

REVIEW

Excipients and Their Role in Approved Injectable Products: Current Usage and Future Directions

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ABSTRACT: This review article is a current survey of excipients used in approved injectable products. Information provided includes concentration ranges, function, frequency of use, and role in dosage form. This article is an update of a paper published more than a decade ago (reference 11). Since then many new products have been approved. Safety concerning excipients has evolved as the scientific community continues to learn about their usage. New excipients are being used in early phases of clinical trials to support novel therapeutic entities like RNAi, aptamers, anti-sense, fusion proteins, monoclonal antibodies, and variant scaffolds. Because these excipients are not inert, various pharmacopoeias are responding with monographs or informational chapters addressing excipient functionality. The final sections of this article discuss new excipients, serving specific needs that traditional excipients are unable to provide and for which safety studies are necessary to support a novel excipient for marketing applications.

KEYWORDS: Antioxidant, Buffer, Chelating agent, Excipients, Inactive ingredients, Injectable, Parenteral, Surfactant

LAY ABSTRACT: Excipients are added to parenteral dosage forms to serve a variety of functions including stabilization and as vehicles. This review article is a survey of excipients used in approved injectable products. Information provided includes excipient concentrations, functional roles, and frequency of use. This article is an update of an article originally published over a decade ago. Since then new products have been approved and safety concerns have evolved as the scientific community has learned about the usage of excipients. In addition, new excipients are being used in early phases of clinical trials to support novel therapeutic entities such as RNAi, aptamers, anti-sense, fusion proteins, monoclonal antibodies, and variant scaffolds. Because these excipients are not inert, various pharmacopoeias are responding with monographs or informational chapters addressing excipient functionality. The final sections of this article discuss new excipients, serving specific needs that traditional excipients are unable to provide and for which safety studies are necessary to support a novel excipient for marketing applications.

I. Introduction

Excipients are typically the major components in a drug product. The active drug molecule comprises only a small percentage of the total composition. Excipients are traditionally referred to as inactive or inert ingredients to distinguish them from active pharmaceutical ingredients. Pharmaceutical excipients or additives are compounds added to the finished drug products to serve a specific function. They are added to increase bulk, aid manufacturing, improve stability, enhance drug delivery and targeting, and modify drug

safety or pharmacokinetic profile. Ingredients that are used during drug product manufacturing but may not be present in the finished drug product are also considered excipients (examples include water for lyophilized products, and inert gases in the head space of containers) (1). In recent years the “functionality” of excipients in a dosage form (similar to pharmacological activity of an active pharmaceutical ingredient or drug substance) has been recognized by various pharmacopoeias (2). Many excipient monographs do not address this aspect of excipient functionality or its control.

Recent emphasis on quality by design (QbD) has led pharmaceutical companies to better understand how excipient functionality and performance influence a drug product (3). It has been recognized for many years that pharmacopoeial excipient monographs do

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not address excipient functionality per se. To overcome this deficiency, the USP general chapter on the functionality of excipients has been proposed; the European Pharmacopeia (Ph. Eur.) has introduced a non-mandatory Functionality Related Characteristics section in monographs of some excipients. A QbD approach will enable better understanding of excipient variability and its potential impact on product quality. International Conference on Harmonization (ICH) Q8 and QbD acknowledge excipient variability. Design space studies of excipient variability and functional performance are needed to assure that excipient standards accurately reflect excipient quality (4).

Excipients may not be as inert as the term *inactive* suggests. Due to safety issues, several countries have restrictions on the type or amount of excipient that can be included in the formulation of parenteral drug product. For example, in Japan, the U.S., and the E.U., amino mercuric chloride or thimerosal use is prohibited, despite the presence of these excipients in products in other regions.

As defined in Ph. Eur. and the British Pharmacopeia (BP), “parenteral preparations are sterile preparations intended for administration by injection, infusion, or implantation into the human or animal body.” In the present article, only sterile preparations for administration by injection or infusion into the human body will be surveyed (5, 6). Injectable products require a unique formulation strategy. The formulated product must be sterile, pyrogen-free, and, in the case of solution, free of particulate matter. No coloring agent may be added solely for the purpose of coloring the parenteral preparation. The formulation should preferably be isotonic, and depending on the route of administration, certain excipients are not allowed. The injected drug by-passes natural defense barriers; hence, for any given drug, the risk of an adverse event may be greater or the effects difficult to reverse if administered as an injection rather than a non-parenteral route. Sterility requirements demand that an excipient is able to withstand terminal sterilization or aseptic processing. These factors limit the choice of excipients available.

Knowledge of excipients that have been deemed safe by the Food and Drug Administration (FDA) or are already present in a marketed product provides increased assurance to a formulator that these excipients will probably be safe for a new drug product. But safety is not guaranteed when excipients are combined

with other additives and/or with a new drug molecule creating unforeseen potentiation or synergistic toxic effects. Regulatory bodies may favorably view an excipient previously approved in an injectable dosage form, and will require less safety data. A new additive in a formulated product always requires additional studies, adding to the cost and timeline of product development. Importantly, inclusion of an excipient in the GRAS (Generally Recognized as Safe) list or pharmacopoeia does not mean that the excipient has been deemed safe by the FDA for use in parenteral products.

In Japan if a drug product contains an excipient with no precedence of use, the quality and safety attributes of the excipient must be evaluated by the Subcommittee on Pharmaceutical Excipients of the Central Pharmaceutical Affairs Council concurrently with the evaluation of the drug product application (7). Precedence of use means the excipient has been used in a drug product in Japan which is administered via the same route and in a dose level equal to or greater than the excipient in question in the new application.

This article is a comprehensive review of excipients that have been included in injectable products marketed in the USA, Europe, and Japan. A literature review indicates that few articles have been published dealing specifically with selection of parenteral excipients (8–17). This review does not cover excipients included in other sterile dosage forms not administered parenterally, such as solution for irrigation, ophthalmic, or otic drops and ointments.

Several sources were used to summarize the information compiled in this paper (9–22). Formulation information on commercially available injectable products was entered in a worksheet. Tables presented have been condensed from this worksheet. Each table has been categorized based on an excipient's primary function in a formulation. For example, citrates are classified as buffers, not as chelating agents. Ascorbates are categorized as antioxidants, although they can also serve as buffers. This classification system minimizes redundancy and provides a reader-friendly format. Concentration of excipients is listed as percent weight by volume (w/v) or volume by volume (v/v). If the product was listed as lyophilized or powder, percentages were derived based on reconstitution volume commonly used. The tables list the concentration

TABLE I
Solvents and Co-Solvents

Excipient	Frequency	Range	Example
Benzyl benzoate	3	20–44.7% w/v	Delestrogen® 40 mg/mL (Bristol Myers) 44.7% w/v
Castor oil	2	11.50%	Delestrogen® 40 mg/mL (Bristol Myers)
Cottonseed oil	1	73.6%–87.4% w/v	Depo®Testosterone (Pfizer) 73.6% w/v
N,N dimethylacetamide	2	6–33% w/v	Busulfex® (Orphan Medical) 33%
Ethanol/ethanol dehydrated	34	0.6–100%	Prograf® (Fujisawa) 80% v/v, Alprostadil (Bedford Lab) 100%
Glycerin (glycerol)	17	1.6–70% w/v	Multitest CMI® (Pasteur Merieux) 70% w/v
N-methyl-2-pyrrolidone	1	*	Eligrad 7.5 mg (Sanofi)
Peanut oil	1	*	Bal in Oil® (Becton Dickinson)
Polyethylene glycol			
PEG**	5	0.15–50%	Secobarbital sodium (Wyeth-Ayerst) 50%
PEG 300	4	50–65%	VePesid® (Bristol Myers) 65% w/v
PEG 400	4	11.2–67% v/v	Busulfex® (Orphan Medical) 67%
PEG 600	1	5% w/v	Persantine® (Dupont-Merck)
PEG 3350	4	0.3–3%	Depo-Medrol® (Upjohn) 2.95% w/v
PEG 4000	1	0.3–3%	Invega Sustenna® (Janssen)
Poppyseed oil	1	*	Ethiodol® (Savage)
Propylene glycol	32	0.0025–80%	Ativan® (Wyeth-Ayerst) 80%
Safflower oil	2	5–10%	Liposyn II® (Abbott) 10%
Seasme oil	7	100%	Solganal Injection® (Schering)
Soybean oil	1	10% w/v	Diprivan Injection (Zeneca)
Vegetable oil	2	*	Virilon IM Injection® (Star Pharmaceuticals)

* Not applicable or no data available.

** PEG molecular weight not specified.

range and examples of products containing the excipient, especially those using an extremely low or high concentration.

II. Types of Excipients

II.A. Solvents and Co-Solvents

Table I lists solvents and co-solvents used in parenteral products. Water for injection (WFI) is the most common solvent, but there are differences in the pharmacopeial specifications. Ph. Eur. does not recognize WFI produced by reverse osmosis even though the finished excipient will meet all specifications (23, 24). WFI can be combined or substituted with a co-solvent to improve drug solubility or stability (25, 26). Dielectric constant and solubility parameters are among the most commonly used polarity indices for solvent blending (27, 28). Ethanol and propylene glycol are used alone or in combination with other solvents in

more than 50% of parenteral co-solvent systems. Surprisingly, propylene glycol is used more often than polyethylene glycols (PEGs) despite its higher myotoxicity and hemolyzing effects (29–32). A toxicity review of commonly used parenteral co-solvents is summarized in an article by Mottu (33). The hemolytic potential of co-solvents is as follows (31): dimethyl acetamide < PEG 400 < Ethanol < propylene glycol < dimethylsulfoxide.

It is possible that the presence of residual peroxide from bleaching of PEG or generation of peroxides in PEG may result in degradation of drug in a co-solvent system. It is important to use unbleached and/or peroxide-free PEGs in a formulation.

Oils such as safflower and soybean are used in total parenteral nutrition products where they serve as a fat source and as carriers for fat-soluble vitamins. The USP requirements (34) for injectable oils are as follows:

Fixed oils (of vegetable origin)

Saponification value (185–200)

Iodine Number (79–141); the Japanese Pharmacopoeia (JP) recommends value between 79–137

Test for unsaponifiable matter

Test for free fatty acid

Solid paraffin test at 10 °C

Acid value not more than 0.56 (JP only) (35)

Synthetic mono- and di-glycerides of fatty acids (which are liquid and remain so when cooled to 10 °C)

Iodine Number (<140)

Solid paraffin test at 10 °C

Oils are used to dissolve drugs with low aqueous solubility and provide a mechanism for slow drug release over a long period of time. Deterioration of fixed oils, leading to rancidity and production of free fatty acids, must be avoided in injectable products. Fixed oils or fatty acid esters must not contain mineral oil or paraffin that the body cannot metabolize.

II.B. Polymeric and Surface Active Compounds

Table II includes a broad category of excipients whose function in a formulation could be

1. To impart viscosity or act as suspending agents: carboxy methyl cellulose, sodium carboxy methyl cellulose, acacia, Povidone, hydrolyzed gelatin, sorbitol
2. To act as solubilizing, wetting or emulsifying agents: Cremophore EL, sodium desoxycholate, Polysorbate 20 or 80, PEG 40 Castor oil, PEG 60 castor oil, sodium dodecyl sulfate, lecithin or egg yolk phospholipid
3. To form gels, as when aluminum monostearate is added to fixed oil, forming a viscous or gel-like suspension medium

Polysorbate 80 is the most common and versatile solubilizing, wetting, and emulsifying agent. Again, one must be concerned with the level of residual peroxides present in polysorbates and protecting them from air to prevent further oxidation (36). Polysorbate 80 is a polyoxyethylene sorbitan ester of oleic acid (unsaturated fatty acid) while polyoxyethylene Polysorbate 20 is a sorbitan ester of lauric acid (saturated fatty acid). Thus, there could be stability differences in a drug product formulated with Polysorbate 80 versus Polysorbate 20. One example is Neupogen® which, when exposed to a high concentration of Polysorbate 20, exhibited substantially less oxidation than when exposed to a similar concentration of Polysorbate 80 (37).

II.C. Chelating Agents

A limited number of chelating agents are used in parenteral products (Table III). They serve to complex heavy metals and therefore improve the efficacy of antioxidants or preservatives. Citric acid, tartaric acid, and some amino acids act as chelating agents. There has been misunderstanding that ethylenediaminetetraacetic acid (EDTA) (as calcium or sodium salt) has not been used in an approved injectable product in Japan. Some currently marketed drug products do contain calcium disodium EDTA in Japan. This excipient is listed as an official excipient in Japan (refer to section II.H. for details). One possible advantage of calcium EDTA over tetrasodium salt is that it does contribute little sodium and does not chelate calcium from the blood.

A complexing agent should not be used in metalloprotein formulations, where protein sub-units are held by the metal (38). EDTA, in rare instances, can increase oxidation rate due to binding of EDTA-metal complex to protein, resulting in site-specific generation of radicals (39).

II.D. Antioxidants

Antioxidants are used to prevent oxidation of active substances and excipients in the finished product. Antioxidant can be classified into three main types:

1. True antioxidants: those that act via a chain termination mechanism by reacting with free radicals (e.g. butylated hydroxytoluene)
2. Reducing agents: those that have a lower redox potential than the drug and are preferentially oxidized

TABLE II
Solubilizing, Wetting, Suspending, Emulsifying, or Thickening Agents

Excipient	Frequency	Range	Example
Acacia	2	7%	Tuberculin Old Test® (Lederle) 7%
Aluminum monostearate	1	2%	Solganal Injection® (Schering) 2%
Carboxy methyl cellulose	4	0.50–0.55%	Bicillin® (Wyeth-Ayerst) 0.55%
Carboxy methyl cellulose, sodium (Crosscarmellose sodium)	21	0.15–3.0%	Nutropin Depot® (Genentech) 3%
Cremophor EL*	3	50–65% w/v	Sandimmune® (Sandoz) 65% w/v
Cyclodextrin, gamma	1	5.0%	Cardiotec (BMS)
Cyclodextrin, alpha	1	0.14%	Edex (Schwartz)
Hydroxypropyl-beta-cyclodextrin	2	16–40%	Sporanox (Janssen)
Sulfobutylether cyclodextrin sodium	3	15–29.4%	Geodon (Pfizer)
Desoxycholate sodium	1	0.4% w/v	Fungizone® (Bristol Myers) 0.41% w/v
Egg yolk phospholipid	3	1.2%	Cleviprex® (The Medicines Co.)
Gelatin, hydrolyzed	1	16% w/v	Cortone® (Merck) 16% w/v
Lecithin	8	0.4–1.2% w/v	Diprivan® (Zeneca) 1.2% w/v
Polyoxyethylated fatty acid	1	7% w/v	AquaMephyton® (Merck) 7% w/v
Polysorbate 80 (Tween 80)	72	0.001–100%	Aquasol A parenteral® (Astra) 12% Taxotere® (Aventis) 100%
Polysorbate 20 (Tween 20)	22	0.001–0.4%	Calcijex® (Abbott) 0.4% w/v
PEG 40 castor oil**	1	11.5% v/v	Monistat® (Janssen) 11.5% v/v
PEG 60 castor oil***	1	20% w/v	Prograf® (Fujisawa) 20% w/v
Poloxamer 188 (Pluronic F68)	5	0.005–0.3%	Norditropin (NovoNordisk) 0.3%
Povidone (Polyvinyl pyrrolidone, Crosspovidone)	7	0.5–0.6% w/v	Bicillin® (Wyeth-Ayerst) 0.6% w/v
Sodium dodecyl sulfate (Na lauryl sulfate)	1	0.018% w/v	Proleukin® (Cetus) 0.018% w/v
Sorbitol	3	25–50%	Aristrospan® (Fujisawa) 50% v/v
Triton X-100 (Octoxynol-9)	1	0.0085% w/v	Fluarix® (GSK)

* Cremophor EL, Etocas 35, polyethoxylated castor oil, polyoxyethylene 35 castor oil.

