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Dimethyl Sulfoxide USP, PhEur in Approved Pharmaceutical Products and Medical Devices

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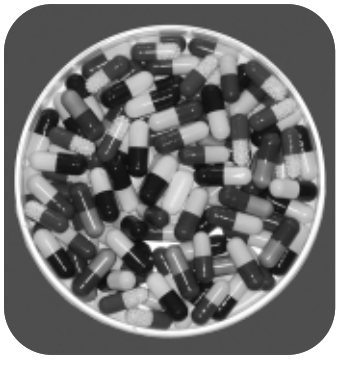

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Dimethyl sulfoxide (DMSO) is a reaction solvent useful in the synthesis of pharmaceutical compounds. Several regulated, marketed products include DMSO as a component of the finished dose. The authors survey the approved applications of dimethyl sulfoxide USP, PhEur across the healthcare industry and consider the suitability of DMSO from a regulatory and formulation compatibility standpoint.

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Dimethyl sulfoxide (DMSO) has long been recognized as an important reaction solvent for the synthesis of drug compounds and is becoming increasingly important as an excipient in finished pharmaceutical dosage forms. The powerful solvating properties of DMSO, coupled with a favorable and well-documented toxicological profile, have encouraged formulation scientists to develop applications in topical, transdermal, and other parenteral drug delivery technologies. DMSO is currently approved as an active pharmaceutical ingredient (API) and is being evaluated as an API in several orphan-status drugs worldwide.

Many pharmaceutical formulators are surprised to learn that a number of regulated products currently available include DMSO as a component of the finished dose. The commercial availability of a DMSO product (Procipient, Gaylord Chemical Co.), which is manufactured under current good manufacturing practice (CGMP) protocols to conform to *US Pharmacopeia* (USP) and *European Pharmacopeia* (PhEur) standards, has spurred this developmental activity.

Dimethyl sulfoxide USP in dosage forms and devices

Worldwide, there are a number of products that use dimethyl sulfoxide USP, PhEur. The established roles that dimethyl sulfoxide USP, PhEur currently plays in approved pharmaceutical products include:

- Stabilizing product formulations: DMSO may be present in product formulations as a cosolvent intended to keep formulation components in solution.
- The delivery of medical polymers: polymers such as polyvinyl alcohol (PVA) and poly(lactic-co-glycolic acid) (PLGA) may be dissolved in DMSO and administered in solution into the body. *In situ* precipitation of the polymer, followed by dissipation of DMSO, produces an implant than can serve various purposes. Polymer implants may function to provide structural support in the body or as bioerodible depot systems that release impregnated drug substances in a controlled fashion.
- Sustained-release applications: Dimethyl sulfoxide USP, PhEur has been a carrier solvent in subcutaneously im-

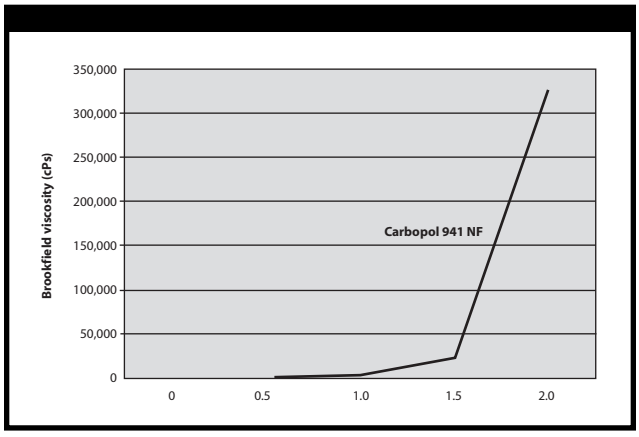

Figure 1: DMSO gel viscosity as a function of polymer loading.

planted delivery systems. Precise delivery of the therapeutic agent is controlled by osmotic technology.

- Transdermal penetration enhancement: Using DMSO in concentrations of 70% or greater has been shown to improve the penetration of agents across the skin. At present, all products approved using this DMSO functionality are approved outside of the United States.
- Cryopreservative: When water and DMSO are blended, a eutectic mixture results, which causes a significant depression of the freezing point of water. When mixed at 50% w/w, the solution remains liquid at −80 °C, preventing cellular damage when preserving cells.
- Active pharmaceutical ingredient: There is a long established application wherein DMSO has functionality as an active ingredient in the treatment of interstitial cystitis.

