Review Article

An Overview and Review of Methods for Estimation of Polyethylene Glycol in Sweetened Aqueous Solutions

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ABSTRACT

Polyethylene glycol (PEG) is a widely used pharmaceutical excipient, solvent, and polymeric carrier employed in oral liquid formulations, protein PEGylation, nanomedicine, and biomedical applications. Despite its favorable safety profile, PEG may be adulterated or contaminated with low-molecular-weight glycols such as ethylene glycol (EG) and diethylene glycol (DEG), which are highly toxic and have been responsible for repeated global poisoning incidents. Accurate estimation of PEG in sweetened aqueous solutions and reliable detection of EG and DEG impurities are therefore essential for pharmaceutical quality control and patient safety. Analytical methodologies for PEG, PEGylated proteins, and glycol contaminants relied on basic separation and colorimetric techniques, while modern methods employ advanced hyphenated technologies such as RP-HPLC-ELSD, LC-MS/MS for pharmacokinetic and biodistribution studies, FT-IR for rapid contaminant screening, and high-resolution GC-Orbitrap mass spectrometry for regulatory testing. These developments reflect a clear trend toward enhanced sensitivity, specificity, and robustness for complex pharmaceutical matrices. Emphasis is placed on analytical strategies suitable for sweetened aqueous formulations and oral liquid medicines, by qualitative identification tests; spectroscopic and chromatographic quantification techniques and current regulatory limits and public-health risk are particularly significant.

Keywords: Polyethylene glycol; Ethylene glycol; Diethylene glycol; Sweetened aqueous solutions; Toxic contamination, Regulatory limits.

INTRODUCTION

Polyethylene glycol (PEG) is a synthetic polyether polymer composed of repeating ethylene oxide units and is available in a wide molecular-weight range, typically from PEG 200 to PEG 6000. Its physical form varies accordingly from clear, colorless liquids to waxy solids [1].PEG is freely soluble in water and many organic solvents and is extensively used as a pharmaceutical excipient, solvent, osmotic laxative, drug-delivery modifier, and biomaterial due to its chemical stability, low toxicity, and biocompatibility[2].

However, PEG and other polyols used in pharmaceutical formulations are susceptible to contamination or intentional adulteration with low-cost industrial glycols, particularly ethylene glycol (EG) and diethylene glycol (DEG). These compounds are toxic and have been repeatedly implicated in fatal mass-poisoning events worldwide, especially in pediatric oral liquid formulations [3]. As a result, international regulatory agencies have mandated strict analytical testing for EG and DEG in excipients and finished pharmaceutical products[4].

1.1 Properties of Solvents

1.1.1 Polyethylene Glycol (PEG)

PEG is a non-volatile, hydrophilic polymer with molecular weights ranging from 200 to 6000. Lower-molecular-weight PEGs are viscous liquids, while higher-molecular-weight grades appear as waxy solids. PEG is commonly used as an osmotic laxative, solvent for oral solutions, plasticizer, and PEGylation agent to enhance drug stability and circulation time. Regulatory limits for impurities such as EG and DEG in PEG are typically ≤ 0.1% w/w according to pharmacopeial specifications [4,5].

1.1.2 Diethylene Glycol (DEG)

Diethylene glycol ($C_4H_{10}O_3$; MW 106.12 g/mol) is a colorless, odorless, hygroscopic liquid with a sweet taste, a boiling point of 245 °C, and a melting point of −12.8 °C. DEG is nephrotoxic, and exposure can result in acute kidney failure and death. Regulatory authorities restrict its presence in pharmaceutical products to not more than 0.10% w/w, with significantly lower toxicological thresholds reported for ingestion [5,6].

1.1.3 Ethylene Glycol (EG)

Ethylene glycol ($C_2H_6O_2$; MW 62.07 g/mol) is a colorless, viscous, sweet-tasting liquid miscible with water and ethanol. EG is highly toxic when ingested, leading to metabolic acidosis, renal failure, and death. Its boiling point is 197.3 °C, and pharmacopeial limits generally restrict EG content to < 0.1% w/w in pharmaceutical products[6].

1.2 Applications of Solvents

EG and DEG are primarily industrial chemicals used in antifreeze, polymer production, solvents, resins, and plasticizers, but their unauthorized presence in pharmaceutical products poses severe health risks [6].

