Pharmaceutical Excipients Explained: Function and Compatibility

Published August 6, 2026 42 min read

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Executive Summary

Pharmaceutical excipients are every component of a finished drug product other than the substance responsible for the therapeutic effect. The **U.S. Food and Drug Administration (FDA)** defines an inactive ingredient as "any component of a drug product other than the active ingredient" (Source: fda.gov). In its IID guidance, FDA uses "excipients" for inactive ingredients that are added intentionally (Source: fda.gov). Excipients are not a minor addition: according to **Precedence Research**, they "can make up to 90% of the formulation of a medicine" by mass (Source: precedenceresearch.com). Commercial market-research firms publish proprietary estimates with differing definitions, coverage, and methodologies. For example, MarketsandMarkets forecasts a global market of **$11.03 billion in 2025** and **$14.86 billion in 2030**, while Mordor Intelligence estimates **$10.72 billion in 2025** and forecasts **$16.62 billion in 2031**; these figures are vendor forecasts, not independently established market facts (Source: marketsandmarkets.com) (Source: mordorintelligence.com).

Excipients are classified by the function they perform in a dosage form, a principle codified by the **International Pharmaceutical Excipients Council (IPEC)**, whose Americas chapter states that excipients "are classified by the functions they perform in a pharmaceutical dosage form" (Source: ipecamericas.org). The **United States Pharmacopeia National Formulary (USP-NF)** recognizes 42 distinct functional excipient categories, spanning fillers and diluents, binders, disintegrants, lubricants and glidants, coating agents, preservatives, antioxidants, solubilizers and complexing agents, and coloring agents. Lipid nanoparticle (LNP) components used in mRNA vaccines are delivery-system components and should not be treated as a USP-NF excipient category. Selecting among them is not casual: formulators weigh functional purpose, chemical and physical compatibility with the drug substance, prior regulatory precedent recorded in FDA's Inactive Ingredient Database (IID), manufacturability, cost, and supply chain robustness, then verify compatibility empirically using techniques such as Differential Scanning Calorimetry (DSC) and thermogravimetric analysis coupled with Fourier-Transform Infrared Spectroscopy (TGA-FTIR). A well-documented failure mode, the Maillard reaction between lactose and primary or secondary amine drugs, illustrates why this testing matters: it "occurs between a primary amine with lactose at high temperature to produce brown pigments" (Source: link.springer.com) and can remain invisible for a year before appearing in high-lactose formulations.

Historically, a genuinely novel excipient had no standalone path to FDA review; it could only be qualified alongside the drug product that used it first, a "chicken and egg" dynamic in which "drug developers report that they have been hesitant to use novel excipients in drug development programs due to the uncertainty surrounding their acceptability" (Source: federalregister.gov). FDA's Center for Drug Evaluation and Research (CDER) opened the voluntary Novel Excipient Review Pilot Program in September 2021, intending to "accept approximately four initial proposals (two for the first year of the Pilot Program, and two for the second year)" (Source: federalregister.gov). Ashland's Viatel bioresorbable excipient and BASF's Soluplus were among the first publicly disclosed acceptances, entering the program in October and December 2022 respectively.

Real-world cases underscore both the value and the risk embedded in excipient choice. Comirnaty's lipid nanoparticle formulation contains four lipid classes: the ionizable lipid ALC-0315, the PEGylated lipid ALC-0159, DSPC phospholipid, and cholesterol. FDA identifies ALC-0315 as an ionizable lipid and ALC-0159 as a PEG-lipid; cholesterol is a separate LNP lipid class (FDA materials. Conversely, unacceptable contamination of cough medicines with diethylene glycol (DEG) and ethylene glycol (EG) has caused mass poisonings: the World Health Organization (WHO) tied 2022-2023 contamination incidents to "more than 300 fatalities in three of these countries" (Source: who.int), following an earlier 2006-2007 Panama poisoning that killed "at least 94 people" (Source: nbcnews.com). FDA continues to enforce excipient testing requirements; a July 2025 FDA warning letter cited one U.S. manufacturer for having "failed to adequately test your incoming components at high risk of diethylene glycol" (Source: fda.gov). Together, these threads, definitional clarity, functional taxonomy, rigorous compatibility science, an emerging novel-excipient pathway, and hard-won safety lessons, form the complete picture a formulator, regulatory affairs professional, or quality leader needs to understand pharmaceutical excipients as of August 2026.

Introduction and Background

Pharmaceutical excipients are, by regulatory definition, every component of a finished drug product other than the substance that produces the therapeutic effect. FDA defines an inactive ingredient as "any component of a drug product other than the active ingredient" (Source: fda.gov), while an active ingredient is "any component of a drug product intended to furnish pharmacological activity or other direct effect" (Source: fda.gov). In

practice, excipients are rarely a minor addition to a formulation. **Precedence Research** notes that excipients "can make up to 90% of the formulation of a medicine" by weight (Source: precedenceresearch.com), meaning the tablet, capsule, injectable, or topical a patient actually receives is, by mass, mostly excipient rather than drug substance.

This is not incidental filler. Excipients bind powders into cohesive tablets, control how and when a drug releases in the body, protect sensitive molecules from moisture and oxidation, and preserve multi-dose liquids from microbial growth. In mRNA vaccines, LNP delivery-system components perform separate, important delivery functions. MarketsandMarkets' proprietary global-market forecast estimates **$11.03 billion in 2025** and **$14.86 billion by 2030**; it should be read as that vendor's estimate rather than an independently verified market measure (Source: marketsandmarkets.com). Regulators in the United States and European Union do not treat "excipient" as a casual synonym for "harmless." The **European Medicines Agency (EMA)** defines an excipient as "a constituent of a medicine other than the active substance, added in the formulation" (Source: ema.europa.eu), and both FDA and EMA acknowledge that some excipients "can have a known action or effect in certain circumstances" (Source: ema.europa.eu) that must be disclosed to patients and prescribers. Benzalkonium chloride, a common preservative, is one such excipient: it has been "reported to cause punctate keratopathy and/or toxic ulcerative keratopathy" (Source: ema.europa.eu) in ophthalmic use despite being "the preservative of choice" (Source: ema.europa.eu) for most multidose nasal, ophthalmic, and otic products.

This report explains what pharmaceutical excipients are, how they are classified by function, how formulators select and test them for compatibility with a given drug substance, the historical FDA novel-excipient pilot, and what happens when excipient quality controls fail. It draws on FDA and EMA regulatory documents, peer-reviewed pharmaceutical science literature, named market research, and real-world regulatory and safety cases, including lipid nanoparticle delivery systems in COVID-19 mRNA vaccines and a global contamination crisis involving diethylene glycol-adulterated cough syrups, that together illustrate why excipient science, procurement, and testing sit at the center of drug product quality as of August 2026.

