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Advances in the Regulated Pharmaceutical Use of Dimethyl Sulfoxide *USP, Ph.Eur.*

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The authors review the regulatory changes associated with the use of dimethyl sulfoxide in finished pharmaceutical dosage forms.

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Dimethyl sulfoxide (DMSO) has long been appreciated as a versatile reaction solvent for the production of active pharmaceutical ingredients. It is also established as an important material in medicinal chemistry and as a compound storage medium. The most significant use trend for DMSO in the past 10 years has, however, been its increased adoption in finished pharmaceutical dosage forms and medical devices. In these applications, DMSO is directly administered to humans and animals as a component of regulated pharmaceutical formulations.

This article updates an earlier review (1) on this subject to include developments from the years 2007–2014, and in particular, new drug formulation approvals and changes in the regulatory affairs associated with the use of Dimethyl Sulfoxide *USP, Ph.Eur.*

Approvals since 2007

Topicals. The November 2009 launch of Pennsaid (diclofenac sodium topical 1.5%) was notable in that it was the first DMSO-containing topical formulation to obtain FDA marketing approval. The product is manufactured in Canada by its originator company, Nuvo Research (formerly Dimethaid Research). The US approval followed earlier approvals in other parts of the world.

Pennsaid is a nonsteroidal anti-inflammatory formulation indicated for treatment of osteoarthritis of the knee. The active ingredient in Pennsaid is diclofenac sodium; Dimethyl Sulfoxide *USP, Ph.Eur.* is included as an excipient in the formulation at the significant concentration of 45.5% w/v. The formulation includes other inactive ingredients (alcohol, propylene glycol, type H hydroxypropyl cellulose, and water). Pennsaid is packaged as a dropping dispenser with patient instructions to apply 40 drops by hand or directly to the knee, four times per day.

In 2011, the original intellectual property protection surrounding the Pennsaid formulation expired. Generic competition to produce bioequivalent products immediately emerged. Nuvo initiated litigation against the generic

entrants based on a newly issued patent (US 8,217,078) (2). This patent discloses safe and effective methods to use the Pennsaid formulation and is among related patents listed in FDA's list of Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book) (3). A settlement agreement reached in January 2013 allowed Apotex to launch its generic version of the Pennsaid product in May of 2014, after Nuvo's commercial delivery of its next generation Pennsaid product. Verresfield (UK) Ltd. also sells a dichlofenac sodium 1.5% w/w formulation that contains DMSO; apparently this product (Inflaforte) is only marketed in Greece.

Nuvo received FDA approval for its Pennsaid 2% (diclofenac sodium topical solution) 2% w/v in 2014. Advantages for this product relative to the original include a metered dose pump bottle, simplified dosing regimen (two versus four applications per day) and increased viscosity. Pennsaid 2% is also composed of 45.5% w/v Dimethyl Sulfoxide *USP*. The company continues to innovate beyond its original DMSO-based platform. Nuvo has developed a novel DMSO foam product (Ibufoam) designed for the topical application of ibuprofen. At the time of writing, the Ibufoam product is in preclinical trials (4).

Topical 5% idoxuridine in DMSO for the treatment of Herpes Zoster has been marketed in the United Kingdom (Herpid, Astellas Pharma) and elsewhere (5). An ophthalmic idoxuridine product (Antizona) was sold by Sanofi-Aventis.

There are other topicals, which include DMSO as an excipient, that have been approved outside of the US. In eastern Europe and Russia, there is a healthy market for DMSO-based over-the-counter (OTC) topical "sports medicine" products, containing popular pain-relief ingredients (i.e., capsicum, heparin, menthol, and methyl salicylate) (5). These products include Espol (Nitzpharm), Chondroxide (Nitzpharm), Assan Rem (Permamed), Onychofissan (GlaxoSmithKline), Roll-Bene (Mepha), Venugel (Permamed, Lubapharm), and Neo-Liniment (Neomed). These products have been marketed in Europe and the former Central and Eastern European (CEE) and the Commonwealth of Independent States (CIS) countries for many years.