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2. Case Studies and Evolution of Analytical Methods for PEG, EG, and DEG

2.1 Public Health Case Studies Highlighting DEG and EG Contamination

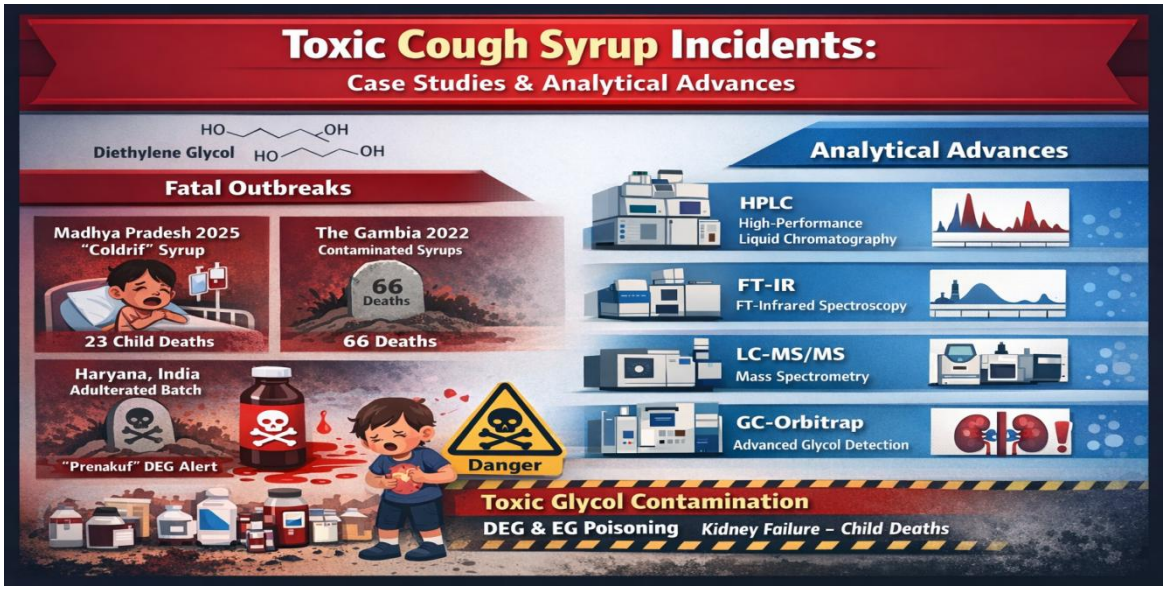

Figure 1: Toxic cough syrups incidents

2.1.1 Ban of Coldrif Syrup, Madhya Pradesh (2025)

In 2025, a severe public health tragedy was reported in the Indian state of Madhya Pradesh, where at least 23 pediatric deaths due to acute kidney failure were linked to the consumption of a contaminated cough syrup marketed under the brand name Coldrif. The formulation was manufactured by Sresan Pharmaceuticals, Tamil Nadu, and the affected batch (Batch No. SP-13, manufactured May 2025) was implicated in nine child fatalities in Chhindwara district alone[6]. Regulatory investigations revealed that the cough syrup contained 48.6% diethylene glycol (DEG), a highly toxic industrial chemical not permitted for pharmaceutical use. The contamination was traced to unethical sourcing practices, wherein the manufacturer procured industrial-grade propylene glycol from local paint dealers and chemical traders, bypassing certified pharmaceutical suppliers. This resulted in gross violation of Good Manufacturing Practices (GMP) and pharmacopeial standards[7].

In response, the Controller, Food and Drug Administration (FDA), Madhya Pradesh, imposed an immediate and complete statewide ban on the manufacture, sale, and distribution of the product.The Chief Minister of Madhya Pradesh announced financial compensation of ₹4 lakh for each affected family and assured full coverage of medical expenses for surviving children. This incident reinforced the critical need for routine analytical screening of excipients for EG and DEG impurities prior to formulation[7,8].