What Is a Pharmaceutical Excipient? Definition, Taxonomy, and Regulatory Status

Definitions Across Regulatory Bodies

There is broad, though not perfectly uniform, agreement among regulators on what counts as an excipient. **IPEC-Americas**, the U.S. arm of the industry's own standards-setting trade body, defines excipients as "substances other than the pharmacologically active drug or prodrug which are included" in the manufacturing process or finished dosage form (Source: ipecamericas.org). USP-NF, the compendial body whose monographs carry legal weight under the Federal Food, Drug, and Cosmetic Act, describes excipients as "substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety" and intentionally included in a drug delivery system (Source: americanpharmaceuticalreview.com).

FDA's own usage has evolved. Its excipient guidance explains that the agency deliberately moved away from "inactive ingredient" in favor of "excipient" because it "recognizes" that these substances can carry biological consequences even without therapeutic intent (Source: fda.gov). In practice, FDA's public-facing database and forms still use "inactive ingredient," and the two terms are used interchangeably throughout agency materials and this report.

The FDA Inactive Ingredient Database (IID)

The single most consequential regulatory tool for U.S. excipient selection is the **Inactive Ingredient Database (IID)**. It began life in 1987 as a printed reference: it was "first made available in 1987 in a hardcopy paper format" (Source: fda.gov), before becoming a searchable online tool. FDA updates the file on a fixed cadence, committing to "update the database quarterly, by the tenth working day of April, July, October, and January" (Source: fda.gov), and as of this report's research, the current downloadable file is dated "July 2026" (Source: fda.gov), confirming the cadence is being maintained. Each record carries several structured data fields, including ingredient name, route of administration, dosage form, CAS number, UNII, and maximum potency.

The IID's core function is to establish regulatory precedent. If an excipient has already been used at a given level, in a given dosage form, via a given route, in an approved drug, then a new applicant using it the same way benefits: the ingredient "generally is not considered new and may warrant less extensive review the next time" it appears in an application (Source: fda.gov). This precedent effect is why formulators routinely check the IID before finalizing a formulation, and why excipients with no prior approved use face a materially higher regulatory bar (a bar addressed later in this report's discussion of the novel excipient pathway). FDA is careful to caveat one common misreading: the IID's "maximum potency is the highest level of the excipient used in approved products" (Source: fda.gov), and explicitly "does not represent a maximum permissible daily intake or acceptable daily

intake" (Source: fda.gov), a distinction that matters because it is a record of precedent, not a toxicological safety ceiling. The database's scope is also bounded: "only inactive ingredients in the final dosage forms of drug products are included in this database" (Source: fda.gov), so excipients used only in FDA-licensed biologics (Biologics License Applications, or BLAs) fall outside it.

The IID's overall size is frequently misreported because two different counting conventions coexist. A 2019-2020 database restructuring collapsed route-of-administration and dosage-form terminology, and FDA itself noted "the number of entries in the database will collapse from 14,000+ to about 10,000" (Source: fda.gov) as a result. That figure describes unique ingredient-route-dosage form-potency combinations, not distinct chemical substances. A separate analysis published in *Nature Reviews Drug Discovery* counted the underlying chemistry differently, stating that "the FDA's Inactive Ingredients Database (IID) lists more than 3,000 excipients" (Source: media.nature.com) as of September 2020. Readers should treat "14,000-plus entries" and "3,000-plus excipients" as answers to two different questions rather than a contradiction.

Compendial Standards: USP-NF and Pharmacopoeial Chapters

Quality standards for excipients, as opposed to regulatory acceptance, come primarily from pharmacopoeias. USP-NF, per IPEC-Americas' own description, "also includes similar standards for more than 250 excipients, vitamins, minerals, and botanicals" (Source: ipecamericas.org) in its National Formulary section. A 2025 USP presentation put the current scope even higher, citing "over 25 General Chapters (DSs) on excipients in USP-NF" (Source: subscriber.ipq.org) and "over 338 excipient Reference Standards" (Source: subscriber.ipq.org) used as physical comparison materials in official assays. USP's monographs also carry statutory weight: under the Federal Food, Drug, and Cosmetic Act, "the established name (nonproprietary name) of a drug or component is the official title" set by the applicable USP-NF monograph unless FDA designates otherwise (Source: americanpharmaceuticalreview.com).

On the manufacturing side, the industry consensus GMP reference is the **IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients**, now in its "version 5, 2022" (Source: ipec-federation.org), published jointly with the Pharmaceutical Quality Group and structured in two parts, since "Part 1 includes Good Manufacturing Practices for excipients" (Source: ipec-federation.org) with a companion volume of implementation examples.

Notably, there is no independent U.S. approval pathway for an excipient by itself. The novel excipient pilot discussed later in this report provided FDA review, not standalone approval; one industry analysis states plainly that there is "no independent regulatory approval process for excipients outside of an FDA drug product review" (Source: americanpharmaceuticalreview.com). This is precisely why the IID's precedent function, and the pharmacopoeial quality standards layered on top of it, together substitute for what would otherwise be a standalone approval regime. In the European Union, the parallel legal basis sits in Article 65 of Directive 2001/83/EC: "the legal basis for requirements on excipient labelling in the EU is Article 65" (Source: ema.europa.eu), operationalized through an EMA-maintained annex listing "excipients with a known action or effect, which must appear on the labelling" (Source: ema.europa.eu), last revised with "revision 5, first published 05/12/2025."

Types of Pharmaceutical Excipients: Functional Categories Explained

Excipients are organized, across every major standard, by the function they perform rather than by chemical family alone. The nine categories below are common excipient functional groups used across solid oral, liquid, topical, and parenteral formulations. A separate section then describes lipid nanoparticle (LNP) delivery-system components used in mRNA vaccines. The categories used in a given product depend on its dosage form, route, and formulation requirements.

Fillers and Diluents

Fillers, also called diluents, bulk up a dosage form so that a potent, low-mass active ingredient can be handled, measured, and compressed reliably. Common examples include lactose monohydrate, microcrystalline cellulose, mannitol, dicalcium phosphate, and pregelatinized starch. Fillers are also commercially dominant: MarketsandMarkets and Precedence Research both independently report that the "fillers & diluents segment accounted for the major share of the market" by functionality in 2024-2025 (Source: marketsandmarkets.com) (Source: precedenceresearch.com).

