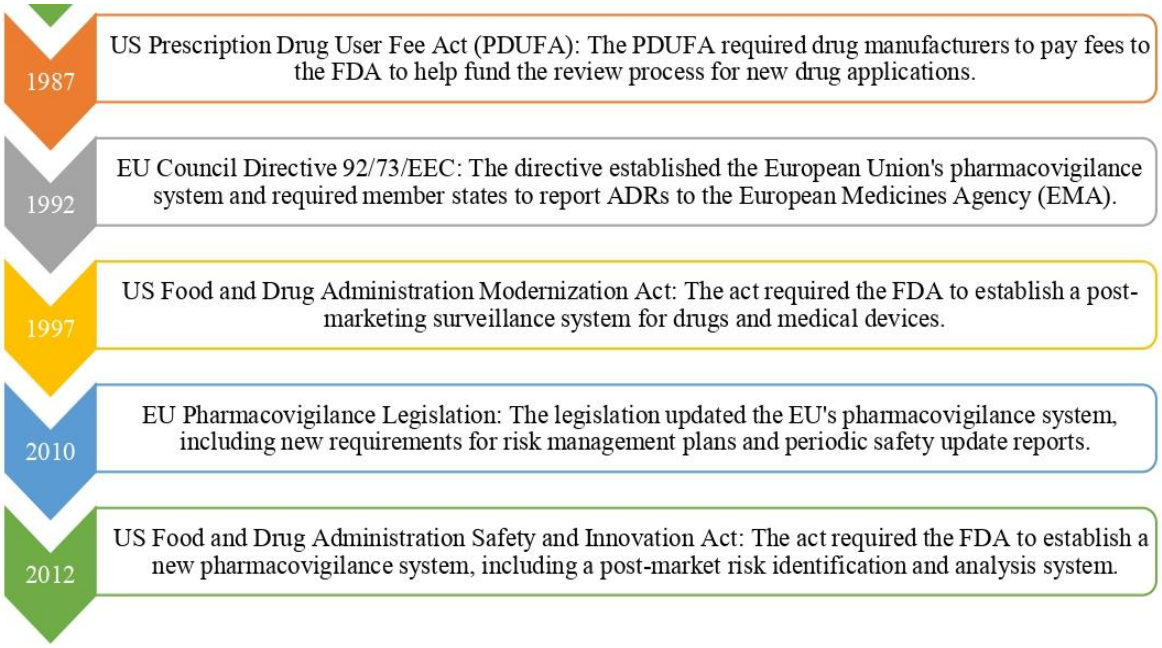


Fig 3: Regulatory milestones in the history of pharmacovigilance.[13]

These regulatory milestones reflect the ongoing effort to improve drug safety and the importance ofpharmacovigilance in protecting public health.[5] [6]

DISCUSSION

A. USFDA on Pharmacovigilance

The United States Food and Drug Administration (FDA) plays a crucial role in pharmacovigilance, which is the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem. The FDA is responsible for ensuring the safety and efficacy of drugs and medical devices before they are marketed to the public, and for monitoring their safety after theyare approved.

The FDA has a well-established pharmacovigilance program that includes post-market surveillance, adverse event reporting, risk assessment and management, and communication of drug safety information. The agency works closely with healthcare professionals, patients, and other stakeholders to identify and evaluate potential risks associated with medical products.[5]

The FDA also plays an important role in promoting pharmacovigilance globally. The agency works with other regulatory agencies around the world to share information and best practices, and to ensure that drugsand medical devices are safe and effective for patients worldwide.

Overall, the FDA's pharmacovigilance efforts are essential in protecting public health and ensuring the safety and efficacy of medical products in the United States and around the world. The agency's ongoing work is critical in detecting and preventing adverse drug reactions, and in promoting the safe and effectiveuse of drugs and medical devices.[7]

The United States Food and Drug Administration (FDA) has developed several guidelines and regulations to ensure the safety and efficacy of drugs and medical devices, as well as to promote pharmacovigilance.

Here are some of the key guidelines on pharmacovigilance issued by the FDA

Table 1: Pharmacovigilance Guidelines issued by FDA.[5]

FDA guidance on Good Pharmacovigilance Practices (GVP)	The FDA has developed a set of principles and recommendationsfor pharmacovigilance, called GVP. This guidance outlines the requirements for pharmacovigilance systems, including the collection, evaluation, and reporting of adverse events.
FDA guidance on Risk Evaluationand Mitigation Strategies (REMS)	The FDA has developed REMS to manage risks associated with certain drugs and medical devices. REMS includes requirementsfor post-market monitoring, communication of risk information, and development of educational programs for healthcare professionals and patients.
FDA guidance on Post-Market Adverse Event Reporting for Medical Products	This guidance provides instructions to manufacturers, importers,and distributors of drugs and medical devices on how to report adverse events to the FDA. The guidance outlines the criteria for serious adverse events and the required timeframes for reporting.
FDA guidance on Product-Specific Guidance for Generic Drug Development	This guidance provides specific recommendations for the development of generic drugs, including the evaluation of safetyand efficacy data and the identification of potential adverse events.
FDA guidance on Drug-Induced Liver Injury:	This guidance provides recommendations for the assessment andmanagement of drug-induced liver injury, including the evaluation of liver function tests, the identification of risk factors, and the development of risk management strategies.