2.1.2 Gambia Pediatric Poisoning Incident (2022)

Between June and September 2022, health authorities in The Gambia reported an alarming cluster of pediatric cases presenting with acute kidney injury (AKI) of unknown origin. By late September, 78 suspected cases were identified, of which 66 resulted in fatalities. Subsequent investigations by national authorities and the World Health Organization (WHO) linked the deaths to the consumption of four contaminated cough syrups manufactured by Maiden Pharmaceuticals, India [8].

Laboratory analyses confirmed the presence of unacceptable and lethal concentrations of both diethylene glycol (DEG) and ethylene glycol (EG) in the syrups. The incident triggered global regulatory alerts, product recalls, and heightened scrutiny of pharmaceutical supply chains, particularly in low- and middle-income countries. This tragedy highlighted the catastrophic consequences of inadequate quality control and the absence of validated analytical testing for toxic glycol contaminants[8,9].

2.1.3 Contaminated Cough Syrup Incident, Haryana (India)

A more recent regulatory alert was issued in Haryana, India, concerning a cough syrup marketed as Plenakuf, manufactured by Shreya Life Sciences Private Limited. The affected batch (Batch No. R2503I01; Mfg: Feb, Exp: Jan 2027) was found to contain diethylene glycol (DEG) and was officially classified as "Adulterated and Not of Standard Quality (NSQ)"[9].

DEG exposure is known to cause acute poisoning, renal failure, neurological complications, and death, particularly in pediatric populations. Consequently, a state-wide ban was enforced, and Drug Control Officers (DCOs) were instructed to intensify surveillance and sample collection[10] . Strict advisories prohibited the sale, stocking, prescription, or administration of the product, and the public was urged to report any circulation of the affected batch. This case further emphasizes the need for rapid screening and confirmatory analytical techniques in post-marketing surveillance[11].

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2.2 Evolution of Analytical Methods for PEG, EG, and DEG (1995–2024)

The analytical determination of polyethylene glycols (PEGs) and their toxic contaminants ethylene glycol (EG) and diethylene glycol (DEG) has undergone significant advancements over the past three decades, driven by increasing regulatory demands and public health concerns.

One of the earliest instrumental approaches was reported by Moldovan (1995) in the Journal of Chromatography A, where reversed-phase high-performance liquid chromatography (RP-HPLC) with multiple detectors was employed to separate PEG oligomers and their degradation products formed during ozonation of water samples. The study demonstrated that PEG degradation profiles were strongly influenced by pH and reaction time, establishing RP-HPLC as a reliable technique for PEG characterization[10,11].

In the same year, Alo Nag (1995) introduced a colorimetric assay for PEG and PEGylated proteins using ammonium ferrothiocyanate, published in the Journal of Analytical Biochemistry[12]. The method involved extraction of a colored chromophore into chloroform and spectrophotometric measurement at 510 nm. This assay was notable for its minimal protein interference, making it suitable for PEG-protein conjugates. Subsequently, Zhiqian Tian (2008) reported a modified Dragendorff reagent–based UV–visible spectrophotometric method for PEG quantification, providing improved linearity and reproducibility for routine PEG analysis[13].

The introduction of mass spectrometric techniques significantly improved analytical sensitivity and specificity. V. Vijaya Bhaskar (2013) developed an LC-MS/MS method for the quantitative estimation of PEG-400 in plasma, enabling accurate pharmacokinetic studies through multiple reaction monitoring (MRM) of PEG oligomer ions[14].

Further refinements were made by Graham Cleaver (2015) using RP-HPLC coupled with evaporative light scattering detection (ELSD), which allowed effective detection of PEG oligomers lacking chromophores. In the same year, Jiachang Gong (2015) demonstrated the use of in-source collision-induced dissociation (CID) LC-MS/MS for direct quantification of PEG and PEGylated proteins in biological tissues[15,16].

In parallel, rapid screening techniques for DEG gained prominence. Safwan Obeidat (2019) and Ayman Hammoudeh (2020) independently demonstrated the application of ATR-FT-IR spectroscopy for the detection and quantification of DEG in glycerin and pharmaceutical products, achieving detection limits as low as 0.051% DEG[17].

Most recently, Astrid Hyldbakk (2024) reported advanced LC-MS-based PEG fragment analysis for biodistribution studies of nanomedicines. Additionally, GC-Orbitrap high-resolution mass spectrometry has emerged as a gold-standard confirmatory technique for regulatory testing of volatile glycols, offering ultra-low detection limits and high specificity for EG and DEG [18,19].