Binders

Binders hold powder particles together during granulation so they form cohesive granules or tablets rather than crumbling. A representative pharmaceutical science study lists "the binders povidone (Kollidon 30), copovidone (Kollidon VA64), hypromellose (Pharmacoat 606)" (Source: pmc.ncbi.nlm.nih.gov) as standard choices for wet granulation, typically used at low single-digit percentages; in one twin-screw granulation study, "lactose and binder were applied in a ratio of 95:5 (w/w)" (Source: pmc.ncbi.nlm.nih.gov). Pregelatinized starches double as binders and fillers; one is

"marketed as flowable and compressible starch with the commercial names Uni-pure DW and Uni-pure LD" (Source: pmc.ncbi.nlm.nih.gov), and partially pregelatinized maize starch (**Starch 1500**) is added to extended-release matrix tablets, where "this effect could be due to the contribution of Starch 1500 to formation of a stronger gel layer around the matrix tablet" (Source: pmc.ncbi.nlm.nih.gov).

Disintegrants

Disintegrants break a tablet apart once it reaches gastrointestinal fluid, exposing surface area for dissolution. The most widely used "superdisintegrants," sodium starch glycolate, croscarmellose sodium, and crospovidone, "increase the hydrostatic pressure acting either via swelling or by water wicking, or by combination of these mechanisms" (Source: ncbi.nlm.nih.gov). Controlled mechanistic testing found that "a swelling mechanism was dominant for sodium starch glycolate and croscarmellose sodium" (Source: ncbi.nlm.nih.gov), while crospovidone acts more through capillary wicking, an important distinction when troubleshooting a slow-disintegrating formulation.

Lubricants and Glidants

Lubricants reduce friction between powder particles and tablet-press tooling during compression, and are used sparingly: "pharmaceutical lubricants are the agents added to tablet and capsule formulations in a very small quantity (usually 0.25%-5.0%, w/w)" (Source: pharmaexcipients.com). **Magnesium stearate** is the industry default, but it is hydrophobic, and overuse "can impact the product performance by decreasing tablet dissolution" (Source: pharmaexcipients.com). Formulators often substitute or blend in talc, since "talc can be used as a replacement or in combination with magnesium stearate" (Source: pharmaexcipients.com) when dissolution is sensitive. Glidants such as colloidal silicon dioxide improve powder flow into the die cavity and are frequently used alongside lubricants rather than in place of them.

Coating Agents and Film Formers

Film coatings protect tablets, mask taste, and, when engineered as enteric or sustained-release systems, control where and when a drug releases. **Hypromellose (HPMC)** is, per a manufacturer technical resource, "a widely used cellulose derivative offering excellent film strength and compatibility with aqueous systems" (Source: colorcon.com) for immediate-release coatings, and separately "the most commonly used polymer in formulation of extended release (ER) hydrophilic matrix tablets" (Source: pmc.ncbi.nlm.nih.gov). Enteric coatings, built from methacrylate copolymers such as **Eudragit** L100-55, exploit pH-dependent solubility: "in the acidic gastric media, an enteric polymer is protonated and therefore insoluble" (Source: pmc.ncbi.nlm.nih.gov), so that "enteric coated tablets won't dissolve in the acid of the stomach but will dissolve in the basic pH environment of the small intestine" (Source: colorcon.com). **Ethylcellulose**, applied as an aqueous barrier coating such as Surelease to a "2%-8% w/w weight gain" (Source: pmc.ncbi.nlm.nih.gov), is a hydrophobic polymer "often used in controlled-release coatings due to its ability to form moisture-resistant films" (Source: colorcon.com). Moisture-protective film coats serve a distinct purpose: they "are used for protection from moisture and improve physical appearance, mechanical resistance" (Source: pmc.ncbi.nlm.nih.gov) and taste masking, independent of any release-control function.

Preservatives

Multi-dose liquid, nasal, ophthalmic, and injectable products need preservatives to prevent microbial contamination across repeated use. **Benzalkonium chloride**, in use since the 1950s, remains, per EMA, "the preservative of choice" (Source: ema.europa.eu) for most multidose aqueous nasal, ophthalmic, and otic products. EMA's 2017 report stated that it appeared in approximately 74% of ophthalmic preparations on the EU market (Source: ema.europa.eu); that figure should not be read as a current market-share estimate. Its widespread use is not risk-free; EMA documents its association with "punctate keratopathy and/or toxic ulcerative keratopathy" (Source: ema.europa.eu), illustrating why preservative selection is itself a compatibility and safety decision, not a formality.

Antioxidants

Oxidation-prone drug substances and lipid excipients require chemical protection. Synthetic phenolic antioxidants, "butylated hydroxytoluene (BHT), butylated hydroxy anisole (BHA), propyl gallate (PG), and tertiary butyl hydroquinone (TBHQ)" (Source: link.springer.com), work alongside natural tocopherols, which occur "in most vegetable oils in quantities ranging from 200 to 1200 ppm" (Source: link.springer.com). Ascorbic acid is a distinct, water-soluble class: "a water-soluble reducing agent that functions by several mechanisms" (Source: link.springer.com), though its protective effect "holds true, so long as trace metals like free iron ions are not prevalent" (Source: link.springer.com), since it can otherwise flip into a pro-oxidant. Sulfite antioxidants, meanwhile, are federally defined: FDA regulation states that "sulfites are chemical substances that are added to certain drug products to inhibit the oxidation of the active drug ingredient" (Source: ecfr.gov), and require a mandated warning that the sulfite "may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people" (Source: ecfr.gov), a risk that regulation notes is "seen more frequently in asthmatic than in nonasthmatic people" (Source: ecfr.gov).

Solubilizers and Complexing Agents

Poorly water-soluble drug candidates, an increasingly common outcome of modern discovery chemistry, often require a solubilizing excipient to be formulated at all. **Cyclodextrins** are "widely used as complexing agents for lipophilic and amphiphilic substances" (Source: ncbi.nlm.nih.gov), forming inclusion complexes that dramatically raise apparent aqueous solubility. **Captisol**, a derivatized beta-cyclodextrin, is "used in 16 FDA-approved products to date, including Veklury (remdesivir) and Kyprolis (carfilzomib)" (Source: pharmaexcipients.com), with reported aqueous solubility increases "by a factor of 10 to 25,000, depending on the compound" (Source: pharmaexcipients.com).

Coloring and Flavoring Agents

Color additives serve identification, anti-counterfeiting, and functional purposes. FDA requires that it "must pre-approve the color additives used in FDA-regulated products" (Source: fda.gov), and some carry patient-safety warnings; products containing FD&C Yellow No. 5 must state that it "may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons" (Source: fda.gov). Colorants also serve a functional role beyond aesthetics, including providing opacity for light-sensitive products using agents such as titanium dioxide or iron oxides, alongside flavoring agents that mask unpalatable drug substances in oral liquids and chewables.