Marketed products containing dimethyl sulfoxide USP

The earliest accounts of DMSO use in therapeutic applications were published in the early 1960s, and great interest in this material as a pharmacologic agent occurred throughout that decade. Although investigational new drug (IND) status was granted for DMSO in 1963, concerns about its safety temporarily resulted in a FDA ban on studies using human subjects in 1965 (1, 2)

During the following 15 years, FDA relaxed its policies concerning human investigations with DMSO. This process culminated in an abandonment of its policy to regulate DMSO research in 1980 (3) and the first preparation containing DMSO was approved for marketing in the US in 1978.

Parenteral products approved in the US. The earliest product approved in the US was RIMSO-50 (recently acquired by Bioniche Pharma USA, LLC).The product is indicated for the symptomatic relief of patients with interstitial cystitis, a condition involving inflammation of the bladder wall (4). It is a sterile, nonpyrogenic aqueous DMSO formulation (50% w/w DMSO aqueous solution) supplied in 50-mL bottles. RIMSO-50 is instilled directly into a patient's bladder using an aseptic syringe or a catheter and is allowed to remain in the bladder for 15 min before discharge.

Bayer Healthcare Pharmaceuticals (Leverkusen, Germany) has released Viadur, a subcutaneously implanted device that uses DMSO as a solubilizing excipient, for the treatment of prostate cancer (5). The device is implanted in the upper arm and must be removed when a 12-month treatment course has completed. Alza's Duros technology is used to administer leuprolide acetate in a sustained fashion over 12 months. This device contains a solution of dimethyl sulfoxide USP (104 mg) and leuprolide acetate (72 mg) and represents an alternative to other implanted depot delivery systems.

With regard to injectable products, there is currently one application listed in FDA's Center for Drug Evaluation and Research (CDER) inactive ingredient database (6). The product is intended for administration by intravenous infusion. The dosage form of this product is described as "powder, for injection suspension, lyophilized." The amount of DMSO in this product is not described.

There are two device applications referenced by FDA's Center for Devices and Radiological Health (CDRH). These applications are similar in that they use DMSO as a solubilizing excipient to deliver a medical polymer (ethyl vinyl alcohol copolymer, EVOH) into the body to provide a structural benefit. The first of these device products (Onyx, EV3 Inc.) is a liquid embolic system intended for use in the brain as a treatment of brain arteriovenous malformations (7). The medical polymer is injected as a DMSO solution, containing either 6 or 8% EVOH copolymer, at a controlled rate into the bloodstream. As the DMSO dissolves in the bloodstream, a polymeric embolus forms that contains a micronized contrast agent. The other device TegressTM (C.R. Bard) serves as bulking agent in the urethra. The action is similar to the Onyx product by means of *in situ* precipitation of injected DMSO-EVOH copolymer solution in the body (8) .

One product referenced for topical application is listed in the CDER inactive ingredients database and is described as a topical dressing (6). The maximum potency of DMSO is 16.5 mg. A number of other topical or transdermal products that include DMSO are under FDA review for approval at the time of this writing.

Oral products approved in the US. No approved applications have been developed in the US that incorporate DMSO as a component of an orally administered product. DMSO is essentially nontoxic when ingested, having an oral single-dose LD-50 value of 17.4–28.3 g/kg (rat) (9). The low chronic and acute oral toxicity may offer pharmaceutical formulators a delivery option for difficult-to-dissolve medications.

Products for animal health approved in the US. Currently there are two products approved for veterinary use in the US. Domoso is indicated for use in horses for acute swelling and is prepared both as a liquid and gel formulation (10). Domoso is 90% DMSO. Synotic contains 60% DMSO and 0.01% fluocinolone acetonide and is approved for otic treatment in canines (10).

Cryopreservation. Dimethyl sulfoxide USP, Ph Eur has long been appreciated as a media for the cryopreservation of bone

marrow and blood components. DMSO is an example of a substance "that would be generally acceptable" as a cryoprotectant for use in human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined by FDA (11). HCT/Ps intended for use in human recipients are regulated by the Center for Biologics Evaluation and Research (CBER). Among the applications referenced by CBER is an HIV test kit (Nuclisense HIV-1QT) (12). Dimethyl sulfoxide USP is widely used in United States for the cryopreservation of hematopoietic stem cells supplied from umbilical cord blood at childbirth. Cord blood can be used to treat certain genetic disorders (i.e., acute lymphoblastic leukemia) that affect the blood and immune system by means of allogenetic or autologous injection.