** PEG 40 castor oil, polyoxyl 40 castor oil, castor oil POE-40, Croduret 40, polyoxyethylene 40 castor oil, Protachem CA-40.

*** PEG 60 hydrogenated castor oil; Cremophor RH 60, hydrogenated castor oil POE-60, Protachem CAH-60.

dized (e.g., ascorbic acid). Consequently, they can be consumed during the shelf life of the product.

3. Antioxidant synergists: those that enhance the effect of antioxidants (e.g., EDTA)

Table IV summarizes antioxidants, their frequency of use, concentration range, and examples of products containing them. Sulfite, bisulfite, and metabisulfite constitute the majority of antioxidants used in parenteral products despite several reports of incompatibility and toxicity (40, 41). Butylated hydroxy anisole, butylated hydroxy toluene, alpha tocopherol, and pro-

pyl gallate are primarily used in semi/non-aqueous vehicles because of their low aqueous solubility (42). Ascorbic acid/sodium ascorbate may serve as an antioxidant, buffer, and chelating agent in the same formulation. Some amino acids (cysteine) function as effective antioxidants.

The Committee for Medicinal Products for Human Use (CHMP, which replaced the Committee for Proprietary Medicinal Products) guideline requires a full explanation and justification for including antioxidants in a formulation (43, 44). It further states that antioxidants should be included in a formulation only

TABLE III
Chelating Agents

Excipient	Frequency	Range	Example
Calcium disodium EDTA*	11	0.01–0.1%	Wydase® (Wyeth-Ayerst) 0.1% w/v
Disodium EDTA	48	0.01–0.11%	Calcijex® (Abbott) 0.11% w/v
Sodium EDTA	1	0.20%	Folvite® (Lederle) 0.20%
Calcium Versetamide Na	1	2.84% w/v	OptiMARK® (Mallinckrodt)
Calteridol	1	0.023% w/v	Prohance® (Bracco Diagnostics, Inc.)
DTPA**	3	0.04%–1.2%	Omniscan™ (GE Healthcare) 1.2%

* EDTA = Ethylenediaminetetraacetic acid.

** DTPA = Diethylenetriaminepentaacetic acid; Pentetic acid.

if it has been demonstrated that their use cannot be avoided. Thus, it is imperative to try an inert gas such

as nitrogen or argon in the container head space to prevent oxidation. If an antioxidant must be included,

TABLE IV
Antioxidants and Reducing Agents

Excipient	Frequency	Range	Example
Acetone sodium bisulfite	4	0.2–0.4% w/v	Novocaine® (Sanofi-Winthrop) 0.4% w/v
Argon	-	100%	Used to fill headspace of lyophilized or liquid products. TechneScan MAG3® (Covidien)
Ascorbyl palmitate	1		Visudyne® (QLT)
Ascorbate (sodium/acid)	10	0.1–4.8% w/v	Vibramycin® (Pfizer) 4.8% w/v
Bisulfite sodium	31	0.02–0.66% w/v	Amikin® (Bristol Myers) 0.66% w/v
Butylated hydroxy anisole (BHA)	3	0.00028–0.03% w/v	Aquasol A® (Astra) 0.03% w/v
Butylated hydroxy toluene (BHT)	4	0.00116–0.03% w/v	Aquasol A® (Astra) 0.03% w/v
Cystein/cysteinate HCl	4	0.07–1.3% w/v	Acthrel® (Ferring) 1.3% w/v
Dithionite sodium (Na hydrosulfite, Na sulfoxylate)	1	0.10%	Numorphan® (Endo Lab) 0.10%
Gentisic acid	1	0.02% w/v	OctreoScan® (Mallinckrodt) 0.02% w/v
Gentisic acid ethanolamine	1	2%	M.V.I. 12® (Astra) 2%
Glutamate monosodium	1	0.1% w/v	Varivax® (Merck) 0.1% w/v
Glutathione	1	0.01% w/v	Advate® (Baxter) 0.01% w/v
Formaldehyde sulfoxylate sodium	10	0.075–0.5% w/v	Terramycin solution (Pfizer) 0.5% w/v
Metabisulfite potassium	1	0.10%	Vasoxyl® (Glaxo-Wellcome) 0.10%
Metabisulfite sodium	33	0.02–1% w/v	Intropin® (DuPont) 1% w/v
Methionine	5	0.01–0.15%	Depo-subQ provera 104 (Upjohn)
Monothioglycerol (Thioglycerol)	8	0.1–1%	Terramycin solution (Pfizer) 1%
Nitrogen	-	100%	Used to fill headspace of lyophilized or liquid products
Propyl gallate	3	0.02%	Navane® (Pfizer) 0.02%
Sulfite sodium	8	0.05–0.2% w/v	Enlon® (Ohmeda) 0.2% w/v
Tocopherol alpha	2	0.005–0.075%	Torisel (Wyeth) 0.075%
α-Tocopherol hydrogen succinate	1	0.02% w/v	Fluarix® (GSK) 0.02% w/v
Thioglycolate sodium	1	0.66% w/v	Sus-Phrine® (Forest) 0.66% w/v

TABLE V
Antimicrobial Preservatives

Excipient	Frequency	Range	Example
Benzalkonium chloride	1	0.02% w/v	Celestone Soluspan® (Schering) 0.02% w/v
Benzethonium chloride	4	0.01%	Benadryl® (Parke-Davis) 0.01% w/v
Benzyl alcohol	90	0.75–5%	Dimenhydrinate Injection, USP (APP Pharmaceuticals) 5%
Chlorbutanol	19	0.25–0.5%	Codine phosphate (Wyeth-Ayerst) 0.5%
m-Cresol	13	0.1–0.315%	Humalog® (Lilly) 0.315%
Myristyl gamma-picolinium chloride	2	0.0195–0.169% w/v	Depo-Provera® (Pharmacia-Upjohn) 0.169% w/v
Paraben methyl	55	0.05–0.18%	Inapsine® (Janssen) 0.18% w/v
Paraben propyl	45	0.005–0.1%	Xylocaine w/Epinephrine (Astra) 0.1% w/v
Phenol	55	0.15–0.5%	Calcimar® (Rhone-Poulanc) 0.5% w/v
2-Phenoxyethanol	4	0.50%	Havrix® (SmithKline Beecham) 0.50% w/v
Phenyl mercuric nitrate	3	0.001%	Antivenin® (Wyeth-Ayerst) 0.001%
Thimerosal	50	0.003–0.012%	Atgam® (Pharmacia-Upjohn) 0.01%

its concentration must be justified in terms of efficacy and safety. Antioxidants, like sulfites and metabisulfites, are especially undesirable.

Some antioxidants possess antimicrobial properties. Propyl gallate and butylated hydroxy anisole are somewhat effective against bacteria. Butylated hydroxy toluene has demonstrated some anti-viral activity. Compatibility of antioxidants with the drug, packaging system, and the body should be studied carefully. For example, tocopherols may be absorbed on plastics; ascorbic acid is incompatible with alkalis, heavy metals, and oxidizing materials like phenylephrine and sodium nitrite; propyl gallate forms complexes with metal ions like sodium, potassium, and iron.

II.E. Preservatives

Benzyl alcohol is the most common antimicrobial preservative present in parenteral formulations (Table V). This observation is consistent with other surveys (12, 45). Parabens are the second most common preservatives. Surprisingly, thimerosal is also common, especially in vaccines, even though some individuals are sensitive to mercurics. Several preservatives can volatilize easily (benzyl alcohol, phenol) and should not be used for a lyophilized dosage form. Chlorocresol is purported to be a good preservative for parenterals, but our survey did not find any examples of commercial products containing chlorocresol. The

British Pharmaceutical Codex and Martindale lists chlorocresol as a preservative to be used in multidose aqueous injections at a concentration of 0.1%, but no examples of injectable products were provided (46, 47).

Antimicrobial preservatives are allowed in multi-dose injections to prevent growth of microorganisms that may accidentally enter the container during withdrawal of the dose. In the U.S., preservatives are discouraged from being used in single-dose injections, while Ph. Eur. and BP allow aqueous preparations manufactured using aseptic techniques to contain suitable preservatives. Ph. Eur. and BP prohibit antimicrobials for single-dose injections where the dose volume is greater than 15 mL or if the drug product is to be injected intracisternally, or via any route giving access to the cerebrospinal fluid (e.g., retro-ocular). It should be emphasized that preservatives should never be used as a substitute for inadequate cGMP (current good manufacturing practice). Toxicity is the primary reason for minimizing use of antimicrobial preservatives. For example, many individuals are allergic to mercury preservatives and benzyl alcohol is contraindicated in children under the age of 2 years. The USP has placed some restrictions on the maximum concentration of preservatives allowed in a formulation to address toxicity and allergic reactions (Table VI). The World Health Organization has set an estimated total acceptable daily intake for sorbate (as acid, calcium, potassium, and sodium salts) as not more than 25

TABLE VI
Maximum Permissible Amount of Preservatives
and Antioxidants

Excipient	Maximum Limit in USP
Mercurial compounds	0.01%
Cationic surfactants	0.01%
Chlorobutanol	0.50%
Cresol	0.50%
Phenol	0.50%
Sulfur dioxide or an equivalent amount of the sulfite, bisulfite, or metabisulfite of potassium or sodium	0.20%

mg/kg body weight. Recently, concerns have been raised on the safety of parabens in pediatric formulations, based primarily on reports by one Japanese laboratory between 2001 and 2004 indicating effects on reproductive apparatus of juvenile male rats given propyl (48) or butyl paraben (49), but lack of effects for methyl and ethyl parabens (50), though a vast majority of toxicological data suggests otherwise (51). Until a comprehensive assessment is performed, formulators should consider the current view of regional regulatory agencies (e.g., AFSSAPS, Scandinavian, *et al.*) and may investigate other preservative options for pediatric products.

The efficacy of a preservative should be assessed during product development using antimicrobial preservative effectiveness testing (PET) (52–54). A preserved aqueous parenteral product can be used up to a maximum of 28 days after the container has been opened (55). This time period must be qualified by performing PET on the finished product in the final package. Conversely, un-preserved product should preferably be used immediately or within a short period of time upon opening, reconstitution, or dilution.

Similar to antioxidants, addition of preservatives in parenteral products requires justification. Their use should be avoided, particularly for pediatric products, but if used, their concentration should be as low as possible (44).

II.F. Buffers

Buffers are added to a formulation to adjust and stabilize pH and optimize drug solubility and stability.

For parenteral preparations, it is desirable that the product pH be close to physiologic pH. Selection of a buffer concentration (which contributes to the ionic strength of the formulation) and a buffer species is important. For example, citrate buffers in the range of 5–15 mM are typically used in formulations but increasing the buffer concentration to >50 mM will result in excessive pain on sub-cutaneous injection and toxic effects due to chelation of calcium in the blood.

Buffers have maximum buffer capacities near their pK_a . Products which may be subjected to excessive temperature fluctuations during processing (steam sterilization, freeze-thaw or lyophilization), buffers with a small $\Delta pK_a/^\circ\text{C}$ should be selected. For example, Tris, whose $\Delta pK_a/^\circ\text{C}$ is large ($-0.028/^\circ\text{C}$), the pH of buffer made at 25 °C will change from 7.1 to 5.0 at 100 °C. This may dramatically alter stability or solubility of a drug. Similarly, the best buffers for a lyophilized product may be those which show the least pH change upon cooling, do not crystallize out, and remain in the amorphous state, protecting the drug. For example, replacing succinate with glycolate buffer improves the stability of lyophilized interferon- γ (56). During the lyophilization of mannitol containing succinate buffer at pH 5, monosodium succinate crystallizes, reducing the pH and resulting in the unfolding of interferon- γ . This pH shift is not seen with glycolate buffer.

Table VII lists buffers and chemicals used for pH adjustment and maintenance of the drug product pH range. Phosphate, citrate, and acetate are the most common buffers used in parenteral products. Mono- and di-ethanolamines are added to adjust pH and form corresponding salts. Hydrogen bromide, sulfuric acid, benzene sulfonic acid, and methane sulfonic acids are added to drugs that are salts of bromide (Scopolamine HBr, Hyoscine HBr), sulfate (Nebcin, Tobramycin sulfate), besylate (Tracrium Injection, Atracurium besylate), or mesylate (DHE 45 Injection, dihydroergotamine mesylate). Glucono delta lactone is used to adjust the pH of Quinidine gluconate. Benzoate buffer, at a concentration of 5%, is used in Valium Injection. Citrates are common buffers that serve a dual role as chelating agent. Amino acids—histidine, arginine, and glycine—function as buffers and stabilize proteins and peptide formulations. These amino acids are also used as lyo-additives and may prevent cold denaturation. Lactate and tartrate are occasionally used as buffer systems. Acetates are good buffers at low pH, but they are not frequently used for lyophilization because of the potential sublimation of acetates.