3. ANALYTICAL METHODS FOR PEG, EG, AND DEG

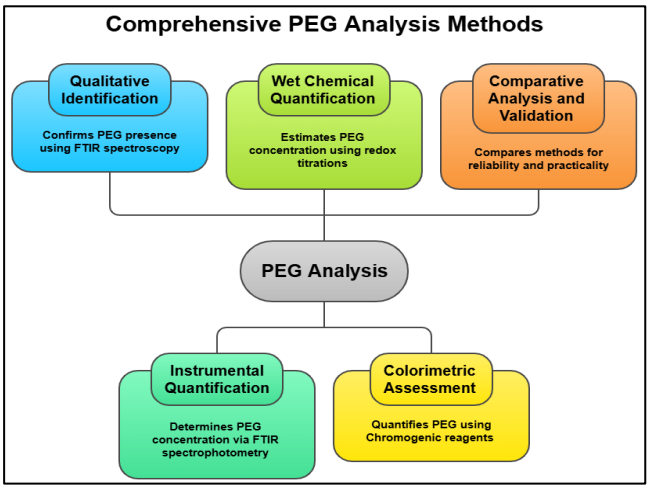

Figure 2: Comprehensive PEG Analysis methods

3.1 Early Colorimetric and Qualitative Methods (1995–2008)

Moldovan et al. first reported RP-HPLC separation of PEG oligomers in water. Nag et al. introduced a colorimetric assay using ammonium ferrothiocyanate for PEG and PEGylated proteins, offering simplicity and protein tolerance Modified Dragendorff reagent methods later improved linearity and reproducibility for PEG quantification using UV-Vis spectroscopy [20].

3.2 Spectroscopic Techniques

FT-IR spectroscopy has been successfully applied for rapid screening and quantification of DEG contamination in glycerin-based and aqueous formulations, achieving limits of detection as low as 0.051% w/w. UV-Vis and fluorescence methods have also been explored for PEG-based nanocomposites and controlled-release systems[21].

3.3 Chromatographic and Hyphenated Techniques

Advanced techniques such as RP-HPLC-ELSD enable sensitive detection of low-molecular-weight PEG oligomers. LC-MS/MS methods allow precise quantification of PEG 400 and PEGylated proteins in biological matrices, supporting pharmacokinetic and biodistribution studies[22]. High-resolution GC-Orbitrap mass spectrometry provides highly selective detection of volatile EG and DEG at trace levels, resolving false positives associated with GC-FID.

4. Various Qualitative Identification Tests for Polyethylene Glycol (PEG), Ethylene Glycol (EG), and Diethylene Glycol (DEG)

4.1 Qualitative Identification Tests for Polyethylene Glycol (PEG)

Qualitative identification of polyethylene glycol (PEG) is primarily based on its polyether structure, terminal hydroxyl groups, and characteristic physicochemical behavior. PEG is freely soluble in water and other polar solvents such as ethanol and acetone, while being practically insoluble in

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non-polar solvents, a property commonly used as a preliminary identification test[23] . Although these qualitative tests are useful for preliminary screening, definitive identification and molecular weight characterization of PEG require confirmatory chromatographic and spectrometric techniques[24].

Table 1: Comparison of Analytical Techniques for EG and DEG Detection

Method	Sensitivity	Specificity	Cost	Regulatory Acceptance
TLC	Low	Low	Very Low	Screening only
FT-IR	Medium	Medium	Low	Screening
GC-FID	High	Medium	Medium	Accepted
GC-MS	Very High	High	High	Accepted
GC-Orbitrap	Ultra-high	Ultra-high	Very High	Gold standard

Table 2: Qualitative Identification Tests for Polyethylene Glycol (PEG)