Overall, these guidelines and regulations demonstrate the FDA's commitment to promoting pharmacovigilance and ensuring the safety and efficacy of drugs and medical devices. By following these guidelines, manufacturers, importers, and distributors of medical products can help to identify and preventadverse events, ultimately improving patient outcomes.[10] [11]

Here are some of the key timelines in the history of pharmacovigilance in accordance with the USFDA[5][4]

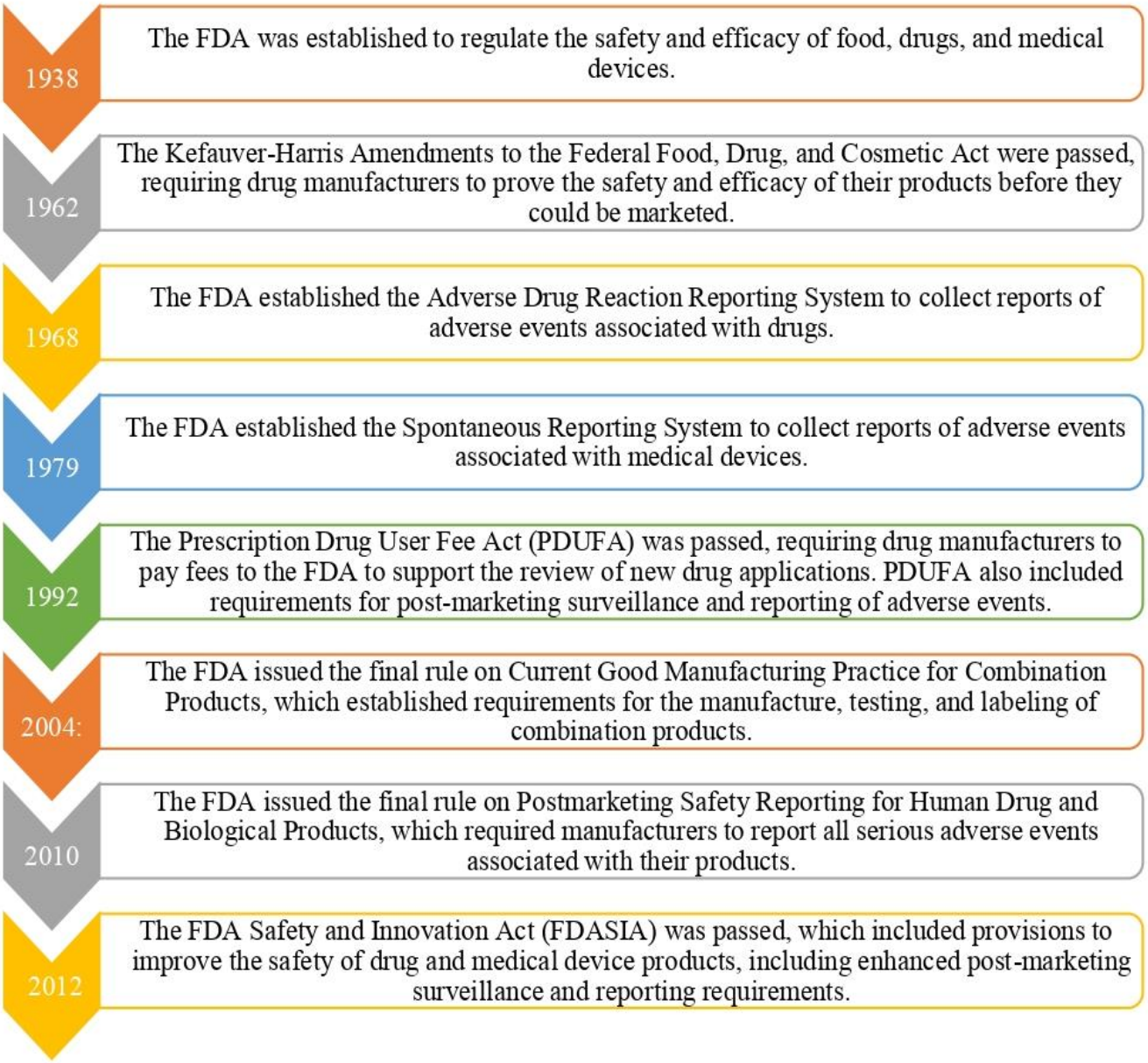


Fig 4: History of pharmacovigilance in accordance with the USFDA.[14]

B. EMA on Pharmacovigilance

Pharmacovigilance is a critical aspect of the European Medicines Agency's (EMA) work, as it is responsible for the safety monitoring of medicines in the European Union (EU). The agency's pharmacovigilance activities aim to ensure that medicines available in the EU are safe and effective, and to minimize the risksassociated with their use.