TABLE VII
Buffers and pH Adjusting Agents

Excipient	pH Range	Example
Acetate		
Sodium	2.5–7.0	Syntocinon® (Novartis)
Acetic acid	2.5–7.2	Syntocinon® (Novartis)
Glacial acetic acid	3.5–7.0	Brevibloc® (Ohmeda)
Ammonium	6.8–7.8	Bumex Injection® (Roche)
Ammonium sulfate	-	Innovar® (Astra)
Ammonium hydroxide	-	Triostat® (Jones Medical)
Arginine	7.0–7.4	Retavase® (Boehringer)
Aspartic acid	5.0–5.6	Pepcid® (Merck)
Benzene sulfonic acid	3.25–3.65	Nimbex® (Glaxo Wellcome)
Benzoate sodium/acid	3.5–6.9	Valium® (Roche)
Bicarbonate, sodium	5.5–11.0	Cenolate® (Abbott)
Boric acid/sodium		Comvax® (Merck)
Carbonate, sodium	4.0–11.0	Hyperab® (Bayer)
Carbon dioxide	-	Serentil® (Boehringer) used to fill headspace
Citrate		
Acid	2.5–9.0	DTIC-Dome® (Bayer)
Sodium	3.0–8.5	Amikin® (Bristol Myers)
Disodium	6.1	Cerezyme® (Genzyme)
Trisodium	6.1	Cerezyme® (Genzyme)
Diethanolamine	9.5–10.5	Bactim IV® (Roche)
Glucono delta lactone	5.5–7.0	Quinidine Gluconate (Lilly)
Glycine/glycine HCl	2.5–10.8	Hep-B Gammagee® (Merck)
Histidine/histidine HCl	5.0–6.5	Doxil® (Sequus)
Hydrochloric acid	Broad range	Amicar® (Immunex)
Hydrobromic acid	3.5–6.5	Scopolamine (UDL)
Lactate sodium/acid	2.7–5.8	Innovar® (Janssen)
Lysine (L)	-	Eminase® (Roberts)
Maleic acid	3.0–5.0	Librium® (Roche)
Meglumine	6.5–11.0	Magnevist® (Berlex)
Methanesulfonic acid	3.2–4.0	DHE-45® (Novartis)
Monoethanolamine	8.0–9.0	Terramycin (Pfizer)
Phosphate		
Acid	6.5–8.5	Saizen® (Serono Labs)
Monobasic potassium	6.7–7.3	Zantac® (Glaxo-Wellcome)
Dibasic potassium	6.7–7.3	Aminosyn® (Hospira)
Monobasic sodium*	2.5–8.0	Pregnyl® (Organon)
Dibasic sodium**	2.5–8.3	Zantac® (Glaxo-Wellcome)
Tribasic sodium	-	Synthroid® (Knoll)
Sodium hydroxide	Broad range	Optiray® (Mallinckrodt)
Succinate sodium/disodium	5.0–6.0	AmBisome® (Fujisawa)
Sulfuric acid	3.0–7.0	Nebcin® (Lilly)
Tartrate sodium/acid	2.5–6.2	Methergine® (Novartis)
Tromethamine (Tris)	6.5–9.0	Optiray® (Mallinckrodt)

* Sodium biphosphate, sodium dihydrogen phosphate, or Na dihydrogen orthophosphate.

** Sodium phosphate, disodium hydrogen phosphate.

TABLE VIII
Bulking Agents, Protectants, and Tonicity Adjusters

Excipient	Example
Alanine	Thrombate III® (Bayer)
Albumin	Bioclata® (Arco)
Albumin (Human)	Botox® (Allergan)
Amino acids	Havrix® (Smith Kline Beecham)
Arginine (L)	Activase® (Genentech)
Asparagine	Tice BCG® (Organon)
Aspartic acid (L)	Pepcid® (Merck)
Calcium chloride	Xyntha® (Wyeth)
Cyclodextrin-alpha	Edex® (Schwartz)
Cyclodextrin-gamma	Cardiotec® (Squibb)
Dextran 40	Etopophos® (Bristol Myers)
Dextrose	Betaseron® (Berlex)
Gelatin (crosslinked)	Kabikinase® (Pharmacia-Upjohn)
Gelatin (hydrolyzed)	Acthar® (Rhone-Poulanc Rorer)
Lactic & glycolic acid copolymers	Lupron Depot® (TAP)
Glucose	Iveegam® (Immuno-US)
Glycerine	Tice BCG® (Organon)
Glycine/glycine hydrochloride	Atgam® (Pharmacia-Upjohn)
Histidine	Antihemophilic factor, human (American Red Cross)
Imidazole	Helixate® (Armour)
Inositol	OctreoScan® (Mallinckrodt)
Lactose	Caverject® (Pharmacia-Upjohn)
Magnesium chloride	Terramycin solution (Pfizer)
Magnesium sulfate	Tice BCG® (Organon)
Maltose	Gamimune N® (Bayer)
Mannitol	Elspar® (Merck)
Polyethylene glycol 3350	Bioclata® (Arco)
Polylactic acid	Lupron Depot® (TAP)
Potassium chloride	Varivax® (Merck)
Povidone (PVP)	Alkeran® (Glaxo-Wellcome)
Sodium chloride	WinRho SD® (Univax)
Sodium cholesteryl sulfate	Amphotec® (Sequus)
Sodium succinate	Actimmune® (Genentech)
Sodium sulfate	Depo-Provera® (Pharmacia-Upjohn)
Sorbitol	Panhematin® (Abbott)
Sucrose	Prolastin® (Bayer)
L-Threonine	Temodar® (Schering)
Trehalose (alpha, alpha)	Herceptin® (Genentech)

II.G. Bulking Agents, Protectants, and Tonicity Adjusters

Table VIII lists additives used as bulking or lyo/cryo-protective agents and to modify osmolality. Dextrose

and sodium chloride are the most commonly used tonicity adjusters. Some amino acids such as glycine, alanine, histidine, imidazole, arginine, asparagine, and aspartic acid are used as bulking agents for lyophilization and may also serve as stabilizers and/or as

buffers. Monosaccharides (dextrose, glucose, maltose, lactose), disaccharides (sucrose, trehalose), polyhydric alcohols (inositol, mannitol, sorbitol), glycols (PEG 3350), Povidone (polyvinylpyrrolidone, PVP), and proteins (albumin, gelatin) are commonly used as lyo-additives. Hydroxyethyl starch (hetastarch) and pentastarch, currently used as plasma expanders in commercial injectable products like Hespan and Pentaspan, are being evaluated as protectants during freeze-drying of proteins.

PVP has been used in injectable products (except in Japan) as a solubilizing agent, protectant, and bulking agent. Only pyrogen-free grade, with low molecular weight (K value less than 18) should be used in parenteral products to allow for rapid renal elimination. PVP not only solubilizes drugs like rifampicin, but it also reduces local toxicity, as seen in the case of Oxytetracycline Injection.

Many proteins can be stabilized in a lyophilized state if the stabilizer and protein do not phase separate during freezing or if the stabilizer does not crystallize. In the case of Neupogen® (GCSF), the original formulation was modified by replacing mannitol with sorbitol to prevent loss of activity of the liquid formulation if accidentally frozen (37). Mannitol crystallizes if the solution freezes, while sorbitol remains in an amorphous state, protecting GCSF. A recent report suggests that sorbitol (and even trehalose) can also crystallize under certain conditions (57). Similarly, it is useful that the drug remains dispersed in the stabilizer upon freezing of the solution. Consequently, Cefoxitin, a cephalosporin, is more stable when freeze-dried with sucrose rather than with trehalose, although the glass transition temperature and structural relaxation time is much greater for trehalose than sucrose (58). Fourier transform infrared spectroscopy data indicated that the trehalose-cefoxitin system phase-separated into two nearly pure components resulting in no protection (stability). Similarly, dextran was not found to be as useful a cryoprotectant for protein as sucrose because dextran and protein underwent phase segregation as the solution began to freeze. The mechanism of cryoprotection in the solution has been explained by the preferential exclusion hypothesis (59).

Trehalose is a non-reducing disaccharide composed of two D-glucose monomers. It is found in several animals that can withstand dehydration and therefore had

been suggested to stabilize drugs that undergo denaturation during spray or freeze-drying (60). Herceptin® (Trastuzumab) is a recombinant DNA-derived monoclonal antibody (MAb) used for treating metastatic breast cancer. The MAb has been stabilized in the lyophilized formulation using α,α -trehalose dihydrate. Trehalose has also been used as a cryoprotectant to prevent liposomal aggregation and leakage. In the dried state, carbohydrates like trehalose and inositol exert their protective effect by acting as a water substitute (61).

Additives may be included in a formulation to adjust the specific gravity. This is important for drugs which, upon administration, may come in contact with cerebrospinal fluid (CSF). CSF has a specific gravity of 1.0059 at 37 °C. Solutions having the same specific gravity as that of CSF are termed *isobaric*, while those solutions which have specific gravity greater than that of CSF are called *hyperbaric*. Upon administration of a hyperbaric solution in the spinal cord, the injected solution will settle and affect spinal nerves at the end of the spinal cord. For example, Dibucaine hydrochloride solution (Nupercaine® 1:200) is isobaric, while Nupercaine® 1:500 is hypobaric (specific gravity of 1.0036 at 37 °C). Nupercaine® heavy solution is made hyperbaric by addition of 5% dextrose solution. This solution will block (anesthetize) the lower spinal nerves as it will settle in the lower spinal cord.

II.H. Special Additives

These additives have been included in pharmaceutical formulations to serve specific functions (Table IX). The following is a summary of some special additives along with their intended use:

1. Calcium gluconate injection (American Regent) is a saturated solution of 10% w/v; calcium d-saccharate tetrahydrate 0.46% w/v is added to prevent crystallization during temperature fluctuations.
2. Cipro IV® (ciprofloxacin, Bayer) contains lactic acid as a solubilizing agent for the antibiotic.
3. Premarin Injection® (conjugated estrogens, Wyeth-Ayerst Labs) is a lyophilized product that contains simethicone to prevent formation of foam during reconstitution.
4. Dexamethasone acetate (Dalalone DP, Forest, Decadron-LA, Merck) and dexamethasone sodium

TABLE IX
Special Additives

Excipient	Example
Acetyl tryptophanate	Human Albumin (American Red Cross)
Aluminum hydroxide	Recombivax HB® (Merck)
Aluminum phosphate	Tetanus Toxoid Adsorbed (Wyeth)
Aluminum potassium sulfate	TD Adsorbed Adult (Pasteur Merieux)
Amino acids (leucine, isoleucine, lysine (as acetate or HCl salt), valine, phenylalanine, threonine, tryptophan, alanine, aspartic acid, glutamic acid, proline, serine, tyrosine, taurine)	Travasol 10% Injection (Baxter) Aminosyn-PF10% (Hospira)
ε-Aminocaproic acid	Eminase® (Roberts)
Calcium D-saccharate	Calcium Gluconate (American Regent)
Caprylate sodium	Human Albumin (American Red Cross)
8-Chlorotheophylline	Dimenhydrinate® (Steris)
Creatine	Dalalone DP® (Forest)
Creatinine	Decadron® (Merck)
Cholesterol	Doxil® (Sequus)
Cholesteryl sulfate sodium	Amphotec® (Sequus)
Cyclohexanedione dioxime	Cardiotec® (BMS)
Diethanolamine	Bactrim® IV Infusion (Roche)
Distearyl phosphatidylcholine	DaunoXome® (Nexstar)
Distearyl phosphatidylglycerol	MiKasome® (NeXstar)
L-alpha-dimyristoylphosphatidylcholine	Abelcet® (The Liposome Co.)
L-alpha-dimyristoylphosphatidylglycerol	Abelcet® (The Liposome Co.)
Dioleoylphosphatidylcholine (DOPC)	DepoCyt® (Chiron)
Dipalmitoylphosphatidylglycerol (DPPG)	DepoCyt® (Chiron)
(R)-hexadecanoic acid, 1-[(phosphonoxy)methyl]-1,2-ethanediyl ester, monosodium salt (DPPA)	Definity® (Lantheus Medical Imaging)
(R)-4-hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,4,9-trioxa-4-phosphapentacosan-1-aminium, 4-oxide, inner salt (DPPC)	Definity® (Lantheus Medical Imaging)
(R)-[6-hydroxy-6-oxido-9-[(1-oxohexadecyl)oxy]-5,7,11-trioxa-2aza-6-phosphahexacos-1-yl]-ω-methoxypoly(ox-1,2-ethanediyl), monosodium salt (MPEG5000 DPPE)	Definity® (Lantheus Medical Imaging)
MPEG-distearoyl phosphoethanolamine	Doxil® (Sequus)
Ethyl lactate	Ergotrate maleate (Lilly)
Ethylenediamine	Aminophylline (Abbott)
L-Glutamate sodium	Kabikinase® (Pharmacia-Upjohn)
Hyaluronate sodium	Trivaris® (Allergan)
Hydrogenated soy phosphatidylcholine	Doxil® (Sequus)
Iron ammonium citrate	Tice BCG® (Organon)
Lactic acid	Cipro IV® (Bayer)
D,L-lactic and glycolic acid copolymer	Zoladex® (Zeneca)
Meglumine	Magnevist® (Berlex)
Methyl boronic acid	Cardiotec® (BMS)

TABLE IX
(continued)

Excipient	Example
Niacinamide	Estradurin® (Wyeth-Ayerst)
Paraben methyl	Adriamycin RDF® (Pharmacia-Upjohn)
Phosphatidylglycerol, egg (EPG)	Visudyne® (QLT)
Potassium sodium tartrate	CEA-Scan® (Immunomedics)
Protamine (as sulfate)	Insulatard NPH® (Novo Nordisk)
Simethicone	Premarin Injection® (Wyeth-Ayerst)
Saccharin sodium	Compazine Injection® (Smith Kline Beecham)
Sodium D-gluconate	Myoview® (Amersham)
Sodium hypochlorite	Ultratag™ RBC (Covidien)
Sodium sulfate	Depo-Provera® (Pfizer)
Stannous chloride	Myoview® (Amersham)
Sulfosalicylate disodium	Myoview® (Amersham)
Tin chloride (stannous and stannic)	Ultratag™ RBC (Covidien)
Tri-n-butyl phosphate	Venoglobulin® (Alpha Therapeutic)
Tricaprylin	DepoDur® (SkyePharma)
Triolein	DepoCyt® (Chiron)
von Willebrand factor	Bioclote® (Arco)
Zinc	Lente Insulin® (Novo Nordisk)
Zinc acetate	Nutropin Depot® (Genentech)
Zinc carbonate	Nutropin Depot® (Genentech)
Zinc oxide	Humalog® (Lilly)

phosphate (Merck) are available as a suspension or as a solution. These dexamethasone formulations contain creatine or creatinine as additives.

- Adriamycin RDF® (doxorubicin hydrochloride, Pharmacia-Upjohn) contains methyl paraben, 0.2 mg/mL to increase dissolution (62).
- Ergotrate maleate (ergonovine maleate, Lilly) contains 0.1% ethyl lactate as a solubilizing agent.
- Estradurin Injection® (polyestradiol phosphate, Wyeth-Ayerst Labs) uses Niacinamide (12.5 mg/mL) as a solubilizing agent. Hydeltasol® also contains niacinamide. The concept of hydrotropic agents to increase water solubility has been tried on several compounds, including proteins (63, 64).
- Aluminum, in the form of aluminum hydroxide, aluminum phosphate, or aluminum potassium sulfate, is used as adjuvant in vaccine formulations to elicit an increased immunogenic response.
- Lupron Depot Injection® is lyophilized microspheres of gelatin and glycolic-lactic acid for intra-muscular injection. Nutropin Depot consists of polylactate-glycolate microspheres.
- Sodium caprylate (sodium octoate) has antifungal properties, but is also used to improve stability of albumin solution against the effects of heat. Albumin solution can be heat-pasteurized by heating at 60 °C for 10 h in the presence of sodium caprylate. Acetyl tryptophanate sodium is also added to albumin formulations.
- Meglumine (N-methylglucamine) is used to form in-situ salt. For example, diatrizoic acid, an X-ray contrast agent, is more stable when autoclaved as meglumine salt than as sodium salt (65). Meglumine is also added to Magnevist®, a magnetic resonance contrast agent.
- Tri-n-butyl phosphate is present as an excipient in human immune globulin solution (Venoglobulin®). Its exact function in the for-

mulation is not known, but it may serve as a scavenging agent.