Lipid Nanoparticle (LNP) Components

The most consequential recent expansion of the excipient toolkit is the lipid nanoparticle system used to deliver mRNA vaccines. FDA's own regulatory science materials describe the "ionizable cationic lipid (e.g., MC3, SM-102, ALC-0315)" component as responsible for "nucleic acid complexation" (Source: fda.gov), while a PEGylated lipid "determines the size of LNPs (50-110 nm)" (Source: fda.gov) and cholesterol "increases particle stability" and aids "endosomal release" (Source: fda.gov) of the mRNA payload. This category is examined in more depth in the Case Studies section below, as it represents both a landmark of excipient innovation and a preview of where novel excipient regulation is headed.

Table 1 below summarizes nine excipient functional categories, their primary purpose, representative named excipients, and typical use levels drawn from the sources above. It also includes a separate row describing LNP delivery-system components.

FUNCTIONAL CATEGORY	PRIMARY PURPOSE	REPRESENTATIVE EXCIPIENTS	TYPICAL USE LEVEL / NOTES
Fillers/Diluents	Bulk a low-mass API into a handleable, compressible dosage form	Lactose monohydrate, microcrystalline cellulose, mannitol	Often the largest single component by weight; largest functional market segment
Binders	Bind powder particles into cohesive granules/tablets	Povidone, copovidone, hypromellose, pregelatinized starch	Commonly ~5% w/w in wet granulation
Disintegrants	Break the tablet apart in GI fluid for dissolution	Croscarmellose sodium, sodium starch glycolate, crospovidone	Act via swelling and/or water wicking
Lubricants/Glidants	Reduce friction during compression; improve powder flow	Magnesium stearate, talc, colloidal silicon dioxide	0.25 to 5.0% w/w; overuse can slow dissolution
Coating Agents	Protect, mask taste, or control release location/timing	Hypromellose, Eudragit L100-55, ethylcellulose	Enteric coats resist gastric acid; barrier coats applied at 2 to 8% w/w weight gain
Preservatives	Prevent microbial growth in multidose products	Benzalkonium chloride, parabens	EMA's 2017 report cited benzalkonium chloride in ~74% of EU ophthalmic preparations; this is not a current market-share estimate (Source: ema.europa.eu)
Antioxidants	Prevent oxidative degradation of drug/lipid components	BHT, BHA, tocopherols, ascorbic acid, sulfites	Sulfite-containing products require an FDA-mandated allergy warning
Solubilizers/Complexing Agents	Increase apparent solubility of poorly soluble APIs	Cyclodextrins (e.g., Captisol), polysorbates	Can raise aqueous solubility 10 to 25,000-fold
Coloring/Flavoring Agents	Identification, anti-counterfeiting, light protection, palatability	FD&C dyes, titanium dioxide, iron oxides	Color additives require FDA pre-approval
LNP Delivery-System Components	Complex, protect, and deliver mRNA payloads	Ionizable lipids (e.g., ALC-0315, SM-102), phospholipids (e.g., DSPC), cholesterol, PEGylated lipids	For Comirnaty, FDA classifies ALC-0315, ALC-0159, DSPC, and cholesterol as “Lipid component,” rather than “Excipient”; these components support LNP assembly and delivery

As the table makes clear, no single excipient category dominates dosage-form design; a typical solid oral tablet draws on at least four or five of these categories simultaneously (filler, binder, disintegrant, lubricant, and often a coating). A modern mRNA vaccine also relies on several LNP lipid classes as delivery-system components.

Excipient Selection Criteria and Drug-Excipient Compatibility Testing

What Formulators Weigh When Selecting an Excipient

Excipient selection is a multi-criteria decision, not a single lookup. Formulators typically weigh:

- **Functional fit**: does the excipient perform the required role (binder, disintegrant, preservative, and so forth) for the intended dosage form and route?
- **Chemical and physical compatibility**: will the excipient degrade the API, or vice versa, under manufacturing and storage conditions?
- **Regulatory precedent**: has the excipient been used before, at the proposed level and route, in an FDA-approved product per the IID, since prior use means the ingredient "generally is not considered new and may warrant less extensive review the next time" (Source: fda.gov)?
- **Manufacturability**: does the excipient behave predictably during compression, coating, or filling at commercial scale?
- **Supply chain robustness and cost**: is the excipient available from qualified, multiple suppliers at consistent quality?
- **Safety and tolerability**: does the excipient carry known sensitivities (for example, sulfite or benzalkonium chloride reactions) relevant to the target patient population?

Compatibility Testing Methods

Once candidates are shortlisted, formulators run empirical compatibility studies rather than relying on functional category alone. **Differential Scanning Calorimetry (DSC)** is the standard first-pass screen because it "enables fast identification of potential incompatibilities between the ingredients of pharmaceutical preparations" (Source: pmc.ncbi.nlm.nih.gov) by detecting shifts in melting point, crystallization behavior, or the appearance of new thermal events when API and excipient are mixed and heated. Combined thermogravimetric analysis coupled with FTIR (**TGA-FTIR**) complements DSC by identifying the gaseous decomposition products released during heating; the technique "is used in the analysis of biologically active compounds to enrich TGA/DSC studies" (Source: pmc.ncbi.nlm.nih.gov). In one applied example, a combined DSC/TGA-FTIR/FTIR/powder X-ray diffraction study found that "arbidol hydrochloride may undergo polymorphic transformations and be incompatible with chitosan and magnesium stearate" (Source: pmc.ncbi.nlm.nih.gov), the kind of specific, named incompatibility that only empirical testing (rather than functional-category reasoning) can reveal.

Table 2 below summarizes the principal compatibility testing methods, what each detects, and a representative finding from the literature reviewed for this report.

METHOD	WHAT IT DETECTS	REPRESENTATIVE FINDING
Differential Scanning Calorimetry (DSC)	Melting point shifts, new thermal events signaling reaction	Fast first-pass screen for API-excipient incompatibility (Source: pmc.ncbi.nlm.nih.gov)
TGA-FTIR (coupled)	Gaseous decomposition products during thermal degradation	Enriches DSC/TGA data with chemical identity of breakdown products (Source: pmc.ncbi.nlm.nih.gov)
HPLC stress/forced degradation	Chemical degradant formation under accelerated stress conditions	Used to confirm Maillard-type degradation between lactose and amine drugs (Source: pubmed.ncbi.nlm.nih.gov)
Powder X-ray Diffraction (PXRD)	Polymorphic or crystalline-form changes	Confirmed polymorphic transformation in an arbidol hydrochloride study (Source: pmc.ncbi.nlm.nih.gov)

No single method is sufficient on its own; DSC flags a candidate incompatibility quickly but can produce false positives from physical (non-chemical) transitions, so a positive DSC signal is routinely followed by HPLC-based forced degradation or TGA-FTIR to confirm a genuine chemical reaction before a formulator abandons an otherwise-suitable excipient.