The EMA operates a robust pharmacovigilance system that includes the collection, evaluation, and analysisof information on the safety of medicines. The agency receives reports of adverse

drug reactions (ADRs) from a variety of sources, including healthcare professionals, patients, and pharmaceutical companies. The EMA's pharmacovigilance experts review these reports and use the data to identify potential safety issues with medicines, and to make recommendations for their safe use.[10][12]

The EMA's pharmacovigilance activities also include the monitoring of medicines once they are on the market, to ensure that any emerging safety concerns are identified and addressed. The agency works closely with national regulatory authorities in the EU member states to coordinate its pharmacovigilance activities and to ensure consistency in the evaluation and regulation of medicines.[6]

Overall, the EMA's pharmacovigilance work is essential in ensuring the safe and effective use of medicinesin the EU. The agency's ongoing efforts to collect and evaluate data on the safety of medicines, and to makerecommendations for their safe use, are critical in protecting public health and improving patient outcomes.

The European Medicines Agency (EMA) has issued guidelines on pharmacovigilance to ensure the safety and efficacy of medicines in the European Union (EU). These guidelines provide a framework for pharmaceutical companies to follow when collecting, evaluating, and reporting safety data on their products.[6]

Here are some of the key EMA guidelines on pharmacovigilance[6][8]

Table 2: Pharmacovigilance Guidelines issued by EMA.

Good Pharmacovigilance Practices (GVP)	The EMA has developed a set of GVP modules that provide guidance on various aspects of pharmacovigilance, such as risk management, signal detection, and post-authorization safety studies. These modules provide a comprehensive approach to pharmacovigilance and serve as a reference for pharmaceutical companies and regulatory authorities.
Periodic Safety Update Reports(PSURs)	PSURs are a key tool for pharmacovigilance and are required for all authorized medicines in the EU. These reports provide an overviewof the safety data on a medicine, including any emerging safety concerns, and are submitted to the EMA and national regulatory authorities.
Risk Management Plans (RMPs)	RMPs are required for all new medicines and for existing medicineswith significant changes to their safety profile. These plans outlinethe measures that pharmaceutical companies will take to minimizethe risks associated with their products and are regularly reviewed and updated.
Signal Detection	The EMA has developed guidelines for the detection, assessment, and management of signals of potential safety concerns with medicines. These guidelines provide a systematic approach toidentifying

	and evaluating safety signals and taking appropriate action.
Post-authorization Safety Studies(PASS)	PASS are studies conducted after a medicine is authorized tomonitor its safety in real-world settings. These studies can berequired as a condition of the medicine's authorization or initiated by the pharmaceutical company or regulatory authorities.

Overall, the EMA's guidelines on pharmacovigilance are essential in ensuring the safety and efficacy of medicines in the EU.

Pharmacovigilance timelines in the European Medicines Agency (EMA) aim to ensure the continuous monitoring of the safety of medicines and the prompt identification and management of any emerging safetyconcerns.[11]

Here are some key timelines in accordance with EMA pharmacovigilance guidelines[8][9]

Initial Marketing Authorization Application: Pharmaceutical companies must provide comprehensive safety data on their products as part of the marketing authorization application. The EMA's Committee forMedicinal Products for Human Use (CHMP) assesses the safety and efficacy of the medicine before granting authorization.
Ongoing Safety Monitoring: Once a medicine is authorized, pharmaceutical companies are required to continuously monitor its safety and report any adverse drug reactions (ADRs) to the EMA and national regulatory authorities.
Periodic Safety Update Reports (PSURs): PSURs are required for all authorized medicines in the EU andmust be submitted to the EMA and national regulatory authorities at regular intervals, typically every sixmonths or annually.
Risk Management Plans (RMPs): RMPs must be submitted for all new medicines and for existing medicines with significant changes to their safety profile. These plans are regularly reviewed and updated,and any emerging safety concerns must be promptly reported to the EMA and national regulatory authorities.
Signal Detection and Management: The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) regularly reviews safety data on medicines and identifies potential safety signals. These signals are further evaluated and appropriate actions, such as updating product information or conducting additional studies, are taken.
Post-Authorization Safety Studies (PASS): PASS may be required as a condition of the medicine's authorization or initiated by the pharmaceutical company or regulatory authorities to monitor the safety ofthe medicine in real-world settings.