DMSO-containing products marketed outside the US. In Europe, there are several topical products in which DMSO acts as an excipient. One of these uses an antiviral (idoxuridine) in the treatment of herpes zoster (13). A second product is approved for use in Canada and in the European Union for the topical treatment of certain types of joint pain.

In Germany, DMSO was approved on an over-the-counter basis for sports-related injuries as Dolicur (Schering AG) and provisions exist in the Russian republics that allow for DMSO self medication (14). DMSO is widely used in China for self-medicated topical pain relief.

Formulation aspects

Solubility of excipients and API compounds. Dimethyl sulfoxide USP, PhEur is chemically compatible with many pharmaceutical excipients and APIs. A database providing solubility data for more than 100 drug compounds and 30 excipients is available on-line (15), dimethyl sulfoxide USP is referenced in *The Handbook of Pharmaceutical Excipients* (16). Some basic physical properties of DMSO are listed in Table I.

DMSO is completely miscible with water, ethanol, propylene carbonate, and propylene glycol. It is practically insoluble–insoluble in many lipophilic ingredients (e.g., light mineral oil USP, soybean oil NF). Table II provides an overview of solubility data for dimethyl sulfoxide USP, with common solubilizing excipients.

It is worthwhile to note that water has a dramatic effect on the properties of dimethyl sulfoxide USP, PhEur (17). Although this may be a useful means to lower the solvent strength of DMSO in limited applications, water contamination in DMSO products may affect formulation stability in a negative sense if formulation components have a low degree of water solubility. Mixtures that are high in water content take on the general solvent properties of water. DMSO is fully hydrated at 67 wt% strength in water (10).

Viscosity and rheology modification. The viscosity of DMSO formulations may be modified using additives that work well in water. Some pharmaceutically acceptable materials that may be used for this purpose include hydroxypropyl cellulose (Klucel, Hercules Aqualon Corp.), hypromellose USP (Methocel E3 Premium LV, Dow Chemical), carbomers (Carbopol, Noveon Corp.), and methylcellulose USP. Although such materials have low solubility levels in DMSO (see Table III), very low loading levels are capable of producing high-viscosity gels.

Table I: Basic physical properties of dimethyl sulfoxide.

Property	Value
Molecular weight	78.13
Boiling point (760 mm Hg)	189 °C (372 8F)
Melting point	18.5 °C (65.3 8F)
Vapor Pressure (25 °C)	0.62 mm Hg
Flashpoint (TOC)	95 °C (203 8F)
Density, at 25°	1.0955 g/cm^3
Viscosity, cP, at 25 °C	2.0 cPs
Dielectric constant, 1 MHz, at 20 °C	48.9
pKa	35.1
Auto ignition temp, in air	300–302 °C (572–575 °F)
Conductivity (Electrical) at 20 °C	3 3 10 (ohm^{-1} cm^{-1})
Surface tension at 20 °	43.53 dynes/cm
pH (50% in water)	8.5

A standard procedure for producing a thickened solution (~10,000 cPs, depending upon the product used) from a DMSO base follows: Dimethyl sulfoxide (100 g) is combined with triethanolamine (0.5 g) and is stirred mechanically. Klucel LF (0.5 g) is sifted into the mixture slowly; hasty addition of Klucel can result in its aggregation into clumps which are difficult to disperse. It can be helpful to sift the Klucel into the mixture by passing it through a screen. The mixture is stirred at room temperature for 30 min., at which point no solids are seen to the naked eye.

For highly viscous gel products, loading levels of 1.5–2.0 wt% are required, and it may be helpful to warm the product (~50 °C) during the mixing process. Carbomer-type thickening agents (e.g., Carbopol) are especially recommended for use with DMSO for their high clarity and gel stability. Figure 1 provides viscosity data at varying loading levels for Carbopol 941.

Carbohydrates and miscellaneous excipients. Some carbohydrates are freely soluble in DMSO (e.g., β- and D-lactose, sucrose). Table IV provides solubility data for various polymeric excipient products, carbohydrates, and some miscellaneous materials.