13. von Willebrand factor is used to stabilize recombinant antihemophilic factor (Bioclone®).
14. Maltose serves as a tonicity adjuster and stabilizer in immune globulin formulation (Gamimune N®).
15. Epsilon amino caproic acid (6-amino hexanoic acid) is used as a stabilizer in anistreplase (Emi-nase Injection®).
16. Zinc and protamine have been added to insulin to form complexes and control the duration of action.

The FDA has published the “Inactive Ingredient Guide,” which lists excipients in alphabetical order (20). The Inactive Ingredient Guide is reasonably comprehensive but does not include several excipients used in recently approved drug products. Each ingredient is followed by the route of administration, and in some cases, the concentration range used in the approved drug product. This list does not provide the commercial product name(s) corresponding to each excipient. Table X is a summary of all parenteral excipients included in the “Inactive Ingredient Guide.” A majority of these parenteral excipients are covered in our survey (as highlighted in the table). There are excipients, particularly those in radio-labeled products, that are not included and some on the list have questionable function as excipients (e.g., insulin, denatured alcohol). Overall, there is a 70% overlap between our survey and the FDA inactive ingredient list for parenterals.

Similarly, in Japan the Japanese Pharmaceutical Excipients Directory (JPED) is published by the Japanese Pharmaceutical Excipients Council with the cooperation and guidance of the Ministry of Health, Labour and Welfare (66). This directory divides excipients into

1. Official Excipients: These include excipients that have been recognized in the JP, Japanese Pharmaceutical Codex (JPC), and Japanese Pharmaceutical Excipients (JPE), and for which testing methods and standards have been determined. Table XI summarizes official excipients that have been used in parenteral products and are described in JPE.

2. Non-Official Excipients: These excipients are not listed in JP, JPC, or JPE but still have precedence of use in pharmaceutical products. The non-official excipients, which have been used in parenteral products, are listed in Table XII.

The JPED lists the excipient, route of administration, and maximum amount or concentration that has been approved. If the excipient falls within these limits it is considered to be “precedented” and no additional data is needed. If it falls outside this range, additional safety information is needed (experimental or published literature). These unprecedented or novel excipients may have to be placed on stability. If the excipient is listed in JP, JPE, or JPC then it must meet the specifications listed in the monograph. If the excipient is not listed in any of the above three books, then in-house specifications must be established. In-house specifications can be based on USP, Ph. Eur., or other pharmacopoeial standards if the excipient is listed there. Proposed in-house specifications are included in the drug product submission where the excipient is reviewed by the Pharmaceuticals and Medical Devices Agency.

III. Regulatory Perspective

Based on available safety testing information, the International Pharmaceutical Excipients Council (IPEC) has classified excipients into four classes (67):

1. New chemical excipients: These excipients require a full safety evaluation program. It is estimated that the cost of safety studies for a new chemical excipient is about \$35 million over 4–5 years. E.U. directive 75/318/EEC states that new chemical excipients will be treated in the same way as new actives. In the U.S. a new excipient requires a Drug Master File (DMF) to be filed with the FDA. Similarly, in Europe a dossier needs to be established. Both the DMF and dossier contain relevant safety information. IPEC Europe has issued a guideline (Compilation of Excipient Master Files Guidelines) providing guidance to excipient producers on constructing a dossier to support MAA (Marketing Authorization Application) while maintaining confidentiality of the data.
2. Existing chemical excipient—first use in man: This class implies that animal safety data exists and that the excipient may have been used in some other

TABLE X
Excipients Listed in the FDA Inactive Ingredient Guide*

Excipient	Route/Dosage Form	Concentration %
1,2-dimyristoyl-sn-glycero-3-(phospho-s-(1-glycerol))	IV (infusion); suspension, injection	0.15
1,2-Dioleoyl-sn-glycero-3-phosphocholine	Epidural; injection, suspension, liposomal	0.42
1,2-Dipalmitoyl-sn-glycero-3-(phospho-rac-(1-glycerol))	Epidural; injection, suspension, liposomal	0.09
1,2-Distearoyl-sn-glycero-3-(phospho-rac-(1-glycerol))	Intravenous; injection, powder, lyophilized, for liposomal suspension	8.4
1,2-Distearoyl-sn-glycero-3-phosphocholine	Intravenous; solution, liposome, injection	2.8
1-Methyl-2-pyrrolidinone	Subcutaneous; injection	25.85
Acetic acid	Intravenous; injection	12.75
Acetic anhydride	Intravenous; injection	
Acetone sodium bisulfite	AN,CNBLK intrathecal; injection	
Acetylated monoglycerides	Intravenous; injection	
Acetyltryptophan	Intravenous; injection	0.02
Activated charcoal	Intramuscular; injectable	0.3
Adipic acid	Intramuscular; injection	1
Alanine	IV (infusion); injection	77
Albumin aggregated	Intravenous; injection	0.15
Albumin colloidal	Intravenous; powder, for injection solution	0.1
Albumin human	IV (infusion); powder, for injection solution, lyophilized	80
Albumin microsphere human serum	Intravenous; injection	0.5
Alcohol	Intravenous; injection	49
Alcohol, dehydrated	IV (infusion); injection	80
Alcohol, denatured	Intravenous; injection	
Alcohol, diluted	IM–IV; injection	10
Alfadex	Intracavitary; powder, for injection solution, lyophilized	0.12
Alpha-tocopherol, DL-	Intravenous; solution, concentrate	0.07
Ammonium acetate	Intramuscular; injection	0.8
Ammonium hydroxide	Intravenous; injection	0.21
Ammonium sulfate	Intravenous; injection, suspension, liposomal	0.2
Anhydrous citric acid	Intravenous; powder, for injection solution, lyophilized	42.18
Anhydrous lactose	Intravenous; powder, for injection solution, lyophilized	28.75
Arginine	IV (infusion); injection	88
Ascorbic acid	Intravenous; injection	62.5
Aspartic acid	IV (infusion); injection	0.68
Benzalkonium chloride	Intramuscular; injection	
Benzenesulfonic acid	Intravenous; injection	
Benzenesulfonic acid	IV (infusion); injection	
Benzethonium chloride	Intravenous; powder, for injection solution	0.05

TABLE X
(continued)

Excipient	Route/Dosage Form	Concentration %
Benzoic acid	IM–IV; injection	5
Benzyl alcohol	Intramuscular; injection	10.96
Benzyl benzoate	Intramuscular; injection	46
Benzyl chloride	Intravenous; injection	1.00E-03
Bibapcitide	Intravenous; injection	0.01
Boric acid	Intravenous; solution, injection	0.31
Brocrinat	IV (infusion); injection	
Butylated hydroxyanisole	Intramuscular; injection	0.03
Butylated hydroxytoluene	Intramuscular; injection	0.03
Butylated hydroxytoluene	Intravenous; powder, for injection solution, lyophilized	1.50E-03
Butylparaben	Intramuscular; injection	
Calcium	Intramuscular; injection	1.20E-03
Calcium chloride	IM–IV; injection	4
Calcium gluceptate	Intravenous; injection	5
Calcium hydroxide	Intravenous; injection	0.37
Caldiamide sodium	Intravenous; solution, injection	1.2
Calteridol calcium	Intravenous; injection	0.02
Captisol	Intravenous; injection	67.5
Carbon dioxide	IM–IV; injection	
Carboxymethylcellulose	Intramuscular; injection	0.9
Carboxymethylcellulose sodium	Intramuscular; injection	3
Castor oil	Intramuscular; injection	
Cellulose, microcrystalline	Intravenous; injection	14.9
Chlorobutanol	IV (infusion); injection	0.6
Chlorobutanol hemihydrate	Intramuscular; injection	0.52
Chlorobutanol, anhydrous	Intramuscular; injection	0.52
Cholesterol	Intravenous; solution, liposome, injection	0.68
Citrate	Intravenous; injectable	0.72
Citric acid	Intravenous; injectable	41.36
Citric acid monohydrate	Intravenous; injection	52.5
Citric acid, hydrous	Intravenous; injection	10.5
Corn oil	Intramuscular; injection	
Cottonseed oil	Intramuscular; injection	87.46
Creatine	Intramuscular; injection	
Creatinine	IM–IV; injection	0.8
Cresol	Subcutaneous; injection	
Croscarmellose sodium	Intramuscular; injection	1
Crospovidone	Intramuscular; injection	0.02
Cysteine	Intravenous; powder, for injection solution, lyophilized	2.6
Cysteine hydrochloride	IV (infusion); injection	2
Cysteine hydrochloride, anhydrous	Intradiscal; powder, for injection solution	
Deoxycholic acid	IV (infusion); powder, for injection solution	
Dextran	Intravenous; liquid, concentrate, injection	

TABLE X
(continued)

Excipient	Route/Dosage Form	Concentration %
Dextran 40	Intravenous; powder, for injection solution, lyophilized	30
Dextrose	Intravenous; injection	30
Dextrose monohydrate	Intravenous; solution, injection	5
Dextrose solution	IV (infusion); powder, for injection solution	5
Dextrose, anhydrous	Spinal; injection	8.25
Diatrizoic acid	Intramuscular; injection	59.7
Diethanolamine	IV (infusion); injection	1.5
Dimethicone 360	Intravenous; injectable	
Dimethyl sulfoxide	IV (infusion); powder, for injection suspension, lyophilized	
Dimyristoyl lecithin	Intravenous; powder, for injection solution, lyophilized	7.05
Disodium sulfosalicylate	IV (infusion); powder, for injection solution, lyophilized	0.03
Disofenin	IV (infusion); injection	2
Docusate sodium	Intramuscular; injection	0.01
Edetate calcium disodium	Intravenous; injection	0.48
Edetate disodium	Intravenous; injection	10
Edetate disodium anhydrous	Intravenous; injection	0.02
Edetate sodium	IV (infusion); solution, injection	0.04
Edetic acid	Submucosal; solution, injection	0.05
Egg phospholipids	IV (infusion); injection	1.8
Ethanolamine hydrochloride	Intravenous; injection	0.15
Ethyl acetate	Intramuscular; injection	
Ethylenediamine	IV (infusion); injection	0.39
Exametazime	Intravenous; injection	
Fampridine	Intravenous; injection	
Ferric chloride	Intravenous; injection	6.05
Fructose	IV (infusion); powder, for injection solution, lyophilized	5
Gadolinium oxide	Intravenous; injection	
Gamma-cyclodextrin	Intravenous; injection	5
Gelatin	IM–SC; injection	16
Gentisic acid	Intravenous; injection	0.05
Gentisic acid ethanolamide	IV (infusion); injection	2
Glucaptate sodium	Intravenous; powder, for injection solution	20
Glucaptate sodium dihydrate	Intravenous; injection	7.5
Gluconolactone	IM–IV; injection	
Glucuronic acid	Intravenous; injection	
Glutathione	Intramuscular; injection, sustained action	0.5
Glycerin	Subcutaneous; injection	32.5
Glycine	IV (infusion); solution, injection	42
Glycine hydrochloride	Subcutaneous; solution, injection	0.01
Glycocholic acid	Intravenous; powder, for injection solution, lyophilized	14

TABLE X
(continued)

Excipient	Route/Dosage Form	Concentration %
Guanidine hydrochloride	Intravenous; injection	0.25
Hetastarch	Intravenous; powder, for injection solution	7.36
Histidine	IV (infusion); injection	37.2
Hyaluronate sodium	Intra-articular; injectable	2.3
Hydrochloric acid	Intravenous; powder, for injection solution, lyophilized	16
Hydrochloric acid, diluted	AN,infiltration; injection	1.36
Hydroxyethylpiperazine ethane sulfonic acid	Intravenous; injection	
Hydroxypropyl- β -cyclodextrin	IV (infusion); injection	0.4
Insulin beef	Subcutaneous; injection	0.1
Insulin pork	Subcutaneous; injection	0.1
Iodine	Intravenous; injection	
Iodoxamic acid	Intravenous; injection	31
Iofetamine hydrochloride	Intravenous; injection	
Isoleucine	IV (infusion); injection	90
Isopropyl alcohol	Intravenous; injection	
Isotonic sodium chloride solution	Intravenous; injection	0.9
Lactic acid	IV (infusion); injection	32.2
Lactic acid, DL-	IV (infusion); injection	2.82
Lactic acid, L-	Intravenous; injectable	0.4
Lactobionic acid	IV (infusion); powder, for injection solution	
Lactose	Intravenous; injection	50
Lactose monohydrate	IV (infusion); powder, for injection solution, lyophilized	90
Lactose, hydrous	Intravenous; powder, for injection solution	75
Lecithin	Intramuscular; injection	2.3
Lecithin, egg	Intravenous; injectable	1.2
Lecithin, hydrogenated soy	Intravenous; injection, powder, lyophilized, for liposomal suspension	21.3
Lecithin, soybean	Intravenous; powder, for injection solution, lyophilized	11.25
Leucine	IV (infusion); injection	52.6
Lidofenin	Intravenous; injection	
Lysine	IV (infusion); injection	61
Lysine acetate	IV (infusion); solution, injection	31
Magnesium chloride	IV (infusion); injection	10.2
Magnesium stearate	Implantation; injection	1.50E-03
Maleic acid	IV (infusion); injectable	0.01
Mannitol	IV (infusion); powder, for injection solution	75
Mebrofenin	Intravenous; injection	
Medronate disodium	Intravenous; injection	1
Medronic acid	Intravenous; injection	2.5
Meglumine	Intramuscular; injection	15.92
Metacresol	Subcutaneous; solution, injection	0.52

TABLE X
(continued)