Fig 5: Timelines in accordance with EMA pharmacovigilance guidelines.

Overall, pharmacovigilance timelines in accordance with EMA guidelines aim to ensure the continuous monitoring of the safety of medicines and the prompt identification and management of any emerging safety concerns. Pharmaceutical companies must comply with these timelines to ensure the safe use of their products in the EU.

Comparison table of some key regulatory aspects of pharmacovigilance in the US FDA and EMA.[5] [6] [9]

Table 3: Comparison of Regulatory Aspects.

Aspect	US FDA	EMA
Guidelines	FDA's PV Guidance Documents	Good Pharmacovigilance Practices (GVP) modules and guidelines
Adverse Event Reporting Timelines	15 calendar days for serious events and 90 days for non-serious	15 calendar days for serious events and 90 days for non-serious
Risk Management Plan (RMP)	Required for all new medicines and some existing medicines	Required for all new medicines and for some existing medicines
Periodic Safety UpdateReports (PSUR)	Not required, but Periodic Benefit-Risk Evaluation Reports (PBRER) are submitted for some medicines	Required for all authorized medicines in the EU
Signal Detection and Management	FDA Adverse Event Reporting System (FAERS)	EudraVigilance and PRAC
Post-Authorization Safety Studies	Required for some medicines	May be required as a condition ofthe medicine's authorization

Comparison table of some key guidelines and directives on pharmacovigilance in the US FDA and EMA.[5] [6] [9]

Table 4: Comparison of Guidelines and Directives.

Guideline/Directive	US FDA	EMA
Guideline for Industry - Postmarketing Safety	Covers postmarketing safety reporting requirements for drug products.	GVP Module VIII - Post- Authorisation Safety Studies (PASS)
Guidance for Industry - Good PharmacovigilancePractices and Pharmacoepidemiologic Assessment	Provides guidance on establishing and maintaining a pharmacovigilance system, including signal detection and management.	GVP modules - 16 modules cover various aspects of pharmacovigilance.
Guideline for Industry - Safety Considerations for Product Design to Minimize Adverse Events	Provides guidance on designing drug products to minimize the risk of adverse events.	EMA guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products
Guideline for Industry -Expedited Programs forSerious Conditions	Provides guidance on expedited development and review programs for drugs that treat serious conditions.	EMA guideline on the scientific principles for the justification ofnon-clinical safety studies to support clinical trial applicationsand marketing authorization applications
Guidance for Industry - Providing Postmarketing Periodic Safety Reports inthe ICH E2C(R2) Format	Provides guidance on preparing PSURs in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2C(R2) format.	EMA guideline on the format and content of the clinical overview, and non-clinical overview for an application for marketing authorization

CONCLUSION

The FDA and EMA have established various guidelines for pharmacovigilance, including adverse event reporting, risk management plans, periodic safety update reports, signal detection and management, and post-authorization safety studies. In terms of adverse event reporting, both agencies require the reporting of serious adverse events within 15 calendar days. However, the FDA requires the reporting of non-seriousevents within 90 days, while the EMA allows for up to 90 days for both serious and non-serious events. This timeline difference means that the FDA requires more frequent reporting for non-serious events, which could help identify potential safety issues earlier.

Another key difference is the requirement for periodic safety update reports (PSURs) and periodic benefit- risk evaluation reports (PBRERs). The EMA requires PSURs for all authorized medicines in the European Union, while the FDA does not require PSURs but instead requires PBRERs for some medicines. This difference in requirements may reflect differences in the approach to risk management between the agencies.

In addition to regulations, both agencies have issued guidance documents for pharmacovigilance. The FDA has issued guidance on postmarketing safety reporting, good pharmacovigilance practices, and safety considerations for product design. The EMA has established the Good Pharmacovigilance Practices (GVP) framework, which consists of 16 modules covering various aspects of pharmacovigilance. The GVP framework aims to provide a comprehensive approach to pharmacovigilance that covers the entire product lifecycle.

Both the FDA and EMA also emphasize signal detection and management, which involves identifying potential safety issues through data analysis and taking appropriate actions. The FDA has established the Sentinel Initiative, a national electronic system that enables the FDA to proactively monitor the safety of drugs on the market. The EMA has a similar system called EudraVigilance, which collects and analyzes adverse event reports from across the European Union.

In conclusion, the FDA and EMA have established regulations and guidelines to ensure the safety of drugs on the market. While there are differences in the specific requirements and approaches, both agencies aim to protect public health through rigorous monitoring and assessment of drug safety. Pharmaceutical companies must adhere to these regulations and

guidelines to ensure the safety and efficacy of their products. The comparison of these guidelines helps identify best practices that can be adopted globally to improve pharmacovigilance and ultimately promote patient safety.

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