Consideration of packaging components. DMSO interacts physically with many polymeric materials (swelling, dissolution). As such, high-density polyethylene, high-density polypropylene, and polytetrafluoroethylene are the only materials suitable for packaging a product containing high levels of DMSO. Product formulations using DMSO with other cosolvents or ingredients should perform package testing to confirm compatibility.

Product odor. Dimethyl sulfoxide, USP, PhEur is a highly

Table II: Common solubilizing excipient solubilities in dimethyl sulfoxide (solvent).*

Solubilizing excipient	Representative commercial product	Solubility**
Ethanol (absolute)		very soluble
Light mineral oil NF	Drakeol 5 (Penreco)	practically insoluble/ insoluble
Mineral oil USP	Drakeol19 (Penreco)	practically insoluble/ insoluble
Oleic acid	Oleic acid (Aldrich)	very soluble
PEG 300 NF	Carbowax Sentry 300 (Dow)	very soluble
PEG 50 Stearate	Ritox 53 (Rita)	very slightly soluble
PEG 8000 NF	Carbowax Sentry 8000 (Dow)	practically insoluble insoluble
Polyoxyl 35 castor oil NF	Cremophor EL (BASF)	very soluble
Polysorbate 80 NF	Tween 80 (Uniqema)	very soluble
Propylene glycol (USP)	Propylene Glycol (Dow)	very soluble
Sorbitan monopalmitate	Span 40 (Uniqema)	insoluble
Soybean oil NF	Super Refined Soybean Oil NF (Croda)	practically insoluble insoluble
Water		very soluble
White petrolatum USP	Super White PET USP (Penreco)	practically insoluble insoluble

*See Reference 18. Adapted from *USP* 28–*NF* 23 (2005), p. 9. All measurements were performed at. 21 °C.
**Descriptive terms refer to parts of solvent required for one part of solute: very soluble 5 <1; freely soluble 5 from 1 to 10; soluble 5 from 1 0 to 30; sparingly soluble 5 from 30 to 100; slightly soluble 5 from 100 to 1000; very slightly soluble 5 from 1000 to 10,000; practically insoluble >10,000.

pure pharmaceutical product and does not have the odor that has been associated with some industrial materials. When purified, DMSO is essentially odorless.

Regulatory affairs

Compendial status and manufacturing aspects. Three monographs exist in the 2005 *USP–NF* that reference DMSO (19). These are dimethyl sulfoxide gel, dimethyl sulfoxide irrigation, and dimethyl sulfoxide topical solution. A monograph is established in the *European Pharmacopoeia* under dimethyl sulfoxide (20).

Dimethyl sulfoxide USP, PhEur is manufactured in the US under Q7 good manufacturing guidelines established by the International Conference on Harmonization (ICH) for APIs.

Table III: Common viscosity modifying excipient solubilities in dimethyl sulfoxide.*

Viscosity modifying excipient	Representative Commercial product	Solubility**
Carrageenan NF	Gelcarin GP 911NF (FMC)	practically insoluble insoluble
Ethylcellulose NF	Ethocel Standard 4 (Dow)	sparingly soluble
Hydroxypropyl cellulose	Klucel LF (Aqualon)	sparingly soluble
Hypromellose USP	Methocel E3 Premium LV (Dow)	sparingly soluble

*See Reference 18.
**Descriptive terms refer to parts of solvent required for one part of solute: very soluble 5 <1; freely soluble 5 from 1 to 10; soluble 5 from 10 to 30; sparingly soluble 5 from 30 to 100; slightly soluble 5 from 100 to 1000; very slightly soluble 5 from 1000 to 10,000; practically insoluble >10,000.

These guidelines have been adopted by FDA. The chemistry, manufacturing, and controls (CMC) of DMSO are described in a type II drug master file on file with FDA and Health Canada. Applicants may reference the drug master file through its holder, Gaylord Chemical Co. LLC. Dimethyl sulfoxide USP, PhEur is certified kosher parve.

Dimethyl sulfoxide USP, PhEur does not hold generally regarded as safe (GRAS) status as defined in sections 201(s) and 409 of the US Federal Food, Drug, and Cosmetic Act. As such, the product is not intended for food use and is subject to premarket review in food applications. DMSO has no existing food applications.

As provided in its "Q3C Impurities: Residual Solvents" guidelines, ICH further designates DMSO a Class 3 residual solvent when used in the manufacture of pharmaceutical products. Class 3 solvents are those considered to represent a low toxic potential (21).