Excipient	Route/Dosage Form	Concentration %
Metaphosphoric acid	IV (infusion); injection	0.13
Methanesulfonic acid	IV (infusion); powder, for injection solution, lyophilized	8.07
Methionine	IV (infusion); injection	49.2
Methyl boronic acid	Intravenous; injection	0.2
Methylcellulose	Intra-articular; injection	0.1
Methylene blue	Intravenous; injection	1
Methylparaben	Intravenous; injection	1.8
Myristyl-gamma-picolinium chloride	Intramuscular; injection	0.01
N-(carbamoyl-methoxy PEG-40)-1,2-distearoyl-cephalin sodium	Intravenous; injection, suspension, liposomal	0.31
N,N-dimethylacetamide	Intravenous; injection	1.8
Niacinamide	IM–IV; injection	2.5
Nioxime	Intravenous; injection	0.2
Nitric acid	IV (infusion); injection	
Nitrogen	Intravenous; injection	
Octanoic acid	Intravenous; injection	0.01
Oxidronate sodium	Intravenous; injection	0.2
Oxyquinoline	Intravenous; injection	5.00E-03
Peanut oil	Intramuscular; injection	
PEG sorbitan isostearate	Intramuscular; injection	
PEG vegetable oil	IM–SC; injection	7
Pentetate calcium trisodium	Intrathecal; injection	
Pentetate pentasodium	Intravenous; injection	0.5
Pentetic acid	Intravenous; injection	0.2
Perflutren	Intravenous; injection	
Phenol	IM–IV; injection	1
Phenol, liquefied	IM–IV; injection	0.5
Phenylalanine	IV (infusion); injection	52.6
Phenylmercuric nitrate	Intramuscular; powder, for injection solution	
Phosphatidyl glycerol, egg	Intravenous; powder, for injection solution, lyophilized	4.87
Phospholipid	IV (infusion); emulsion, injection	12
Phospholipid, egg	IV (infusion); injection	1.2
Phosphoric acid	IV (infusion); injection	11.5
Poloxamer 188	Intravenous; injection	0.6
Polyethylene glycol 200	Intramuscular; injection	30
Polyethylene glycol 300	Intravenous; injection	65
Polyethylene glycol 3350	Intra-articular; injection	3
Polyethylene glycol 400	IM–IV; injection	20.3
Polyethylene glycol 4000	Intramuscular; injection	3
Polyethylene glycol 600	Intravenous; injection	5
Polyglactin	Intramuscular; injection, microspheres	56.64
Poly lactide	Intramuscular; powder, for injection suspension, lyophilized	26.48

TABLE X
(continued)

Excipient	Route/Dosage Form	Concentration %
Polyoxyethylene fatty acid esters	IM–SC; injection	7
Polyoxyl 35 castor oil	IV (infusion); injection	65
Polyoxyl 40 castor oil	IM–SC; injection	7
Polyoxyl 60 castor oil	IV (infusion); injection	20
Polypropylene glycol	IM–IV; injectable	40
Polysiloxane	Intravenous; injectable	
Polysorbate 20	IV (infusion); injection	2.4
Polysorbate 40	IM–IV; injection	
Polysorbate 80	Intramuscular; injection	12
Polyvinyl alcohol	Intramuscular; injection, microspheres	
Potassium bisulfite	Intravenous; injection	
Potassium chloride	Intravenous; solution, injection	0.38
Potassium hydroxide	Intravenous; injection	
Potassium metabisulfite	IV (infusion); solution, injection	5
Potassium phosphate, dibasic	IV (infusion); injection	55.2
Potassium phosphate, monobasic	Nerve block; injection	2.72
Povidone K17	Subcutaneous; suspension, injection	0.5
Proline	IV (infusion); injection	80
Propyl gallate	Intramuscular; injection	
Propylene glycol	IM–IV; injection	82.04
Propylparaben	IM–IV–SC; injection	20
Protamine sulfate	Intradermal; injection	0.12
Saccharin sodium	IM–IV; injection	0.09
Saccharin sodium anhydrous	IM–IV; injection	0.09
Serine	IV (infusion); injection	50
Sesame oil	Intramuscular; injection	70
Silicone	IM–IV; injection	
Simethicone	IM–IV; powder, for injection solution	
Sodium acetate	IV (infusion); injection	59.4
Sodium acetate anhydrous	IV (infusion); injection	6.25
Sodium ascorbate	Intravenous; injection	1
Sodium benzoate	IM–IV; injection	10
Sodium bicarbonate	IV (infusion); injection	83
Sodium bisulfate	IM–IV; injection	0.32
Sodium bisulfite	IV (infusion); injection	10
Sodium carbonate	IM–IV; powder, for injection solution	70.8
Sodium carbonate decahydrate	Intravenous; injection	12.42
Sodium carbonate monohydrate	Intracardiac; injection	
Sodium chlorate	IV (infusion); injection	15.4
Sodium chloride	Intravenous; injection	90
Sodium chloride injection	Intramuscular; injection	
Sodium chloride injection, bacteriostatic	Intravenous; injection	
Sodium cholesteryl sulfate	IV (infusion); powder, for injection suspension, lyophilized	5.67

TABLE X
(continued)

Excipient	Route/Dosage Form	Concentration %
Sodium citrate	IM–IV; injection	40
Sodium cysteinat hydrochloride	Intradiscal; powder, for injection solution	
Sodium desoxycholate	IV (infusion); powder, for injection solution	4.1
Sodium dithionite	Intravenous; injection	3
Sodium formaldehyde sulfoxylate	Intramuscular; injection	0.2
Sodium gluconate	Intravenous; injection	2.3
Sodium hydroxide	IV (infusion); injection	13
Sodium hypochlorite	IV (infusion); injection	1
Sodium iodide	Intravenous; powder, for injection solution	5
Sodium lactate	Intravenous; powder, for injection solution, lyophilized	1.87
Sodium lactate, L-	IM–IV–SC; injection	0.18
Sodium metabisulfite	IM–IV; injection	27.5
Sodium phosphate	IV (infusion); injection	79
Sodium phosphate dihydrate	Subcutaneous; injection	0.24
Sodium phosphate, dibasic	IM–IV; injectable	1.74
Sodium phosphate, dibasic anhydrous	IM–IV; injection	13.92
Sodium phosphate, dibasic, dihydrate	Intravenous; solution, injection	1.09
Sodium phosphate, dibasic, heptahydrate	Intravenous; injection	43
Sodium phosphate, monobasic	IM–IV; injection	1.47
Sodium phosphate, monobasic anhydrous	Subcutaneous; injection	3.31
Sodium phosphate, monobasic, dihydrate	Intravenous; injection	0.76
Sodium phosphate, monobasic, monohydrate	Intravenous; injection	6.21
Sodium pyrophosphate	Intravenous; injection	1.2
Sodium succinate	Intravenous; injection, powder, lyophilized, for liposomal suspension	2.7
Sodium sulfate	IM–IV; injection	
Sodium sulfate anhydrous	Intramuscular; injection	
Sodium sulfite	IM–IV; injection	0.2
Sodium tartrate	Intramuscular; injection	1.41
Sodium thioglycolate	Subcutaneous; injection	0.66
Sodium thiomalate	IM–IV; injection	
Sodium thiosulfate	Intravenous; solution	
Sodium thiosulfate anhydrous	Intravenous; solution	0.19
Sodium trimetaphosphate	Intravenous; powder, for injection solution	
Sorbitan monopalmitate	Intramuscular; injection	
Sorbitol	Intrasynovial; injection	45
Sorbitol solution	Intramuscular; injection	25
Soybean oil	Intravenous; injectable	10
Stannous chloride	Intravenous; injection	0.34

TABLE X
(continued)

Excipient	Route/Dosage Form	Concentration %
Stannous chloride anhydrous	Intravenous; injection	5.00E-03
Stannous fluoride	Intravenous; injection	0.07
Stannous tartrate	Intravenous; injection	8.00E-03
Starch	Intramuscular; injection	0.6
Succimer	Intravenous; injection	
Succinic acid	IM–IV; injection	
Sucrose	Intravenous; injection, powder, lyophilized, for liposomal suspension	90
Sulfobutylether β -cyclodextrin	Intramuscular; powder, for injection solution, lyophilized, with additives	44.14
Sulfur dioxide	IV (infusion); solution, injection	0.15
Sulfuric acid	IM–IV; injection	56.6
Sulfurous acid	Intramuscular; injection	
Tartaric acid	Intramuscular; injection	0.35
Tartaric acid, DL-	IM–IV; injection	
Tetrakis(1-isocyano-2-methoxy-2-methyl-propane)-copper(I) tetrafluoroborate	Intravenous; injection	0.1
Tetrofosmin	IV (infusion); powder, for injection solution, lyophilized	0.02
Theophylline	IV (infusion); injection	
Thimerosal	Subcutaneous; injection	0.01
Thioglycerol	Intramuscular; injection	1
Threonine	IV (infusion); injection	45
Tin	Intravenous; injection	8.30E-03
Tricaprylin	Epidural; injection, suspension, liposomal	0.03
Trifluoroacetic acid	IV (infusion); powder, for injection solution, lyophilized	
Triolein	Epidural; injection, suspension, liposomal	0.01
Trisodium citrate dihydrate	Intravenous; powder, for injection solution, lyophilized	23.52
Trisodium citrate, anhydrous	IM–IV; injection	16
Tromethamine	IM–IV; injection, solution	1.21
Tryptophan	IV (infusion); injection	15.2
Tyrosine	IV (infusion); injection	3.4
Urea	Intramuscular; injection	
Valine	IV (infusion); injection	84
Versetamide	Intravenous; injection	2.54
Zinc	Subcutaneous; suspension, injection	3.27
Zinc acetate	Subcutaneous; powder, for injection suspension	0.23
Zinc carbonate	Subcutaneous; powder, for injection suspension	0.16
Zinc chloride	Intradermal; injection	0.04
Zinc oxide	Subcutaneous; injection	0.01

* Highlighted rows are those excipients that were found in our survey.

IM = intramuscular.

IV = intravenous.

SC = subcutaneous.

TABLE XI
Japanese Pharmaceutical Excipients

Name	Uses	Administration Route
Aluminum chloride	Potentiating agent	IM, SC
Aluminum hydroxide	Adsorbent	IM, SC
Anhydrous sodium pyrophosphate	Dispersing agent, Isotonicity, Stabilizer	IV, IM, intraspinal
Calcium disodium edetate	Stabilizer	IV, SC, intra-arterial, intraspinal, other
Calcium D-saccharate	Stabilizer	IV
Creatinine	Buffering agent, Stabilizer	IV, IM, intracutaneous, SC, other injection
Cresol	Preservative	IV, IM, SC
L-Cystine	Stabilizer	IV
Cysteine hydrochloride	Antioxidant, Stabilizer	IM, IV
Dibasic sodium citrate	Buffering agent, Vehicle	IV
Diethanolamine	Buffer, Solubilizer, Stabilizer	IV
N, N-Dimethylacetamide	Solvent	IV
Disodium hydrogen phosphate, Anhydrous	Buffering agent, pH adjustment	IV, SC, IM, other injection
Ethyl oleate	Solvent	IM, intracutaneous
Ethylurea	Solubilizing agent	IM, IV
Ferric chloride	Stabilizer	IV
Gentisylethanolamide	Antiseptic	IV
N-hydroxyethyl lactamide solution	Solubilizing agent	IV
Inositol	Stabilizer, Vehicle	IV, IM
L-Lysine-L-glutamate	Solubilizing agent, Stabilizer	IV
Magnesium gluconate	Stabilizer	IV
Maleic acid	Buffering agent, pH adjustment, Stabilizer	IM
Maleic anhydride	Solubilizer, Stabilizer	IV
Methanesulfonic acid	pH adjustment	IM, SC
DL-Methionine	Stabilizer	IM, intra-arterial, SC, intracutaneous
Monoethanol amine	Buffer agent, pH adjustment, Solubilizer, Stabilizer	IV
Monopotassium L-glutamate monohydrate	Preservative, Stabilizer	SC
Oleic acid and purified oleic acid	Dispersing agent, Solvent	IV
Oleyl alcohol		IV
Phosphoric acid	Buffer agent, Isotonicity, pH adjustment, Solubilizing agent, Stabilizer	IV, IM, SC
Polyoxyethylene castor oil (average added molar ethylene oxide is ~35)	Dispersing agent, Emulsifying agent, Solubilizing agent, Stabilizer, Surfactant, Suspending agent, Vehicle	IV
Polyoxyethylene hydrogenated castor oil 50	Dispersing agent, Emulsifying agent, Solubilizing agent	IM, IV

TABLE XI
(continued)

Name	Uses	Administration Route
Polyoxyethylene hydrogenated castor oil 60	Dispersing agent, Emulsifying agent, Solubilizing agent	SC, IM, IV, intraspinal
Polyoxyethylene[160] polyoxypropylene [30] glycol	Dispersing agent, Emulsifying agent, Solubilizer, Stabilizer, Suspending agent, Vehicle, Surfactant, Wetting agent	IV
Polysorbate 20	Dispersing agent, Emulsifying agent, Solubilizer, Surfactant, Stabilizer, Suspending agent, Vehicle, Wetting agent	IV, SC
Potassium pyrosulfite	Stabilizer	IV
Sodium acetyl tryptophan	Stabilizer	IV, SC
Sodium caprylate	Stabilizer	IV, SC
Sodium chondroitin sulfate	Stabilizer	IV
Sodium desoxycholate	Solubilizing agent	Intracutaneous, IV, intraspinal
Sodium dihydrogen phosphate anhydrous	Buffer agent, Isotonicity, pH adjustment, Stabilizer	IV, IM, SC
Sodium dihydrogen phosphate dihydrate	Buffer agent, Isotonicity, pH adjustment, Stabilizer	IM, IV, intra-arterial, SC, intracutaneous, intraspinal, other injection
Sodium formaldehydesulfoxylate	Stabilizer	IV, IM
Sodium metasulfobenzoate	Stabilizer	IV, IM, other injection
Sodium sulfite	Antioxidant, Stabilizer	IV
Sodium thioglycolate	Antioxidant, Stabilizer	IV, IM, SC
Sodium thiomalate		IM
Stannous chloride	Reducing agent	IV
Succinic acid	Buffering agent, pH adjustment	IV
Sulfuric acid	Buffering agent, pH adjustment	IM, IV, intra-arterial
alpha-Thioglycerol	Antioxidant	IV, IM, SC
Thioglycolic acid	Solubilizing agent, Stabilizer	IV, IM, SC
Tribasic sodium phosphate	Buffering agent, pH adjustment	IV, IM, SC
Triethanolamine	Buffer, pH adjuster, Solubilizing agent, Stabilizer	IV
Purified yolk lecithin	Emulsifier	IV
Zinc acetate	Stabilizer	SC

IM = intramuscular.

IV = intravenous.

SC = subcutaneous.

application. Additional safety information may be necessary to justify use in humans.