The Pharmacircle database (6) discloses the use of DMSO in Actikerall and Verrucare, for the treatment of actinic keratosis (grade I/II) in adult patients. These products are fluorouracil/salicyclic acid formulations and are marketed by Almirall Hermal GmbH and Laboratório Medinfar, respectively. Dendracin Neurodendracin (Physicians Science & Nature Inc.) is a DMSO-containing OTC "sports medicine" formulation sold in the US. It lists capsaicin, methyl salicylate, and menthol *USP* as active ingredients. Related products have been marketed in Europe and the former CEE countries for many years.

Parenterals. The adoption of DMSO as an ingredient in injectable drugs and medical devices is maturing. Some roles for DMSO in injectable products include as a vehicle for the delivery of medical polymers—viz. poly(lactic-co-glycolic acid) (PLGA) and polylactic acid (PLA)—and as a preservation media in stem-cell therapeutics. Prochymal (Osiris Therapeutics, Inc.) is a stem-cell suspension for IV infusion that contains 10% DMSO; the product was approved in Canada and New Zealand in 2012 (7).

Oral dosage forms. DMSO has not been formulated into approved oral delivery systems to this point. DMSO may participate as a component of an active drug substance, either as ligand in a metal complex or as a solvate molecule. There is recent evidence that the use of DMSO as a laboratory solvent for platin chemotherapy drugs is problematic, due to ligand displacement by DMSO (8). In 2013, GlaxoSmithKline received approval to market Mekinist (trametanib dimethyl sulfoxide) as a melanoma treatment. Mekinist is administered once daily and delivers 2 mg equivalent basis of the (non-solvated) active substance trametanib. As such, the concentration of DMSO in the dose is quite low. **Table I** summarizes the pharmaceutical formulations that incorporate DMSO as an active ingredient or as an excipient (9).

Updated regulatory affairs status

The Pharmacircle database shows that there have been a total of seven US drug master files (DMF) for DMSO dating back to 1964. Only one of these is still active: a type II DMF originally submitted in 1997. This DMF is maintained by Gaylord Chemical Company, which manufactures the product in compliance with International Council for Harmonization (ICH) Q7 *Good Manufacturing Practices (GMPs)*. The company uses dedicated manufacturing equipment to produce Procipient (Dimethyl Sulfoxide *USP, Ph.Eur.*) in its production facility located in Tuscaloosa, Alabama, USA. The Tuscaloosa facility went into service in late 2010 and has been inspected by FDA. No form 483s have been issued.

In March of 2014, a certificate of suitability to the European Pharmacopeia Monographs (CEP) was granted for DMSO by the European Directorate for the Quality of Medicines and Healthcare (EDQM). A CEP certificate serves several purposes. It provides a mechanism to certify the suitability of a substance's *European Pharmacopoeia (Ph. Eur.)* monograph to control its chemical and microbiological quality. It also certifies GMP compliance at relevant manufacturing and distribution facilities. A CEP monograph plays many of the same roles of the US DMF for countries of the European Union. It facilitates a relationship between regulatory authorities and industry by assessing the chemistry, manufacturing, and controls (CMC) associated with the production of an active substance or excipient. The drug application process is simplified as the CEP for an ingredient may be used in the quality section of a drug's marketing authorization application. The CEP monograph number for DMSO is 00763; Gaylord Chemical Company is the holder of the CEP certificate.

As DMSO has found use in generic-drug products and has applications as an API, it is subject to the Generic Drug User Fees Amendments of 2012 (GDUFA) in the US. GDUFA

Table I: Overview of regulated pharmaceutical product containing dimethyl sulfoxide, through January 2016 (9).