S.NO.	Test Name	Reagent(s) Used	Principle / Observation	Inference	Reference
1.	Ruthenium Red Test	Ruthenium red solution	Formation of red or pink complex due to interaction with polyether chain	Confirms presence of PEG	IP, BP
2.	Iodine Test	Iodine–potassium iodide	Brown coloration due to weak complex formation	Preliminary PEG indication	IP
3	Solubility Test	Water, ethanol, acetone, ether	Soluble in polar solvents; insoluble in non-polar solvents	Confirms hydrophilic polymer	USP
4.	Flame Test	Heat source	Blue flame with sweet ether-like odor	Indicates polyether nature	Lab method
5.	Ninhydrin Test	Ninhydrin reagent	Faint violet color due to terminal –OH groups	Supports PEG presence	Lab screening
6	Ferric Chloride Test	$FeCl_3$ solution	Pale yellow coloration	Differentiates from phenols	Lab screening
7.	Viscosity Test	Visual/rheological	Liquids (PEG 200–400); waxy solids (PEG ≥6000)	Molecular weight indication	USP

Table 3: Qualitative Identification Tests for Ethylene Glycol (EG)

S.NO	Test Name	Reagent(s) Used	Principle / Observation	Inference	Reference
1.	Sodium Periodate Test	$NaIO_4$	Decolorization or disappearance of turbidity	Vicinal diol presence	IP
2.	Acidified Dichromate Test	$K_2Cr_2O_7 + H_2SO_4$	Color change from orange to green	Oxidizable glycol	IP
3	Iodoform Test	I_2 + NaOH	No yellow precipitate	Negative iodoform confirms EG	IP
4.	Calcium Oxalate Test	$HNO_3 + CaCl_2$	White precipitate of CaC_2O_4	Oxidation to oxalic acid	Lab method
5.	Fehling's Test (after oxidation)	Fehling A & B	Brick-red precipitate	Reducing species formed	IP
6	Acetylation Test	Acetic anhydride + H_2SO_4	Fruity ester odor	Confirms alcohol groups	Lab screening
7.	$KMnO_4$ Test	Alkaline $KMnO_4$	Decolorization with brown MnO_2 precipitate	Oxidizable diol	IP
8.	Ceric Ammonium Nitrate (CAN) Test	CAN reagent	Yellow to red color change	Polyhydric alcohol confirmation	IP

4.2 Qualitative Identification Tests forEthylene Glycol (EG)

Qualitative identification of ethylene glycol (EG) is based on its vicinal diol structure and strong reducing and oxidizable properties[25]. EG is a clear, colorless, odorless liquid that is completely miscible with water and alcohols, which serves as a preliminary physical identification characteristic[26]. These qualitative tests are useful for preliminary screening; however, due to the toxic nature of EG and the potential for interference from other glycols, confirmatory analysis using validated chromatographic techniques such as GC or GC–MS is essential for regulatory and safety assessments[27].

4.3 Qualitative Identification Tests for Diethylene Glycol (DEG)

Qualitative identification of diethylene glycol (DEG) relies on its polyhydric alcohol functionality and characteristic ether linkage[28,29]. DEG is a clear, colorless, hygroscopic liquid that is completely miscible with water and alcohols, a property

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commonly used for preliminary identification[30,31].While these classical tests are useful for initial identification, they lack specificity at low concentrations; therefore, confirmatory analysis using validated chromatographic methods such as GC-FID, GC-MS, or high-resolution GC-Orbitrap is mandatory for regulatory compliance and patient safety[32].

5. Regulatory limits for Ethylene Glycol (EG) and Diethylene Glycol (DEG) in pharmaceutical excipients and oral liquid formulations

All pharmacopeias mandate testing of every batch of glycerin, propylene glycol, and PEG used in oral liquid formulations due to repeated global poisoning incidents[32-40].

Table 4: Qualitative Identification Tests for Diethylene Glycol (DEG)

S.NO	Test Name	Reagent(s) Used	Principle / Observation	Inference	Reference
1.	FT-IR Screening Test	ATR-FTIR	Characteristic peaks at ~881, 1083 cm^{-1}	Rapid DEG identification	[12,13]
2.	Periodate Oxidation Test	$NaIO_4$	Partial oxidation with turbidity change	Glycol functionality	Lab method
3.	Solubility Test	Water, alcohols	Fully miscible	Preliminary identification	USP
4.	Taste/Odor (Not recommended)	Sensory	Sweet taste (hazardous)	**Not permitted**	Safety warning

Table 5: Regulatory limits for Ethylene Glycol (EG) and Diethylene Glycol (DEG) in pharmaceutical excipients and oral liquid formulations