3. Existing chemical excipient: This class designates that the excipient has been used in humans but

TABLE XII**List of Excipients in JPED 2007 and Maximum Amount Specified per Route**

Excipient	Intravenous Injection	Intramuscular Injection	Subcutaneous Injection	Other Injection Routes
2-Phenoxyethanol		2.8 mg	2.8 mg	
4-(2-Hydroxyethyl)-1-piperazine ethanesulfonic acid	6 mg			
Acacia		25 mg		
Acetic acid	20 mg	20 mg	q.s.*	
Acetyltryptophan	461 mg			
Albumin	10 mg			
alpha-Thioglycerol	25 mg	25 mg	25 mg	
Aluminium chloride		1.5 mg	1.5 mg	
Aluminum hydroxide		1 mg	1 mg	
Aluminum monostearate				20 mg
Aluminum potassium sulfate		4.4 mg	4.4 mg	
Ammonia water	q.s.			
Ammonium acetate		2.3 mg		
Anhydrous citric acid	0.2 g	10 mg		6 mg
Anhydrous ethanol	1 mL	1.6 mL	1.5 mL	
Anhydrous stannous chloride	2 mcg			
Ascorbic acid	2.8 g	1.68 g	10 mg	Local anesthetic (50 mg)
Asepsis sodium bicarbonate	80 mg			
Benzalkonium chloride		1.8 mg	1 mg	0.4 mg
Benzethonium chloride	0.02 mg	1 mg		5 mg/mL
Benzoic acid	44 mg	44 mg		
Benzyl alcohol	0.5 mL	0.5 mL	0.5 mL	Intraspinal, intracutaneous, local anesthetic
Benzyl benzoate		371 mg		
Butyl p-hydroxybenzoate				Local anesthetic (2 mg)
Butylhydroxyanisol	75 mcg			Intra-arterial
Calcium disodium edetate	30 mg		0.09 mg	Intra-arterial, intraspinal
Calcium D-saccharate	237.1 mg			
Calcium gluconate	20 mg	20 mg	20 mg	
Calcium oxide	1.08 mg			
Camellia oil		1 mL	1 mL	
Carbazochrome sodium sulfonate	0.5 mcg/kg/min			
Carmellose sodium		50 mg	15 mg	Intracutaneous
Castor oil		0.02 mL		
Chlorobutanol	600 mg	60 mg	500 mg	
Citric acid	882 mg	137.5 mg	113.4 mg	Intra-arterial
Concentrated glycerin	12.5 g	80 mg	80 mg	
Creatinine	160 mg	128 mg	20 mg	Intracutaneous

TABLE XII
(continued)

Excipient	Intravenous Injection	Intramuscular Injection	Subcutaneous Injection	Other Injection Routes
Cresol	20 mg	20 mg	158.2 mg	
Cysteine hydrochloride	16.8 mg	16.8 mg		
Dextran 40	120 mg	5.01 mg		Intra-arterial
Dextran 70			3 mg	
Dibasic potassium phosphate	11.6 mg	6.92 mg	6.92 mg	
Dibasic sodium citrate	16.8 mg			
Dibasic sodium phosphate	816 mg	480 mg	294.5 mg	Intra-arterial, intraspinal, intracutaneous, local anesthetic
Dibutylhydroxytoluene	0.09 mg	26 mcg		
Diethanolamine	12 mg			
Diethylenetriaminepentaacetic acid	8 mg			
Dilute hydrochloric acid	26.25 mL	12 mL	12 mL	Local anesthetic
Disodium edetate	16 mg			Intra-arterial
Disodium hydrogen phosphate anhydrous	875 mg	90 mg	90 mg	Intra-arterial
DL-Methionine		30 mg	1 mg	Intra-arterial, intracutaneous
D-Mannitol	3200 mg	500 mg	210 mg	Intra-arterial, intracutaneous
Dried aluminum hydroxide Gel		0.47 mg	0.47 mg	
Dried sodium carbonate	512 mg	72 mg	20 mg	
Dried sodium sulfite	1 g	0.48 g	0.48 g	Local anesthetic
D-Sorbitol	12 g	800 mg	250 mg	Other
D-Sorbitol solution		50 mg	50 mg	Other
Ethanol	800 mg	0.15 mL	2 mg	
Ethyl lactate		0.1 mg		
Ethyl oleate		Trace amount		Intracutaneous
Ethyl p-hydroxybenzoate		2.5 mg		
Ethylenediamine	30 mg		30 mg	
Ethylurea	3 mg	3 mg		
Ferric chloride	0.2 mg			
Fluorescein sodium				Other
Formalin			0.05 mg	
Fructose	900 mg			
Gelatin		0.1 mg	1 mg	Other
Gentisylethanolamide	100 mg			
Glacial acetic acid	25 mg	25 mg	37.5 mg	
Glucose	8 g	528 mg	300 mg	Intracutaneous, local anesthetic
Glycerin	60 mg	60 mg	48 mg	Other
Glycine	2250 mg	2700 mg	160 mg	Intracutaneous
Glycyl glycine	3.102 mg/kg			

TABLE XII
(continued)

Excipient	Intravenous Injection	Intramuscular Injection	Subcutaneous Injection	Other Injection Routes
Heparin sodium	2000 U			
Highly purified yolk lecithin	36 mg			
Human serum albumin	800 mg	30 mg	5 mg	Intra-arterial, intraspinal
Hydrochloric acid	0.256 mL	30 mL	30 mL	Intra-arterial, intraspinal, intracutaneous, local anesthetic
Hydrolyzed gelatin	40 mg		6.25 mg	
Hydroxypropylcellulose		25 mg		
Inositol	50 mg	60 mg		
Isotonic sodium chloride solution	q.s.	q.s.	q.s.	Intra-arterial, intracutaneous
Lactic acid	214.5 mg	36 mg	34 mg	Other
Lactic acid glycolic acid copolymer (1:1)			14.2 mg	
Lactic acid glycolic acid copolymer (95:5) (high molecular weight copolymer)			6.175 mg	
Lactic acid glycolic acid copolymer (95:5) (low molecular weight copolymer)			18.525 mg	
Lactose monohydrate	1250 mg	193.8 mg	96.9 mg	Intra-arterial, intracutaneous
Lactose, microcrystalline cellulose spheres				
L-Alanine	160 mg	40 mg		
L-Arginine	3240 mg	3240 mg	20 mg	
L-Arginine hydrochloride	120 mg	20 mg	20 mg	
L-Aspartic acid	16 mg	8 mg		
L-Cysteine	8 mg			
L-Cystine	35 mg			
L-Histidine	624 mg	1.07 mg/kg	0.012 mg/kg	
L-Histidine monohydrochloride	50 mg			
Lidocaine	40 mg	2.5 mL		
Lidocaine hydrochloride		320 mg		
L-Leucine		20 mg	20 mg	
L-Lysine hydrochloride	8 mg		0.05 mg	
L-Lysine L-glutamate	600 mg			
L-Methionine				
L-Phenylalanine	10 mg	10 mg		Intra-arterial
Macrogol 300	4875 mg/m ²			
Macrogol 35000				
Macrogol 400	3.2 g	3.2 g	3.2 g	Local anesthetic
Macrogol 4000	120 mg	180 mg	40 mg	Other

TABLE XII
(continued)

Excipient	Intravenous Injection	Intramuscular Injection	Subcutaneous Injection	Other Injection Routes
Macrogol 600	300 mg			
Magnesium chloride	213.6 mg			
Magnesium gluconate	869 mg			
Magnesium sulfate	50 mg	15 mg	1 mg	Local anesthetic
Maleic acid		2 mg		
Maleic anhydride	20 mg			
Maltose	10 g	441 mg	441 mg	Intracutaneous
m-Cresol	30 mg	6 mg	30 mg	Intracutaneous
Medium chain fatty acid triglyceride	360 mg/kg			
Meglumine	15.4 g			
Mepylcaine hydrochloride	0.04 mg	200 mg	200 mg	
Methanesulfonic acid		q.s.	q.s.	
Methyl p-hydroxybenzoate	30 mg	25 mg	25 mg	Intracutaneous, local anesthetic
Monobasic potassium phosphate	350 mg	350 mg	350 mg	Intracutaneous
Monoethanol amine	2.3 mg			
Monopotassium L-glutamate monohydrate			0.48 mg	
Monosodium L-glutamate monohydrate	600 mg	400 mg	400 mg	
Myristoyl gamma-picolinium chloride		0.6 mg		Intracutaneous
N,N-dimethylacetamide	300 mg			
N-hydroxyethyl lactamide solution	8571.4 mg			
Nicotinamide	250 mg	250 mg	75 mg	Other
Oleic acid	4.8 mg			
Peanut oil		q.s.		
Peptone, casein			0.025 g/mL	
Phenol	64 mg	64 mg	50 mg	Intracutaneous
Phenol red			0.02 mg	
Phosphoric acid	69.3 mg	69.3 mg	35 mg	
Polyoxyethylene (160) polyoxypropylene (30) glycol	10 mg	10 mg		Intracutaneous
Polyoxyethylene castor oil	4.68 g			
Polyoxyethylene hydrogenated castor oil	400 mg			
Polyoxyethylene hydrogenated castor oil 50	500 mg	500 mg	500 mg	
Polyoxyethylene hydrogenated castor oil 60	9600 mg	500 mg	500 mg	Intraspinal
Polyoxyethylene sorbitan monolaurate	80 mg	60 mg	60 mg	
Polysorbate 20	40 mg		0.1 mg	

TABLE XII
(continued)

Excipient	Intravenous Injection	Intramuscular Injection	Subcutaneous Injection	Other Injection Routes
Polysorbate 80	500 mg	100.2 mg	50 mg	Intracutaneous
Potassium chloride		0.1 mg	0.1 mg	
Potassium pyrosulfite	1250 mg	6 mg	6 mg	
Potassium sulfate				Local anesthetic
Potassium thiocyanate	5 mg			
Powdered acacia		40 mg	12.5 mg	
Procaine hydrochloride		4 mg		
Propyl p-hydroxybenzoate	4 mg	2.4 mg	4.2 mg	Intracutaneous, local anesthetic
Propylene carbonate				
Propylene glycol	3.32 g	0.5 mL	0.5 mL	Intraspinal
Protamine sulfate			3.5 mg	
Pullulan				
Purified gelatin	200 mg	640 mg	2.5 mg	Intra-arterial
Purified oleic acid	-			
Purified olive oil	200 mg			
Purified soybean lecithin	1.2 g			
Purified soybean oil	500 mg			
Purified yolk lecithin	6 g			
Sesame oil	30 mg	300 mg	300 mg	Other
Sodium acetate	111.39 mg	14 mg	15 mg	Other
Sodium acetate, anhydrous		1.64 mg		
Sodium acetyl tryptophan	536.5 mg		215 mg	
Sodium benzoate	40 mg	20 mg		Intracutaneous
Sodium bicarbonate	1.75 g	2.3g	2.3g	Intraspinal, intracutaneous
Sodium bisulfite	1250 mg	150 mg	150 mg	Intracutaneous, local anesthetic
Sodium borate				
Sodium bromide	10 mg	10 mg	10 mg	
Sodium caldiamide	240 mg			
Sodium caprylate	332.5 mg		135 mg	
Sodium carbonate	28.5 mg/kg	20.8 mg	20.8 mg	
Sodium carbonate, Anhydrous	968 mg	932 mg		Intracutaneous
Sodium chloride	9 g	700 mg	540 mg	Intra-arterial, intraspinal, intracutaneous, local anesthetic
Sodium chondroitin Sulfate	9.8 mg			
Sodium citrate	1764 mg	112 mg	100 mg	Intra-arterial, intraspinal, intracutaneous
Sodium desoxycholate	41 mg			Intraspinal, intracutaneous

TABLE XII
(continued)

Excipient	Intravenous Injection	Intramuscular Injection	Subcutaneous Injection	Other Injection Routes
Sodium dihydrogen phosphate anhydrous	80 mg	70 mg		Other
Sodium dihydrogen phosphate dihydrate	164 mg	91 mg	75 mg	Intra-arterial, intraspinal
Sodium dihydrogen phosphate dihydrate	0.0206 mg	125.5 mg	125.5 mg	Intra-arterial, intraspinal, intracutaneous
Sodium dihydrogen phosphate monohydrate	0.11 mg/kg		0.78 mg	Intracutaneous
Sodium formaldehydesulfoxylate	16 mg	16 mg		Intraspinal
Sodium gluconate	57 mg	57 mg		
Sodium hydroxide	600 mg	300 mg	230 mg	Intra-arterial, intracutaneous, local anesthetic
Sodium lactate solution	50 mg			
Sodium L-tartrate	40 mg			
Sodium metasulfobenzoate	0.2 mg	0.2 mg		Other
Sodium monohydrogen phosphate heptahydrate	4.105 mg	0.0425 mg/kg (body weight)	7.56 mg	
Sodium oleate	2.16 mg/kg			
Sodium pyrophosphate, anhydrous	32 mg	32 mg		Intraspinal
Sodium pyrosulfite	60 mg	60 mg	60 mg	Intracutaneous, local anesthetic
Sodium salicylate	600 mg	100 mg	100 mg	
Sodium sulfite	60 mg			
Sodium thioglycolate	20 mg	20 mg	20 mg	
Sodium thiomalate		2.5 mcg		
Sodium thiosulfate	3 mg	4 mg	4 mg	
Sorbitan esters of fatty acid	37.5 mg			
Sorbitan sesquioleate	50 mg	50 mg		
Soybean oil	300 mg			
Stannous chloride	400 mcg			
Succinic acid	2 mg			
Sucrose	39.84 g		25 mg	
Sulfuric acid	q.s.	87.6 mg		Intra-arterial
Tartaric acid	20 mg	8 mg		
Taurine	40 mg	40 mg		
Thimerosal	12 mg	12 mg	12 mg	
Thioglycolic acid	2.5 mg	2.5 mg	2.5 mg	
Trehalose	3.6 mg/kg			
Tribasic sodium phosphate, sodium phosphate tribasic, trisodium phosphate	32 mg	32 mg	32 mg	
Triethanolamine	30 mg			

TABLE XII
(continued)

Excipient	Intravenous Injection	Intramuscular Injection	Subcutaneous Injection	Other Injection Routes
Trometamol	266.20 mg	2.44 mg	2.4 mg	Intra-arterial, intraspinal, intracutaneous
Urea	50 mg	40 mg	50 mg	
Ursodeoxycholic acid	14 mg			
Water for injection	4000 mL	40 mL	40 mL	Intra-arterial, intraspinal, intracutaneous, local anesthetic
White soft sugar			50 mg	
Xylitol	200 mg	90 mg		Others
Zinc acetate			0.12 mg	
Zinc chloride		6.25 mg	0.42 mg	
Zinc chloride solution			0.356 mg	
Zinc oxide			0.192 mg	

* q.s. = quantity sufficient.

change in route of administration (e.g., from oral to parenteral), new dosage form, higher dose, etc. may require additional safety information.

4. New modifications or combinations of existing excipients: These excipients indicate a physical interaction, *not* a chemical reaction. No safety evaluation is necessary in this case.

Simply because an excipient is listed as GRAS (Generally Recognized As Safe), does not mean it can be used in a parenteral dosage form. The GRAS list may include materials proven safe for food (oral administration) but not deemed safe for use in an injectable product, making it difficult for a formulation development scientist to choose additives during dosage form development.