Historical aspects. Any discussion of DMSO in pharmaceutical applications would be incomplete without mentioning the "wonder drug" status defined for DMSO in the public and lay press in the 1960s and 1970s (22). As important, the public's fascination with—and in some cases, abuse of—DMSO has undoubtedly influenced the approval process for formulated drug products that contain it.

The emergence of DMSO as a cryopreservation agent to preserve living cells and tissue dates back to the early 1960s (24). Dr. Stanley Jacob (an assistant professor of surgery at Oregon Health & Science University) became aware of this property and approached the Crown Zellerbach Corporation. Crown Zellerbach was considering potential commercial applications for the material, which was readily available from its paper–wood products businesses. Dr. Jacob went on to describe the use of DMSO to treat a number of human ailments, including wound treatment, arthritis, and pain relief. In 1964, Crown Zellerbach received IND status for DMSO

Table IV: Miscellaneous excipient solubilities in dimethyl sulfoxide.*

Excipient	Representative commercial Product	Solubility**
Butyl and other patch adhesives	Duro-TAK (National Starch)	practically insoluble/ insoluble
Carnauba Wax	Carnauba wax, No. 1 (Aldrich)	practically insoluble/ insoluble
Cetyl Alcohol NF	Crodacol C-95 NF (Croda)	practically insoluble/ insoluble
Lactose	β- and D-Lactose	freely soluble
Lecithin	Lecithin, refined (Alfa Aesar)	practically insoluble insoluble
Poly (L-lactide)	Resomer L210 S (Boehringer Ingelheim)	practically insoluble insoluble
Poly (DL-lactide-co-glycolide)	Resomer RG502 H (Boehringer Ingelheim)	freely soluble
Polymethacrylates	Eudragit E 100 (Rohm Pharma)	practically insoluble/ insoluble
Poloxamer NF	Lutrol F127 NF (BASF)	practically insoluble/ insoluble
Polyoxyl 35 castor oil NF	Cremophor EL (BASF)	very soluble
Polysorbate 80 NF	Tween 80 (Uniqema)	very soluble
Polyvinyl Alcohol	PVA, fully hydrolyzed (JT Baker)	practically insoluble/ insoluble
Povidone USP	Kollidon 90 F and 17 PF (BASF)	freely soluble
Starch Pregelatinized NF	Starch 1500 (Colorcon)	practically insoluble/ insoluble
Stearic Acid	Stearic acid, Grade I (Aldrich)	sparingly soluble
Sucrose	Sucrose (Domino)	freely soluble

**See Reference 18. Adapted from *USP* 28–*NF* 23 (2005) p. 9. All measurements were performed at. 21 °C.

**Descriptive terms refer to parts of solvent required for one part of solute: very soluble 5 <1; freely soluble 5 from 1 to 10; soluble 5 from 10 to 30; sparingly soluble 5 from 30 to 100; slightly soluble 5 from 100 to 1000; very slightly soluble 5 from 1000 to 10,000; practically insoluble >10,000.

and granted licenses to six major pharmaceutical companies in the US to develop pharmaceutical applications for DMSO. Among these were Merck and Co., American Home products, Squibb and Sons, Schering, and the Syntex Corp. (23).

Rubin's report in 1965 that DMSO could cause lenticular changes in certain laboratory animals caused FDA to temporarily halt clinical trials involving DMSO. FDA relaxed its ban the following year but limited research to certain untreatable conditions (such as scleroderma). Continued research into any ocular effects that DMSO might have on humans suggests that such damage is species dependent and is not seen in human subjects (24–26).

A groundswell of popular interest in the medicinal properties of DMSO arose in the late 1970s, and an effort to legitimize (and legalize) the use of DMSO in medical applications was pursued. In the early 1980s, the public perception that DMSO was being unfairly persecuted by FDA was aired in the popular press. The CBS television show "60 Minutes" presented a segment favorable to this idea (27) and Senator Edward Kennedy (D-MA) chaired a Senate Subcommittee meeting to examine the treatment of DMSO by FDA (22).

During the past two decades, it would seem that many concerns surrounding the safety of DMSO have largely subsided. A DMSO product suitable for use in humans and that is manufactured according to FDA requirements is available for regulated applications, and the products described previously are being marketed worldwide.