Regulatory Authority	Applicable Guideline / Monograph	Substance Covered	Maximum Permitted Limit	Test Requirement / Method
ICH	ICH Q3C (R8): Impurities – Residual Solvents	EG, DEG (Class 2 toxic solvents)	≤ 0.1% w/w (1000 ppm) or lower based on PDE	GC / GC–MS validated methods
FDA (US)	FDA Guidance on Testing of Glycerin, Propylene Glycol, PEG	EG, DEG	Not more than 0.1% w/w	Mandatory identity & limit tests (GC/GC-MS)
USP	USP–NF General Chapter <467> Residual Solvents; Individual monographs	EG, DEG	≤ 0.1% w/w	GC-FID / GC-MS; identity confirmation
BP	British Pharmacopoeia (PEG, Glycerol, PG monographs)	EG, DEG	≤ 0.1% w/w	Specific identification tests + GC
IP	Indian Pharmacopoeia (PEG, Glycerol, PG monographs)	EG, DEG	≤ 0.1% w/w	Mandatory limit tests (GC/FT-IR screening)
WHO	WHO Technical Report Series	EG, DEG	"Absent or trace only" (below toxicological concern)	TLC screening + confirmatory GC
Finished Oral Liquids	All pharmacopeias	EG, DEG	Must comply with excipient limits	Product-level testing mandatory

6. Need of the Study

Polyethylene glycol (PEG) is extensively employed in pharmaceutical formulations as a solvent, stabilizer, and excipient, and is increasingly used for PEGylation of therapeutic proteins and nanomedicines to enhance bioavailability and pharmacokinetic performance. Despite its widespread and generally recognized safety, PEG and related excipients remain vulnerable to contamination with low-molecular-weight glycols, particularly ethylene glycol (EG) and diethylene glycol (DEG), which are highly toxic and have been responsible for multiple fatal poisoning incidents worldwide.[41,42] Recent case studies, including pediatric deaths linked to contaminated cough syrups in India and The Gambia, highlight persistent gaps in excipient quality control, supplier qualification, and analytical surveillance.

Although international regulatory agencies such as the FDA, ICH, USP, BP, and IP mandate stringent limits for EG and DEG impurities, enforcement and analytical implementation remain inconsistent, especially in resource-limited settings. Traditional qualitative tests, while useful for preliminary screening, often lack the sensitivity and specificity required to detect trace-level contamination in complex pharmaceutical matrices[43,45]. Concurrently, rapid advances in analytical science—ranging from FT-IR screening to high-resolution mass spectrometry—have not been comprehensively synthesized in the context of regulatory compliance and public health protection[46]. Therefore, there is a clear need for a consolidated review that integrates real-world case studies with the evolution of analytical methodologies, regulatory requirements, and practical quality control strategies. Such a synthesis is essential to

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guide manufacturers, regulators, and analysts in preventing future contamination events and ensuring patient safety.

CONCLUSION

This review critically examined the evolution of analytical methods for the identification and estimation of polyethylene glycols (PEGs), PEGylated proteins, and toxic glycol contaminants such as ethylene glycol (EG) and diethylene glycol (DEG) from 1995 to 2024. The analysis demonstrates a clear progression from classical colorimetric and chromatographic techniques to advanced, high-sensitivity methods including LC-MS/MS, ATR-FT-IR, and high-resolution GC-Orbitrap mass spectrometry. These advancements have significantly improved detection limits, specificity, and regulatory applicability, enabling reliable monitoring of excipients and finished pharmaceutical products.

The inclusion of recent and historical case studies underscores the severe public health consequences of inadequate analytical control and non-compliance with pharmacopeial standards. Collectively, the findings emphasize that reliance on preliminary qualitative tests alone is insufficient and must be complemented by validated confirmatory methods aligned with FDA, ICH, USP, BP, and IP guidelines. Strengthening analytical surveillance, enforcing stringent supplier qualification, and adopting rapid screening tools alongside confirmatory techniques are critical to preventing future contamination incidents. Ultimately, the harmonization of advanced analytical methodologies with global regulatory frameworks is essential to safeguarding pharmaceutical quality and protecting vulnerable patient populations.

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