Many pharmacopeial monographs for identical excipients differ considerably regarding specifications, test criteria, and analytical methods. When a pharmaceutical manufacturer plans to supply a product throughout the world, repeat testing on the same excipient will be needed to meet USP, JP, Ph. Eur., BP, and other pharmacopoeias. There is ongoing harmonization of excipient monographs under the auspices of the Pharmacopoeial Discussion Group (PDG). The PDG has been working on several of the commonly used excipients in order to achieve a single monograph for each excipient. At present, 26 general chapters and 40 excipient mono-

graphs have been harmonized (Stage 6 of the process). For example, benzyl alcohol undergoes degradation by a free radical mechanism to form benzaldehyde and hydrogen peroxide. The degradation products are much more toxic than the parent molecule. The USP, JP and Ph. Eur. require three different chromatographic systems to test for organic impurity (mainly benzaldehyde). The harmonized monograph of benzyl alcohol has eliminated unnecessary repetition, which does not contribute to the overall quality of the product (68). The following 11 pharmacopoeial tests can be substituted by a single gas chromatography (GC) method:

Ph. Eur.	Benzaldehyde, related substance (GC)
	Halogenated compounds and halides (colorimetric test)
	Assay (hydroxyl value)
JP	Limit test for benzaldehyde
	Limit test for chlorinated compounds
	Distillation range
	Assay (hydroxyl value)
NF/USP	Benzaldehyde (high-performance liquid chromatography)
	Halogenated compounds and halides (colorimetric test)
	Organic volatile impurities (GC)
	Assay (hydroxyl value)

Regulatory bodies are focusing their attention on the manufacturing process used to produce excipients. Major initiatives by the IPEC to improve the quality of additives has resulted in a publication guide titled *Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients* (69). Excipients may be manufactured for food, cosmetic, chemical, agriculture, or pharmaceutical industry; the requirements differ for each area. This guide proposes to develop a quality system framework to be used for suppliers of excipients, one that is acceptable to the pharmaceutical industry and will harmonize the requirements in the U.S., Europe, and Japan.

The United States and Europe require all excipients to be declared, along with their quantity, on the label (what is put on the immediate container) if the product is an injectable preparation. In Japan only the excipient names are required in the labeling (information that is included with the product, such as a package insert); E.U. Article 54(c) requires that all excipients must be declared on the labeling if the medicinal product is an injectable, a topical, or an eye preparation. The European guide for the label and package leaflet also lists excipients with special issues and are addressed in an Annex (70). Table XIII is a summary of some of these ingredients commonly used as parenteral excipients and the corresponding safety information that should be included in a leaflet. A package leaflet must include a list of information on those excipients, knowledge of which is important for the safe and effective use of the medicinal product. Similarly, 21 CFR 201.22 requires prescription drugs containing sulfites to be labeled with a warning statement about possible hypersensitivity. An informational chapter in USP, (1091) Labeling of Inactive Ingredients, provides guidelines for labeling of inactive ingredients present in dosage forms.

According to the Notes for Guidance on Pharmaceutical Development (CHMP/ICH/167068/04), the choice of excipients, their grade, compatibility, concentration, and function should be described in the P2 section of the Common Technical Document. It is necessary to justify inclusion of all ingredients in the drug product and describe their intended function. A specification of $\pm 10\%$ at the end of shelf-life is acceptable except for antioxidants and preservatives where performance data from PET or stability data may justify broader limits.

Bioburden and endotoxin limits of excipients used in the manufacture of sterile medical products shall be stated. Individual testing of excipients may be omitted if bioburden and endotoxin testing of the solution is checked prior to sterilization.

If an excipient is present in Ph. Eur or other major pharmacopoeia, the monograph specifications are usually acceptable in the registration file. For excipients not described in any pharmacopoeia, specifications should include physical characterization, identification tests, purity test, assay, and impurity tests. A certification must be included to confirm that excipients are of non-animal (specifically non-ruminant) origin. If this is not the case, a regulatory agency will require documentation to demonstrate freedom from viral and transmissible spongiform encephalopathies (TSE) risks (71).

IV. Criteria for the Selection of Excipient and Supplier

During the development of parenteral dosage forms, a formulator selects excipients to provide a stable, efficacious, and functional product. The choice and the characteristics of excipients should be appropriate for the intended purpose.

“An explanation should be provided with regard to the function of all constituents in the formulation, with justification for their inclusion. In some cases, experimental data may be necessary to justify such inclusion, e.g., preservatives. The choice of the quality of the excipient should be guided by its role in the formulation and by the proposed manufacturing process. In some cases it may be necessary to address and justify the quality of certain excipients in the formulation” (72).

Normally in the U.S. a pharmaceutical development report is written and should be available at the time of a pre-approval inspection. A development report captures the choice of excipients; their purpose and level in the drug product; their compatibility with other excipients, drug, or package system; and how they may influence the stability and efficacy of the finished product.

The following key points should be considered in selecting an excipient and its supplier for parenteral products:

TABLE XIII

Excipients for Label and Corresponding Information for the Package Leaflet*

Name	Threshold Level	Information for the Package Leaflet
Arachis oil	Zero	Whenever arachis oil appears, peanut oil should appear beside it. If you are allergic to peanut or soya, do not use this medicinal product.
Benzoic acid and benzoates	Zero	It may increase the risk of jaundice in newborn babies.
Benzyl alcohol	Exposures less than 90 mg/kg/day	Must not be given to premature babies or neonates. May cause toxic reactions and allergic reactions in infants and children up to 3 years old.
	90 mg/kg/day	Must not be given to premature babies or neonates. Due to the risk of fatal toxic reactions arising from exposure to benzyl alcohol in excess of 90 mg/kg/day, this product should not be used in infants and children up to 3 years old.
Castor oil polyoxyl and castor oil polyoxyl hydrogenated	Zero	May cause severe allergic reactions.
Chlorocresol	Zero	May cause allergic reactions.
Ethanol	Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per <dose>.
	100 mg to 3 g per dose	This medicinal product contains . . . vol % ethanol (alcohol), i.e., up to . . . mg per dose, equivalent to . . . mL beer, . . . mL wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children, and high-risk groups such as patients with liver disease or epilepsy.
	3 g per dose	This medicinal product contains . . . vol % ethanol (alcohol), i.e., up to . . . mg per dose, equivalent to . . . mL beer, . . . mL wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children, and high-risk groups such as patients with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines. The amount of alcohol in this medicinal product may impair your ability to drive or use machines.
Fructose	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
	5 g	Contains x g fructose per dose. This should be taken into account in patients with diabetes mellitus.

TABLE XIII
(continued)

Name	Threshold Level	Information for the Package Leaflet
Galactose	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. SPC proposal: Patients with rare hereditary problems of galactose intolerance (e.g., galactosaemia) should not take this medicine.
	5 g	Contains x g galactose per dose. This should be taken into account in patients with diabetes mellitus.
Glucose	5 g	Contains x g glucose per dose. This should be taken into account in patients with diabetes mellitus.
Heparin (as an excipient)	Zero	May cause allergic reactions and reduced blood cell counts, which may affect the blood clotting system. Patients with a history of heparin-induced allergic reactions should avoid the use of heparin-containing medicines.
Organic mercury compounds (such as thiomersal phenylmercuric nitrate, acetate, borate)	Zero	This medicinal product contains <(e.g., thiomersal)> as a preservative and it is possible that <you/your child> may experience an allergic reaction. Tell your doctor if <you/your child> have/has any known allergies. Tell your doctor if <you/your child> have/has experienced any health problems after previous administration of a vaccine.
Parahydroxybenzoates and their esters	Zero	May cause allergic reactions (possibly delayed) and, exceptionally, bronchospasm.
Phenylalanine	Zero	This medicine contains phenylalanine. May be harmful for people with phenylketonuria.
Potassium	Less than 1 mmol per <dose>	This medicine contains potassium, less than 1 mmol (39 mg) per <dose>, i.e., essentially “potassium-free.”
	1 mmol per <dose>	This medicine contains x mmol (or y mg) potassium per <dose>. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.
	30 mmol/L	May cause pain at the site of injection.
Propylene glycol and esters	400 mg/kg adults 200 mg/kg children	May cause alcohol-like symptoms.
Sesame oil	Zero	May rarely cause severe allergic reactions.
Sodium	Less than 1 mmol per <dose>	This medicinal product contains less than 1 mmol sodium (23 mg) per <dose>, i.e., essentially “sodium-free.”
	1 mmol per <dose>	This medicinal product contains x mmol (or y mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

TABLE XIII
(continued)

Name	Threshold Level	Information for the Package Leaflet
Sorbitol	Zero	If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. SPC proposal: Patients with rare hereditary problems of fructose intolerance should not take this medicine.
Soya oil (and hydrogenated soya oil)	Zero	(Medicinal product) contains soya oil. If you are allergic to peanut or soya, do not use this medicinal product.

* Information in the table is based on “Excipients in the label and package leaflet of medicinal products for human use,” Vol. 3B, Guidelines for Medicinal Products for Human Use, Safety, Environment and Information, July 2003.

1. Influence of excipient on overall quality, stability, and effectiveness of drug product.
2. Physical, chemical, and biological compatibility of excipient with drug and packaging system (73).
3. Compatibility of excipient with manufacturing process. For example, preservatives may be adsorbed by rubber tubes or filters; acetate buffers will be lost during lyophilization process, etc.
4. Amount or percentage of excipients that can be added to drug product. Table VI summarizes the maximum amounts of preservatives and antioxidants allowed by various pharmacopoeias.
5. Route of administration. USP, Ph. Eur., and BP do not allow preservatives to be present in injections intended to come in contact with brain tissues or cerebrospinal fluid. Accordingly, intracisternal, epidural, and intradural injections should be preservative free. It is preferred for an intravenously administered drug product to be a solution. If the size of the particle is well controlled, and below a certain maximum size (e.g., in a fat emulsion or a colloidal albumin or amphotericin B dispersion) then the drug can be administered by intravenous route.
6. Dose volume. All large volume parenterals (LVPs) and those small volume parenterals (SVPs) in which a single dose injection volume can be greater than 15 mL are required by Ph. Eur./BP to be preservative-free unless otherwise justified. The USP recommends that added substances are carefully chosen for use in injections that are administered in volumes exceeding 5 mL (34).
7. Whether a product is intended for single or multiple dose use. According to the USP, single dose injections should be preservative-free. The FDA's position for single dose injections, which have to be aseptically processed, is that manufacturers should not use a preservative to prevent microbial growth. European agencies have taken a less stringent stance on this subject.
8. The length or duration of time that a drug product will be used once the multi-dose injection is opened.
9. How safe is the excipient? Does it cause tissue irritation, hemolysis, or other toxic effects on cells, tissues, or organs?
10. Does the parenteral excipient contain very low levels of lead, aluminum, or other heavy metals?
11. Does a dossier or DMF exist for the excipient?
12. Has the excipient been used in humans? Has it been used via a parenteral route and in the amount and concentration that is being planned?
13. Has the drug product containing this excipient been approved throughout the world?
14. What is the cost of the excipient; is it readily available?

15. Is the excipient vendor following the GMP guide?
Is the vendor ISO 9000 certified?
16. Will the excipient supplier certify the excipient to meet USP, BP, Ph. Eur., JP and other pharmacopoeias?
17. Has the supplier been audited by the FDA or the company's audit group? How did they fare?

Impurities in excipients can have a dramatic influence on the safety, efficacy, or stability of a drug product. Monomers or metal catalysts used during a polymerization process are toxic and also destabilize a drug product if present in trace amounts. Due to safety concerns, the limit of vinyl chloride (monomer) in polyvinyl pyrrolidone is ≤ 10 ppm and for hydrazine (a side product of polymerization reaction) ≤ 1 ppm. Monomeric ethylene oxide is highly toxic and can be present in ethoxylated excipients like PEGs, ethoxylated fatty acids, etc.

The FDA has issued a guidance suggesting that animal-derived materials (e.g., egg yolk lecithin, egg phospholipid) used in drug products, originating from Belgium, France, and the Netherlands between January and June 1999 should be investigated for the presence of dioxin and polychlorinated biphenyls. Contamination of the animal-derived product was probably caused by consumption of contaminated animal feed.

Excipients manufactured by fermentation processes, such as dextrose, citric acid, mannitol, and trehalose, should be specially controlled for endotoxin levels. Mycotoxins (highly toxic metabolic products of certain fungi species) contamination of an excipient derived from natural material has not been specifically addressed by regulatory authorities. The German health authority issued a draft guideline in 1997 wherein a limit was specified for Aflatoxins M_1 , B_1 , and the sum of B_1 , B_2 , G_1 , and G_2 in the starting material for pharmaceutical products.

Heavy metal contamination of an excipient is a concern, especially for sugars, phosphate, and citrate. Several rules have been proposed or established. For example, Ph. Eur. sets a limit of ≤ 1 ppm of nickel in polyols. California Proposition 65 specifies a limit of ≤ 0.5 μg of lead per day per product (74). Similarly, the USP and FDA limit aluminum content for all LVPs used in TPN therapy to 25 μg per liter (75). Further,

it would require that the maximum level of aluminum in SVPs intended to be added to LVPs and pharmacy bulk packages, at expiration date, be stated on the immediate container label.

Physical and chemical stability of an excipient should be considered in assigning a re-evaluation date. Many drug products have a small amount of active drug and a comparatively high amount of excipients. Degradation of even a small percentage of excipient can lead to levels of impurities sufficient to react with or degrade a large percentage of active material. For example, benzyl alcohol decomposes via a free radical mechanism, in the presence of light and oxygen, to form benzaldehyde ($x\%$ of benzaldehyde is approximately equivalent to $1/3$ $x\%$ of hydrogen peroxide). Hydrogen peroxide can rapidly oxidize sulfhydryl groups of amino acids like cysteine present in peptides or proteins.

Adequate research and thought is essential in the selection of a pharmaceutical excipient supplier. It is not uncommon for a supplier to change its manufacturing process to make it more efficient (less costly). Frequently, excipients are commodity (high volume/low value) products which are used by several industries. The pharmaceutical industry is often not a major customer in terms of volume of material purchased. For example, the pharmaceutical industry uses approximately 20% of gelatin produced. Of this 20%, most is used for production of oral dosage forms. The parenteral portion is approximately 5% of the 20%. It is extremely important that a drug manufacturer has a contract with an excipient supplier, prohibiting the supplier from making any change in the process or quality of the material without informing their customer well in advance. Pharmaceutical manufacturers should investigate all alternate sources that could be used in an emergency. A change in supplier should not be made without consulting the pertinent regulatory bodies because such an event may require prior regulatory approval.