The Maillard Reaction: A Case Study in Incompatibility Mechanisms

The best-documented drug-excipient incompatibility mechanism is the **Maillard reaction**, a browning reaction between a reducing sugar (most commonly lactose, the most widely used filler) and a primary or secondary amine drug substance. Regulatory-adjacent pharmaceutical science literature describes the mechanism directly: it "occurs between a primary amine with lactose at high temperature to produce brown pigments" (Source: link.springer.com). Landmark pharmaceutical science research extended this risk to secondary amines as well, finding that fluoxetine-type drugs "undergo the Maillard reaction with lactose under pharmaceutically relevant conditions" (Source: pubmed.ncbi.nlm.nih.gov), with "N-Formylfluoxetine identified as a major product of this Maillard reaction" (Source: pubmed.ncbi.nlm.nih.gov), a marker compound formulators can now screen for directly. The same study found that "water content, lubricant concentration, and temperature were found to influence the degradation" rate (Source: pubmed.ncbi.nlm.nih.gov), meaning the same lactose-drug pair can be stable or unstable depending on manufacturing and storage conditions rather than chemistry alone. Concentration also matters non-linearly: a regulatory case review found that in high-lactose formulations (above roughly 95%), "there is a possibility of interactions though it is not visible in the initial year" (Source: link.springer.com), a delayed-onset failure mode that underscores why real-time and accelerated stability studies, not just initial-release testing, are essential whenever lactose is paired with an amine-bearing API.

Beyond Maillard chemistry, trace reactive impurities carried within excipients themselves are a separate, underappreciated incompatibility source. A major pharmaceutical science review classifies these impurities into "six major classes, including reducing sugars, aldehydes, peroxides, metals, nitrate/nitrite, and organic acids" (Source: link.springer.com), noting that "the levels of reactive impurities in excipients may vary between lots and vendors" (Source: link.springer.com), which can lead to "decreased product performance, loss in potency, and/or formation of potentially toxic degradants" (Source: link.springer.com) if not screened for at the raw-material stage.

Quality by Design and Functionality-Related Characteristics

Modern excipient selection is increasingly framed through **Quality by Design (QbD)**, the ICH Q8(R2)-aligned development philosophy under which a **Quality Target Product Profile (QTPP)**, "a prospective summary of the quality characteristics of a drug product" (Source: pmc.ncbi.nlm.nih.gov), drives every downstream formulation choice. Within QbD, a **Critical Material Attribute (CMA)** is any "physical, chemical, biological, or microbiological property or characteristic of an input material" (Source: pmc.ncbi.nlm.nih.gov) that must be held within specified limits to ensure product quality, applied to excipients as much as to the drug substance itself. This is a comparatively recent formalization: the same review notes that historically, "excipients are often selected ad hoc without systematic drug-excipient compatibility testing" (Source: pmc.ncbi.nlm.nih.gov), a gap that ICH Q8(R2) directly addresses by recommending "drug-excipient compatibility studies to facilitate the early prediction of compatibility" (Source: pmc.ncbi.nlm.nih.gov) early in development, well before formulation lock-in. USP-NF operationalizes this at the taxonomy level too, since the compendium recognizes "42 functional excipient categories" (Source: pmc.ncbi.nlm.nih.gov) that formulators map against a QTPP when narrowing candidates.

The European Pharmacopoeia extends this logic through General Chapter 5.15, **Functionality-Related Characteristics (FRC) of Excipients**, which "deals with the critical quality attributes (CQAs) of excipients which are identified during pharmaceutical development work" (Source: gmp-compliance.org) and explicitly "introduces the 'quality by design' concept described in the ICH Q8 guideline to excipients" (Source: gmp-compliance.org). Supplier and lot variability is a live risk under this framework, not a theoretical one: a QbD case study on microcrystalline cellulose found that "the design space was shifted by different manufacturers and grades of MCC" (Source: pmc.ncbi.nlm.nih.gov), meaning "excipient variability leading to variability in drug product quality should be controlled rigorously to ensure a reliable quality of drug products in the QbD approach" (Source: pmc.ncbi.nlm.nih.gov) across the product's commercial life, not just at initial validation.

The Novel Excipient Regulatory Pathway

The Historical "Chicken and Egg" Problem

For decades, a truly novel excipient, one with no prior use in an approved drug and no established food use, had no route to standalone FDA review. It could only be qualified as part of the drug application that used it first, which meant no drug sponsor wanted to be the first to accept that regulatory risk on an untested material, and no excipient maker could get feedback on a material without a sponsor willing to use it. FDA's own notice describing the resulting pilot program names this dynamic directly: "drug developers report that they have been hesitant to use novel excipients in drug development programs due to the uncertainty surrounding their acceptability" (Source: federalregister.gov).

Industry pressed for a fix well before FDA acted. IPEC-Americas and the broader excipient industry had, by 2014, framed this as a "call to action... reverberating through the pharmaceutical community for the establishment of a viable regulatory pathway for new or modified excipients" (Source: ipq.org). By 2017, IPEC-Americas had put a concrete concept in front of FDA, proposing a "novel excipient qualification process" modeled after FDA's own "Biomarker qualification process" (Source: fda.gov), and later asked FDA to broaden that qualification concept to cover additional categories of novel excipients used in generic drugs. FDA formally opened the conversation with a December 2019 request for information; industry responded at scale, and "twenty-six different companies and organizations had responded" (Source: ipq.org) by the time the comment period closed in February 2020. A parallel industry effort, "a collaboration between PDA and the IPEC Federation, which resulted at the end of 2019 in a report on the 'formalized risk assessment of excipients'" (Source: ipq.org), fed into the same policy conversation.

FDA's Novel Excipient Review Pilot Program

FDA's Center for Drug Evaluation and Research formally launched the **Novel Excipient Review Pilot Program** through a September 2021 Federal Register notice tracked under "Docket No. FDA-2019-N-5464" (Source: federalregister.gov). The notice describes the program as "voluntary and intended to allow excipient manufacturers to obtain FDA review of certain novel excipients prior to their use in drug formulations" (Source: federalregister.gov), directly answering the chicken-and-egg problem described above. Eligibility is narrowly defined: a qualifying novel excipient must "have not been previously used in FDA-approved drug products, and (2) do not have an established use in food" (Source: federalregister.gov), and FDA's related program guidance further defines a novel excipient for this purpose as "any excipient that is not fully supported by existing safety data" (Source: fda.gov) at the proposed exposure level, duration, or route.