In addition, the case for DMSO as a panacea for an array of health problems also may be eroding. Although it is likely that DMSO has functionality in many therapy types, it is clear that much fervor has resulted from subjective evaluation and anecdotal experience. Many DMSO "wonder drug" claims have been evaluated in the M.D. Anderson Cancer Center's CIMER DMSO National Standard Patient Monograph (28).

The regulatory concerns governing DMSO use in regulated applications may be similarly subsiding. It seems likely that the public's excitement over DMSO had a significant impact on the early development of regulated pharmaceutical products that would benefit from its inclusion. One author makes the interesting point that FDA most strictly regulated DMSO research at the same time as the Kefauver–Harris amendment was being drafted in the US as a response to the Kevadon/thalidomide tragedy in the mid 1960s (22).

Toxicology and health effects

The toxicology, pharmacology, and metabolic aspects of DMSO have been studied extensively (10, 29). Perhaps the most complete summary of acute/chronic toxicity data, ecotoxicity, and environmental pathway information is available as part of the high production volume (HPV) chemical filing on behalf of a Dimethyl Sulfoxide Manufacturing Consortium with the US Environmental Protection Agency (30). Based on the wealth of information available, it is a fair statement that DMSO possesses a low degree of toxicity to humans via oral and parenteral routes. DMSO is not carcinogenic and is not a reproductive toxin. It is worthwhile to point out that DMSO is used as the background solvent in biological assays of mutigenicity (Ames test). As such, it is widely recognized that DMSO is not a mutagen. Table V provides a thumbnail overview of toxicological indicators for DMSO.

Perhaps the most widely held concern around the safety of DMSO is that it "can take everything through the skin."

Table V: Toxicological overview of dimethyl sulfoxide (10).	
Oral LD-50	14500–28300 mg/kg (rat)
Dermal LD-50	40000 mg/kg (rat)
Inhalation	none at 2900 mg/m^3 (rat)
Suspect reproductive toxin?	No

Although it is true that DMSO itself can penetrate skin and does enhance the penetration rates of some chemical compounds (31), no solvent has the universal ability to fully negate the barrier properties of human skin. Indeed, it is not widely recognized that all dipolar aprotic solvents have this ability to some extent, and that N-methylpyrollidone is essentially as effective as DMSO in terms of skin penetration (32). Moreover, when water is present as a cosolvent in the formulation, the penetration kinetics of DMSO are greatly diminished. Unlike other solvents, DMSO itself is largely harmless when applied dermally; the LD-50 dermal value for DMSO is quite high (40 g/kg, rat) (9). The larger issue is its ability to facilitate dermal transport of unwanted materials into the body.

In a general sense, large molecular-weight entities (e.g., polymers, proteins) are unlikely to undergo penetration enhancement when applied in DMSO solution (32, 33). Likewise, DMSO does not uniquely accelerate the absorption of all small-molecule chemical classes (33). In many cases , some assumptions may be made to chemically analogous materials that have been tested for this effect. For situations in which safety is a concern, appropriate tests (e.g., in vitro Franz Cell evaluations, animal study) should be considered to ascertain whether DMSO plays any role in enhancing unwanted dermal penetration of formulation components.

Lastly, some have expressed concern about the garlic- or onion-like taste and odor experienced by patients who have ingested DMSO or have had DMSO applied to their skin. This side effect is attributable to a specific DMSO metabolite: dimethyl sulfide (DMS), a component of natural onion and garlic flavors. The low toxicity level of this compound is further exemplified by its inclusion in the US Food Chemical Codex, and as a synthetic flavoring substance and adjuvant (*CFR* 21 section 172.515) in the United States (12).

Conclusion

Once a medical curiosity, dimethyl sulfoxide (DMSO) is now incorporated into a number of regulated products for healthcare and drug delivery applications. Perhaps the most important features of DMSO as an excipient include its use to stabilize formulated products and its ability to solubilize many difficult-to dissolve materials.

A GMP-produced compendial product (Procipient dimethyl sulfoxide, PhEur) is now commercially available for pharmaceutical applications. This ensures that a pharmaceutically acceptable product which is suitable for use in human applications is reliably attainable.

Regardless of past history, dimethyl sulfoxide USP, PhEur is a versatile and safe material that has much to offer as an excipient product. The number of regulated pharmaceutical products and delivery systems that contain dimethyl sulfoxide USP, PhEur has increased in recent years, and it appears that the positive trends supporting this product will continue.

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