A pharmaceutical manufacturer should have an active Vendor Certification Program. It should assure that vendor is ISO 9000 certified. An audit of an excipient manufacturer is essential because the pharmaceutical manufacturer is ultimately responsible for the quality of the drug product that includes the excipient(s) as one of its components. The IPEC GMP guide may be used as an audit tool because it is written in an ISO 9000 format using identical nomenclature and para-

graph numbering. An audit ensures that quality is being built into the excipient, which may be difficult to measure later by quality control upon receiving the material. This is especially true for parenteral excipients where not only chemical but also microbiological attributes are critical. Bioburden and endotoxin limits may be required for each of the excipients and several guidelines are available to establish specifications (76, 77).

There are no legal requirements for excipient GMPs in Europe (78). A qualified person is responsible to assure that excipient quality is appropriate based on pharmacopeial specifications or a company's quality systems.

Events in Haiti highlight the importance of assuring excipient quality to the same degree that one normally does for active ingredients. From November 1995 through June 1996, acute anuric renal failure was diagnosed in 86 children. This was associated with the use of diethylene glycol contaminated glycerin used to manufacture acetaminophen syrup (79). The FDA is advising pharmaceutical companies to test for melamine down to a 2.5 ppm level in certain nitrogen-rich drug ingredients (raw materials that contain more than 2.5% nitrogen and those for which purity or strength is determined on the basis of nitrogen content) (80). The list of excipients includes albumin, amino acids derived from casein protein hydrolysates, ammonium salts, protamine sulfate, povidone, lactose, gelatin, etc. This guidance is in response to the incidents of pet food and Chinese milk doped with melamine.

The FDA recognizes the importance of excipients in a drug product for performance and safety. An injectable generic product should have identical non-exceptional excipients (qualitatively and quantitatively) as that of reference listed drug if the generic drug product is to follow the simplest path of registration; otherwise additional data must be submitted to demonstrate that the differences do not affect safety or performance (81). For parenteral products, non-exceptional excipients are ingredients other than preservatives, pH adjuster, antioxidant, and buffers.

V. Safety Issues

Handbook of Excipients edited by Bernstein (82) is an excellent reference on the safety and adverse reaction to several excipients. Sensitization reactions have

been reported for parabens, thimerosal, and propyl gallate. Sorbitol, which metabolizes to fructose, can be dangerous when administered to fructose-intolerant patients. Table XIII lists safety concerns that must be included in labeling.

Progress in drug delivery systems and new proteins/peptides being developed for parenteral administration has created a need to expand the list of excipients that can be safely used. An informational chapter in the USP presents a scientifically based approach for safety assessment of new pharmaceutical excipients (83). A new or novel excipient is defined as one not previously used in a pharmaceutical preparation or not fully qualified by existing safety data with respect to the proposed level and duration of exposure or route of administration (84). Table XIV summarizes the approach in developing a new excipient. Besides the baseline toxicity data (either through literature or experimentation), if the drug (excipient) will be administered short-term (<14 days of consecutive days per treatment episode), intermediate-term (14–90 days), or long-term (>3 months) then additional safety information on the excipient is needed (84).

Currently, there are concerns regarding TSE via animal-derived excipients such as gelatin (85). TSEs are caused by prions that are extremely resistant to heat and normal sterilization processes. TSEs have a very long incubation time with no cure and include diseases such as

- Scrapies in sheep and goat
- Bovine spongiform encephalopathy (BSE), otherwise known as Mad Cow Disease, in cattle
- Kuru disease in humans
- Creutzfeldt-Jacob disease in humans, which has been attributed to repeated parenteral administration of growth hormone and gonadotropin derived from human pituitary glands

Several guidelines have been issued that address the issue of animal-derived excipients and scientific principles to minimize the possible transmission of TSE via medicinal products (86, 87). The current situation indicates that there are negligible concerns for lactose, glycerol, fatty acids and their esters, but the situation is less clear for gelatin. Gelatin is still a necessary ingredient for some medicinal products and EMA (Eu-

TABLE XIV
Summary of Safety Evaluation of a New Excipient Used in Injection

Tests	Injectable Route*
Baseline toxicity data	
Acute oral toxicity	Required
Acute dermal toxicity	Required
Acute inhalation toxicity	Conditional
Eye irritation	Required
Skin irritation	Required
Skin sensitization	Required
Acute injectable toxicity	Required
Application site evaluation	Required
Phototoxicity/photoallergy	Required
Genotoxicity assays	Required
ADME/PK-intended route	Required
28 day toxicity (2 species) intended route	Required
Additional data: Short- or intermediate-term repeated use	
90 day toxicity (most appropriate species)	Required
Embryo-fetal toxicology	Required
Additional assays	Conditional
Genotoxicity assays	Required
Immunosuppression assays	Required
Additional data: Intermittent long-term or chronic use	
Chronic toxicity (rodent, nonrodent)	Conditional
Reproductive toxicity	Required
Photocarcinogenicity	Conditional
Carcinogenicity	Conditional

* The term *injectable* includes routes such as IV, IM, SC, intrathecal, etc.

European Medicine Agency, formerly known as EMEA) has updated its guidance to allow gelatin from Category I and II countries if gelatin is produced by the acid process and Category I, II, and III countries if produced by the alkali process (88). Additional information on risk assessment of ruminant materials originating from USA, Canada, and other countries can be found in the references (87, 89, 90).

In the current regulatory environment, if given a choice, it is beneficial to select non-animal-derived excipient. Concerns about bovine serum albumin or human serum albumin (HSA) because of possible derivation from virus-contaminated blood remain. Recombinant human erythropoietin and darbepoetin alfa formulations were changed to replace albumin with polysorbate 80. Presently, recombinant HSA is available from several companies; this reduces probability of TSE (91). The risk of TSE from excipients can be

greatly reduced by controlling the following parameters:

- Sourcing of animal from countries where BSE has not been reported.
- Using young animals
- Category III or IV animal tissue used in manufacture (86)
- Production process which is likely to destroy TSE agents

European Commission directive EMEA/410/01/rev 2 requires manufacturers to provide a "Certificate of Suitability" or the underlying "scientific information" to attest that their pharmaceuticals are free of TSEs.

Vegetable origin polysorbate should be used. If older products contain animal-sourced polysorbate then a switch should be made. EMA has stated that a change of a polysorbate 80 source will not result in re-performing viral inactivation studies (92). The vegetable source (e.g., trehalose from corn or tapioca) must be known as well as if any processing aids (e.g., enzymes during production of lactose) used during manufacturing of the excipient are derived from an animal source.

VI. Future Directions

Several new excipients, such as cyclodextrins, are being evaluated to improve solubility or stability of parenteral drugs. Currently, there are two FDA-approved parenteral products that utilize alpha and gamma cyclodextrins. Beta-cyclodextrin is unsuitable for parenteral administration because it causes necrosis of the proximal kidney tubules upon intravenous and subcutaneous administration (93). Hydroxypropyl beta-cyclodextrin (HP β CD) and sulfobutylether β -cyclodextrin (SBE-7- β -CD) have shown the most promise. Captisol™, the trade name of SBE-7- β -CD, is anionic. Currently, three Captisol™-based drug formulations have been approved in the U.S. One parenteral formulation is in Phase II/III clinical trials that utilize HP β CD (Cavitron®), and another (Sporanox) has been approved by the FDA. Manufacturers of HP β CD and SBE-7- β -CD have established a DMF with the FDA. Detailed reviews of cyclodextrins have been recently published (94, 95). One caution in using cyclodextrin is that they can (in rare cases) accelerate drug product degradation (96) and can sequester preservatives, rendering them ineffective (97).

Chitosan, β -1,4-linked glucosamine, a naturally occurring, biodegradable, nontoxic polycationic biopolymer, is being investigated for its potential as a cross-linked microsphere matrix to deliver antineoplastic drugs. Because of its charge, it can trap several drugs and can bind strongly with cancer cells, minimizing drug toxicity and enhancing therapeutic efficacy (98). Chitosan has also been shown to stabilize liposomes.

Biodegradable polymeric materials (polylactic acid, polyglycolic acid, and other poly-alpha-hydroxy acids) have been used as medical devices and as biodegradable sutures since the 1960s (99). Currently, the FDA has approved for marketing only devices made from homopolymers or co-polymers of glycolide, lactide, caprolactone, p-dioxanone, and trimethyl-

ene carbonate (100). Such bio-polymers are finding increased application as a matrix to deliver parenteral drugs for prolonged delivery (101). At least four drug products—Lupron Depot®, Decapeptyl®, Nutropin Depot®, and Zoladex®—have been approved. All four drug products are microspheres in Polyglycolic acid (PGA), Polylactic acid (PLA), or Poly(lactic-glycolic acid (PLGA) matrix. PGA is highly crystalline (approximately 50%) with a high melting point (220–225 °C). PLA can be produced by polymerization of L-lactic acid (LPLA), D-lactic acid (DPLA), or a blend of D&L-lactic acid (DL-PLA). LPLA is 37% crystalline while DLPLA is amorphous. The degradation time of LPLA is much slower than that of DPLA. By copolymerizing lactic and glycolic acid polymeric matrices, a wide range of properties (tensile strength, crystallinity, and degradation rate) can be obtained. Decapeptyl®, a microsphere for intramuscular administration, is approved in France. It contains drug in a matrix of PLGA and Carboxymethyl cellulose with mannitol and polysorbate 80.

Polyanhydrides degrade primarily by surface erosion and possess excellent in vivo compatibility. In 1996 the FDA approved a polyanhydride-based drug implantable delivery system to the brain for the chemotherapeutic agent 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU).

Several phospholipid-based excipients are finding increased application as solubilizing agents, emulsifying agents, or as components of liposomal formulations. The phospholipids occur naturally and are biocompatible and biodegradable, for example, egg phosphatidylcholine, soybean phosphatidylcholine, hydrogenated soybean phosphatidylcholine (HSPC), dimyristoyl phosphatidylcholine (DMPC), distearoyl phosphatidylcholine (DSPC), 1,2 dioleoyl-sn-glycero-3-phosphocholine (DOPC), distearoyl phosphoethanolamine (DSPE), L-alpha-dimyristoylphosphatidylglycerol (DMPG), 1,2-dipalmitoyl-sn-glycero-3-phospho-rac-(1-glycerol) (DPPG), and distearoylphosphatidylglycerol (DSPG). Spartaject™ technology uses a mixture of phospholipids to encapsulate poorly water-soluble drug, forming a micro-suspension that can be injected intravenously. Busulfan drug product uses this technology and is currently undergoing Phase I clinical trials. Many liposomal and liposomal-like formulations (DepoFoam®) are either approved (DepoCyt®) or are undergoing clinical trials to reduce drug toxicity, improve drug stability, prolong the duration of action, or to deliver drug to the central

nervous system (102). Two amphotericin formulations, a liposomal, or lipid complex between the antifungal drug and the positively charged lipid, have been approved in the U.S. Amphotec® is a 1:1 molar ratio complex of amphotericin B and cholesteryl sulfate while Abelcet® is a 1:1 molar complex of amphotericin B with phospholipids (7 parts of L- α -dimyristoylphosphatidylcholine and L- α -dimyristoylphosphatidyl glycerol).

Poloxamer or pluronic are block copolymers comprised of polyoxyethylene and polyoxypropylene segments. They exhibit reverse thermal gelation and are being tried as solubilizing, emulsifying, and stabilizing agents. A depot drug delivery system can be created using pluronics whereby the product is a viscous injection that gels upon intramuscular injection (103). Pluronics can prevent protein aggregation or ad/absorption and help in the reconstitution of lyophilized products. Pluronic F68 (Polaxamer-188), F38 (Poloxamer-108), and F127 (Poloxamer-407) are the most commonly used pluronics. For example, a liquid formulation of human growth hormone and Factor VIII can be stabilized using pluronics. Fluosol® is a complex mixture of perfluorocarbons with a high oxygen carrying capacity emulsified with Pluronic F-68 and various lipids. It was recently approved by the FDA for adjuvant therapy to reduce myocardial ischemia during coronary angioplasty. A highly purified form of Poloxamer 188 (Flocor™), intended for intravenous administration, is undergoing Phase III clinical trials for various cardiovascular diseases. Purification of Poloxamer 188 reduces nephrotoxicity. Another non-ionic surfactant, Solutol HS 15 (Macrogol-15-Hydroxystearate), has been approved by the Health Canada in a vitamin K1 formulation for human application.

Poloxamer and other polymeric materials like albumin may coat micro- or nanoparticles, alter their surface characteristics, and reduce their phagocytosis and opsonization by reticulo-endothelial system following intravenous injection. Such surface modifications often result in prolongation in the circulation time of intravenously injected colloidal dispersions (104). Poloxamers have also been used to stabilize suspensions (105).

The first successful development of an injectable perfluorocarbons-based commercial product was achieved by the Green Cross Corporation in Japan. They made Fluosol-DA®, a dilute (20% w/v) emulsion based on

perfluorodecalin and perfluorotripropylamine emulsified with potassium oleate, Pluronic F-68, and egg yolk lecithin. These perfluorocarbons are inert and can also be used to formulate non-aqueous preparations of insoluble proteins and small molecules (106). Perfluorocarbons have been approved by the FDA in one ultrasound contrast agent, Optison®, administered via the intravenous route. Optison® is a suspension of microspheres of human serum albumin with octafluoropropane. Heat treatment and sonication of appropriately diluted human albumin, in the presence of octafluoropropane gas, is used to manufacture microspheres in Optison® injection. The protein in the microsphere shell makes up approximately 5–7% (w/w) of the total protein in the liquid. The microspheres have a mean diameter range of 2.0–4.5 μm with 93% of the microspheres being less than 10 μm .

Sucrose acetate isobutyrate (SAIB), a high viscosity liquid system, converts into free flowing liquid when mixed with 10–15% ethanol (107). Upon subcutaneous or intramuscular injection, the matrix rapidly converts to a water-insoluble semi-solid capable of delivering proteins and small molecules for a prolonged period. SAIB is biocompatible, and it biodegrades to natural metabolites.

Several other biodegradable, biocompatible, injectable polymers are being investigated for drug delivery systems. They include polyvinyl alcohol, block copolymer of PLA-PEG, polycyanoacrylate, polyanhydrides, cellulose, alginate, collagen, modified HSA, albumin, starches, dextrans, hyaluronic acid and its derivatives, and hydroxyapatite (108). Efficient parenteral delivery of genes, immunomodulators, RNAi, anti-sense, aptamers, and other novel therapeutic agents will invariably require new excipients, with several excipients in early pre-clinical or clinical use (109).

Recent concerns about swine flu and other infectious diseases have regenerated interest in new vaccines and adjuvants to improve immune response. Some of the adjuvants included in marketed vaccines in Europe but still being evaluated include AS03 and AS04 (GSK) and MF-59 (Novartis). AS04 is composed of 3-O-desacyl-4'-monophosphoryl lipid A. It is present in Cervarix, which was approved in 2010. Newer adjuvants being tested include saponin-based (QS-21, Quil A, ISCOM) or emulsion-based (SA03).

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Conflict of Interest Declaration

The authors declare that they have no competing interests.

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