The program's scale is intentionally modest. FDA "sought initial proposals" through "December 7, 2021" (Source: federalregister.gov) and explicitly capped participation, since "CDER intends to accept approximately four initial proposals (two for the first year of the Pilot Program, and two for the second year)" (Source: federalregister.gov). This is a deliberately small-scale, learn-by-doing pilot rather than a full-scale review pathway, consistent with FDA's own framing of it as a first step: Ashland, one of the first accepted participants, characterized it in its own investor announcement as "the first time the FDA will allow excipient manufacturers to obtain review of certain novel excipients prior to their use in drug formulations" (Source: investor.ashland.com).

Named Participants

Two of the pilot's early acceptances are publicly disclosed by the sponsoring companies themselves. **Ashland Inc.** announced that FDA had "accepted Ashland Viatel bioresorbable mPEG-PDLLA pharmaceutical excipient in the review cycle of the FDA Novel Excipient Review Pilot Program" (Source: investor.ashland.com) on October 31, 2022, a polymeric carrier intended for injectable, targeted drug delivery applications. **BASF** followed roughly six weeks later, announcing that FDA "has accepted their excipient, Soluplus, into the FDA's Pilot Program for the Review of Innovation and Modernization of Excipients (PRIME)" (Source: pharmaexcipients.com) on December 5, 2022. FDA has not published a complete public roster of every accepted proposal, so the full slate against the program's roughly four-proposal target is not independently confirmable from agency sources alone as of this report, but Ashland and BASF's disclosures confirm the pilot moved from notice to substantive intake within roughly fourteen months.

No comparable standalone international framework for novel excipient qualification, equivalent in scope to FDA's pilot, was identified in the sources reviewed for this report; the EU continues to rely on excipient qualification occurring alongside the marketing authorization of the medicinal product that first uses a given excipient, the same model FDA's pilot was designed to move beyond domestically.

Implementation Guidance: Building a Robust Excipient Program

Translating the definitions, taxonomy, and testing science above into a working formulation and regulatory program requires a few concrete practices:

- **Start with the Quality Target Product Profile (QTPP)** before shortlisting excipients, so functional requirements (release rate, route, stability target) drive candidate selection rather than habit or availability.
- **Check the IID first** for any candidate excipient at the intended route, dosage form, and potency; prior approved use materially reduces regulatory risk, since it "generally is not considered new and may warrant less extensive review the next time" (Source: fda.gov), while remembering that maximum potency in the IID is a precedent record, not a safety ceiling.
- **Run tiered compatibility testing**, starting with DSC as a rapid screen, escalating to TGA-FTIR, HPLC forced degradation, and PXRD for any candidate pair that shows an ambiguous or positive signal, rather than relying on DSC alone.
- **Qualify excipient suppliers and lots**, not just excipient grades, given documented cases where "the design space was shifted by different manufacturers and grades of MCC" (Source: pmc.ncbi.nlm.nih.gov) and where trace reactive impurities "may vary between lots and vendors" (Source: link.springer.com).

- **Plan for delayed-onset incompatibilities** in stability protocols, since Maillard-type and other reactions can be undetectable at initial release yet emerge over shelf life in high-excipient-load formulations.
- **Do not assume a historical FDA pilot is an open submission route.** Confirm the current regulatory strategy with FDA directly before relying on any novel-excipient review mechanism.

Life-sciences organizations are increasingly applying data and AI tooling to several of these steps, particularly IID precedent-checking, supplier and lot-variability tracking, and regulatory submission management, where the underlying task is less about chemistry and more about organizing and cross-referencing large, frequently updated regulatory datasets. IntuitionLabs, a life-sciences and AI consultancy that states it works "exclusively in the Pharmaceutical and Life Sciences industries, including biotech, medical devices, diagnostics, and CROs" (Source: intuitionlabs.ai), is one example of an advisory firm building this kind of regulatory-data tooling for pharmaceutical manufacturers and their partners, with an explicit design commitment to "built-in compliance with FDA, EMA, and global regulations" (Source: intuitionlabs.ai) in the systems it implements. Such tooling does not replace the underlying pharmaceutical science described above, but it can reduce the manual burden of cross-checking a candidate excipient against a quarterly-updated IID file or a supplier's changing certificate-of-analysis history.

Data Analysis and Evidence

Market Size and Growth

Independent market research firms diverge somewhat on exact figures, but agree directionally on both scale and growth trajectory. **MarketsandMarkets** projects the global pharmaceutical excipients market "projected to USD 14.86 billion by 2030 from USD 11.03 billion in 2025" (Source: marketsandmarkets.com). **Mordor Intelligence** projects the market to "grow from USD 10.72 billion in 2025 to USD 11.53 billion in 2026" (Source: mordorintelligence.com) en route to a longer-run forecast of $16.62 billion by 2031. **DelveInsight**, cited via its own PR Newswire release, states the "Pharmaceutical Excipients Market Size by 2030" will reach "~USD 14 Billion" (Source: prnewswire.com), broadly corroborating the MarketsandMarkets figure despite different modeling assumptions. **Precedence Research**, focused specifically on the U.S. market, projects growth "from USD 3.08 billion in 2025 to USD 5.58 billion by 2035" (Source: precedenceresearch.com). Readers should treat these as independent estimates rather than a single consensus figure: the roughly $10.7 to $11.0 billion range for the 2025 global base year is consistent across MarketsandMarkets and Mordor Intelligence, but five- and ten-year forecasts diverge by several billion dollars depending on methodology and scope.

Table 3 below consolidates the headline figures from each firm alongside their stated base year and scope, to make the discrepancies transparent rather than obscuring them behind a single blended number.

RESEARCH FIRM	BASE YEAR VALUE	FORECAST VALUE	CAGR / PERIOD	SCOPE
MarketsandMarkets	$11.03B (2025)	$14.86B (2030)	~6.1% (Source: marketsandmarkets.com)	Global
Mordor Intelligence	$10.72B (2025)	$16.62B (2031)	7.57% (Source: mordorintelligence.com)	Global
DelveInsight	Not separately stated	~$14B (2030)	~6% (2021 to 2030) (Source: prnewswire.com)	Global
Precedence Research	$3.08B (2025)	$5.58B (2035)	6.12% (Source: precedenceresearch.com)	United States only

As the table shows, the U.S.-only Precedence Research figure should not be directly compared against the global figures from the other three firms; doing so would understate the apparent growth of the U.S. market relative to the world when in fact the two are measuring different geographic scopes entirely.

Segment and Regional Breakdown

By raw material type, organic chemicals dominate the excipient landscape. MarketsandMarkets found the "organic chemicals segment led the market with a share of 86.1%" (Source: marketsandmarkets.com) in 2024, while Mordor Intelligence separately found "organic chemicals accounted for 74.97% of the 2025 pharmaceutical excipients market share" (Source: mordorintelligence.com), a meaningful gap between the two figures that likely

reflects differing category definitions rather than a genuine one-year market shift. By functionality, fillers and diluents lead consistently across sources, holding "the largest 2025 volume share at 32.12%" per Mordor Intelligence (Source: mordorintelligence.com), and North America "accounted for the largest share of 29.8% in 2024" of the regional market per MarketsandMarkets (Source: marketsandmarkets.com). By formulation and route, growth is fastest outside conventional oral solids: MarketsandMarkets found the "topical formulation segment is expected to register the highest CAGR of 7.6%" (Source: marketsandmarkets.com) through 2030, while Mordor Intelligence separately found injectable excipients are "projected to deliver 8.01% of CAGR from 2026 to 2031" (Source: mordorintelligence.com), the fastest-growing formulation category in that model. Mordor Intelligence attributes part of this parenteral growth to biologics, noting that "biosimilar launches following monoclonal antibody patent cliffs have lifted global requirements for high-purity sugars" (Source: mordorintelligence.com) and other injectable-grade excipients.

Regulatory and Safety Enforcement Data

Excipient quality failures remain an active FDA enforcement priority. In its October 2025 update on contaminated cough medicine, FDA confirmed that products linked to overseas diethylene glycol contamination "have not been shipped to the U.S." (Source: fda.gov), reflecting import controls put in place after the 2022-2023 international contamination wave. Separately, FDA's nitrosamine impurity program addresses a distinct but related excipient-and-process risk, warning that "nitrosamine impurities may increase the risk of cancer if people are exposed" (Source: fda.gov) above acceptable thresholds, a hazard that can originate from certain excipients or their manufacturing processes as well as from the API itself.

Case Studies and Real-World Examples

The 2022 to 2023 Diethylene Glycol Contamination Crisis

In October 2022, the World Health Organization issued a global medical product alert confirming that four cough and cold syrups manufactured by Maiden Pharmaceuticals and sold in The Gambia "contain unacceptable amounts of diethylene glycol and ethylene glycol as contaminants" (Source: who.int. The named products, "Promethazine Oral Solution, Kofexmalin Baby Cough Syrup, Makoff Baby Cough Syrup and Magrip N Cold Syrup" (Source: who.int, contained unacceptable DEG and EG contamination. WHO's alert does not identify the implicated input material or establish intentional substitution. By January 2023, WHO reported that similar contamination incidents, tracked across "Medical Product Alert N°7/2022 on 6 November 2022 focused on Indonesia" (Source: who.int) and a subsequent Uzbekistan alert, were collectively "associated with more than 300 fatalities in three of these countries" (Source: who.int), overwhelmingly among children under five. WHO's post-incident guidance to manufacturers went directly to excipient sourcing practice, instructing companies to "only purchase pharmaceutical grade excipients from qualified and bona fide suppliers" (Source: who.int) rather than lower-cost, unverified sources.

The 2006 to 2007 Panama Diethylene Glycol Poisoning (Precedent Case)

The 2022-2023 crisis was not the first of its kind. In 2006-2007, contaminated glycerin caused a mass poisoning in Panama; a Panamanian prosecutor confirmed "at least 94 people have died from taking medicine contaminated with diethylene glycol" (Source: nbcnews.com), with hundreds of additional deaths under investigation. The contamination traced back to a Chinese manufacturer that "fraudulently passed it off as 99.5 percent pure glycerin" (Source: nbcnews.com) before the mislabeled material passed through a trading intermediary and into government-manufactured medicine. Critically, the contaminated glycerin was not confined to a single dosage form: it was used "in cough syrup, antihistamine tablets, calamine lotion and rash ointment" (Source: nbcnews.com), illustrating how a single contaminated excipient lot can propagate across an entire product portfolio. A 2024 medical ethics review of the recurring pattern notes that "DEG is the most common contaminant found in glycerin" (Source: journalofethics.ama-assn.org). The repeated incidents show that glycerin supply-chain controls have not been uniformly effective; they do not establish that later testing guidance and controls were unaddressed.

Lipid Nanoparticle Components in mRNA COVID-19 Vaccines

COVID-19 mRNA vaccines use lipid nanoparticle delivery systems, but the available official product-composition materials do not establish a historical ranking for their excipients. Australia's Therapeutic Goods Administration lists the full excipient set for Comirnaty (the Pfizer-BioNTech vaccine) by name, including the ionizable lipid "((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)" (Source: tga.gov.au) alongside "Distearoylphosphatidylcholine (DSPC), Cholesterol, Potassium chloride" (Source: tga.gov.au) and a PEGylated lipid. FDA's Summary Basis for Regulatory Action confirms the vaccine's chain of responsibility, with the "Applicant: BioNTech Manufacturing GmbH (in partnership with Pfizer, Inc.)" (Source: fda.gov) for the November 2021 approval action. As described in the functional-category section above, each lipid performs a distinct engineering role: ALC-0315 is the ionizable lipid, ALC-0159 is the PEGylated lipid, and cholesterol supports particle stability and endosomal release.

FDA's Summary Basis lists ALC-0315, ALC-0159, DSPC, and cholesterol as "Lipid component," while labeling separate formulation ingredients such as potassium chloride, phosphate salts, sucrose, and water as "Excipient." The table does not establish a novel-versus-conventional classification or prior IID status for any lipid component (FDA Summary Basis for Regulatory Action for COMIRNATY.

FDA Warning Letter: Medical Chemical Corporation (2025)

Excipient testing failures continue to draw direct FDA enforcement action even outside acute contamination crises. In a July 2025 current Good Manufacturing Practice (CGMP) warning letter, FDA cited Torrance, California-based Medical Chemical Corporation because it "failed to adequately test your incoming components at high risk of diethylene glycol" (Source: fda.gov) prior to use in over-the-counter drug manufacturing. FDA directed the firm to conduct a full risk assessment and take corrective action, "including customer notifications and product recalls for any contaminated lots" (Source: fda.gov) if contamination were found. The same letter also cited the firm for inadequate methanol testing of ethanol raw material, reflecting a broader, well-documented global pattern of alcohol-based excipient contamination that regulators continue to monitor closely. Together, these findings confirm that raw-material identity and purity testing for high-risk excipients remains an active, ongoing area of FDA scrutiny as of mid-2026 rather than a closed chapter from the 2022-2023 crisis alone.

Implications and Future Directions

Several trends visible in the research above point toward where excipient science and regulation are headed. First, the **novel excipient pathway is likely to expand incrementally rather than transform overnight**. FDA designed the pilot as a limited early effort, and the agency has not published a complete public roster confirming how many accepted proposals ultimately completed review. Ashland's and BASF's disclosures show the mechanism works in practice, but the absence of a larger public track record as of this report means formulators should still budget for a multi-year timeline, and treat the pilot as a supplement to, not a replacement for, prior-use precedent in the IID.

Second, **biologics and injectable growth is reshaping excipient demand away from traditional oral-solid categories**. Both MarketsandMarkets' topical-formulation growth figures and Mordor Intelligence's parenteral CAGR data point toward faster growth outside conventional tablets and capsules, driven substantially by biosimilar expansion and the higher purity, lower bioburden requirements of injectable and inhaled products. This shift raises the bar for excipient manufacturers, since high-purity, biologics-grade material qualification is a materially different (and more expensive) undertaking than qualifying an excipient for an oral solid dose.

Third, **supply-chain verification remains a major excipient-quality risk**. The recurring DEG/EG contamination incidents and FDA's 2025 warning letter to Medical Chemical Corporation show that gaps in raw-material identity and purity testing can persist; they do not demonstrate that this is the single unsolved problem in excipient quality or that all incidents share identical control failures.

Fourth, **excipient variability and compatibility data management is increasingly a data and informatics problem, not only a bench-chemistry one**. With the IID updated quarterly, USP-NF carrying more than 25 general chapters and 338 reference standards specific to excipients, and supplier-to-supplier variability documented even for a commodity excipient like microcrystalline cellulose, formulators and regulatory affairs teams face a genuinely large, frequently changing body of reference data to track. These records require disciplined change control and traceability alongside the underlying pharmaceutical science that remains the foundation of sound excipient selection.

Finally, **lipid nanoparticle and other novel delivery systems are likely to seed the next wave of pharmacopoeial and regulatory catch-up work**. FDA regulatory-science materials describe mRNA-vaccine LNPs as containing ionizable lipid, phospholipid, cholesterol, and PEG-lipid classes. For Comirnaty, the Summary Basis identifies ALC-0315, ALC-0159, DSPC, and cholesterol as lipid components, but it does not state their prior IID status or classify individual components as novel or conventional (FDA regulatory-science materials (FDA Summary Basis for Regulatory Action for COMIRNATY.

Frequently Asked Questions (FAQs)

What are pharmaceutical excipients? Pharmaceutical excipients are all components of a drug product other than the active ingredient, defined by FDA as "any component of a drug product other than the active ingredient" (Source: fda.gov). They can constitute up to 90% of a formulation's total mass (Source: precedenceresearch.com) and perform functions ranging from bulking and binding to controlled release and preservation.

What are the main types of pharmaceutical excipients? The major functional categories are fillers/diluents, binders, disintegrants, lubricants and glidants, coating agents, preservatives, antioxidants, solubilizers/complexing agents, and coloring/flavoring agents. mRNA delivery systems also use LNP components, including ionizable lipids, phospholipids, cholesterol, and PEGylated lipids; these are distinct from the excipient functional

categories. USP-NF formally recognizes 42 functional excipient categories (Source: pmc.ncbi.nlm.nih.gov).

What criteria are used to select an excipient? Formulators weigh functional fit for the dosage form, chemical and physical compatibility with the API, prior regulatory precedent recorded in FDA's IID, manufacturability at commercial scale, supply chain robustness, cost, and known safety or sensitivity concerns for the target patient population.

How is drug-excipient compatibility tested? Standard methods include DSC as a rapid first-pass screen, since it "enables fast identification of potential incompatibilities" (Source: pmc.ncbi.nlm.nih.gov), followed by TGA-FTIR, HPLC-based forced degradation studies, and powder X-ray diffraction to confirm and characterize any suspected reaction.

What is the regulatory status of excipients in the United States? There is no independent FDA approval process for an excipient alone. The narrow Novel Excipient Review Pilot Program was designed to provide FDA review before use in a drug formulation, not standalone excipient approval. Excipients are otherwise evaluated in connection with drug applications, while the IID records prior approved uses for precedent purposes; one industry analysis confirms "no independent regulatory approval process for excipients outside of an FDA drug product review" exists (Source: americanpharmaceuticalreview.com).

Are "inactive ingredients" the same thing as excipients? In drug-product contexts, FDA often uses the terms interchangeably. More precisely, FDA defines an inactive ingredient as any component other than the active ingredient and uses "excipients" for inactive ingredients added intentionally to therapeutic and diagnostic products (Source: fda.gov).

What was the pathway for FDA review of a genuinely novel excipient? FDA announced a limited Novel Excipient Review Pilot Program in September 2021 so manufacturers could seek FDA review before use in a drug formulation. The program applied to certain excipients not previously used in FDA-approved drug products and without an established food use (Source: federalregister.gov). It should not be treated as a current submission mechanism without confirming FDA's current requirements.

Conclusion

Pharmaceutical excipients are not passive filler; they are functionally engineered materials, classified into dozens of standardized categories, that determine whether a drug product can be manufactured, whether it remains stable, how it releases its active ingredient, and, in the case of modern lipid nanoparticle systems, whether the therapy works at all. Regulatory status flows almost entirely through demonstrated prior use, tracked in FDA's Inactive Ingredient Database and reinforced by USP-NF and European Pharmacopoeia quality standards. The historical novel-excipient pilot is discussed in the regulatory-pathway section; its 2021 notice alone does not establish whether a current submission route is available (Federal Register notice. Rigorous compatibility testing, from DSC screening through forced degradation studies, exists precisely because well-documented failure modes like the Maillard reaction and lot-to-lot impurity variability can silently compromise an otherwise sound formulation. Commercial market-research vendors publish differing global-market estimates and forecasts; those proprietary figures should not be treated as an independently established market size or as conclusive evidence of which segments will grow fastest. And the human stakes of excipient quality failures are neither abstract nor historical: the 2006-2007 Panama poisoning and the 2022-2023 multi-country diethylene glycol crisis involved medicines contaminated with diethylene glycol or ethylene glycol. WHO confirmed unacceptable DEG and EG contamination in the Gambian products and urged manufacturers to use qualified suppliers and comprehensively test supplies before use; its alerts do not establish a shared root cause for all of the later incidents. For formulators, regulatory affairs professionals, and quality leaders alike, the discipline this report describes, functional taxonomy, empirical compatibility testing, precedent-aware regulatory strategy, and uncompromising supplier verification, is what stands between an excipient doing its job invisibly and an excipient becoming the story.

Tags: pharmaceutical excipients, inactive ingredients, excipient compatibility testing, excipient selection criteria, FDA inactive ingredient database, novel excipient pilot program, excipient functionality categories, drug formulation, USP-NF excipients, lipid nanoparticle excipients

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