Product	Dosage type	Originator	Approval year	Marketing country	DMSO in dose
Pennsaid 2%	topical	Nuvo Research Inc.	2014	US	45.5 % w/v
Dichlofenac sodium 1.5% topical solution	topical	Apotex	2014	US	45.5 % w/v
Mekinist (trametanib dimethyl sulfoxide)	oral	GlaxoSmithKline	2013	US	< 2 mg
Prochymal	intravenous injectable	Osiris Therapeutics	2012	Canada, NZ	10%
Pennsaid 1.5%	topical	Nuvo Research Inc.	2009	US	45.5 % w/v
RIMSO-50	intravesical instillation	Research Industries	1978	US, EU	50% w/w
Onyx	intra-arterial medical device	EV3	2007	US	1.5 mL
Uryx/Tegress	implantable medical device	C.R.Bard	2004/2006	US	3 mL
Acterikall	topical	Almirall Hermal GmbH	-	EU	-
Verrucare	topical	Laboratório Medinfar	-	EU	-
Inflaforte	topical	Veresfield (UK) Ltd	-	UK, Greece	-
Dendracin Neurodendraxcin	OTC topical	Physicians Science & Nature Inc	-	US (OTC)	-
Viadur	implantable medical device	Bayer Healthcare Pharmaceuticals	2000	US	104 mg
Synotic	otic animal health	Zoetis	1972	US	60% w /v
Domoso	topical animal health	Zoetis	1970	US	90% w/v
Dolicur	topical	Schering AG	-	EU	
Dolebene	topical	Ratiopharm	-	EU	15 % w/w
Venogel	topical	Silvanols	-	EU	
Powder, for injection suspension, lyophylized	injectable	FDA Inactive Ingredient database	-	US	
Subcutaneous implant	medical device	FDA Inactive Ingredient database	-	US	-
Topical dressing	topical	FDA Inactive Ingredient database	-	US	-
Topical lotion	topical	FDA Inactive Ingredient database	-	US	45.5 % w/v
Topical solution	topical	FDA Inactive Ingredient database	-	US	45.5 % w/v
Antizona	opthalmic	Sanofi-Aventis	-		
Sinedol gel	topical	Hemopharm AD	-	EU	
Sportusal Gel/ Emgel	topical	Permamed AG	-	CH	50 mg/g
Herpid	topical	Astellas Pharma	-	UK	-
Capsicam	topical OTC	Grindex; Tallinn	-	CEE	-
Histalgan	topical OTC	Spirig Baltikum Ltd.	-	CEE	-

Similar products have been omitted from this table in the interest of brevity. These products include Inducutit (Galenpharma); Iduridine (Ferring, Geymonat); Virexen (Vinas, Ferraze Lynce, Golaz Laboratoire, Will-Pharma); Virpez (Wyeth); Virudonx (Bioglan, Derma UK); Virunguent (Hermal Kurt Herrmann, Boots); Zostrum (Galderma, Allphar Services).

Table II: Pharmaceutical regulatory affairs overview of dimethyl sulfoxide (DMSO). GDUFA is Generic Drug User Fees Amendments; REACH is Registration, Evaluation, Authorization, and Restriction of Chemicals.

Regulatory document	Organization	Year established	Note
Certificate of suitability (CEP) (EU)	Gaylord Chemical Company LLC	2014	active
GDUFA self-identified manufacturer (US)	Gaylord Chemical Company LLC	2013	active
REACH Registration (EU)	DMSO Producer's Consortium	2010	active
Listing as Natural Health Product Ingredient (Canada)	Health Canada	2011	active
Type II US drug master file (US)	Gaylord Chemical Company LLC	1997	active
United States Pharmacopeia (USP)/ National Formulary (NF) monographs	*USP/NF*	-	three
European Pharmacopoeia (Ph. Eur.) monograph	*European Pharmacopoeia*	-	
Type II US Drug Master File (US)	Showa Industry Company	1984	inactive
Type II US Drug Master File (US)	Sigma F and D Div. Ltf	1981	inactive
Type II US Drug Master File (US)	Research Industries Corp.	1975	inactive
Type II US Drug Master File (US)	Arapahoe Chem/Syntex Labs	1967	inactive
Type I US Drug Master File (US)	Crown Zellerbach	1965	inactive
Type II US Drug Master File (US)	National Institute of Health	1964	inactive

requires API (DMF Type II holders) and finished dosage form manufacturers to "self-identify" and pay an annual fee. These funds are intended to address the rising cost of generic-drug applications and reduce the backlog of applications under review. FDA publishes a complete list of GDUFA paid facilities (10).

Since the initial version of this review was published in 2008, a significant regulatory framework has been implemented in the EU: The Registration, Evaluation, Authorization, and Restriction of Chemicals legislation known commonly as REACH. As a requirement to market chemical substances in the EU, a manufacturer must assess and control risks to human health and environmental quality. Compliance with REACH is most often associated with the trade of commodity chemicals; the fee structure and regulatory requirements are tiered based on sales volume. DMSO was successfully registered under REACH by a consortium of producers (registration number 01-2119431362-50-0001). The regulated pharmaceutical DMSO product, Procipient, is not controlled under REACH.

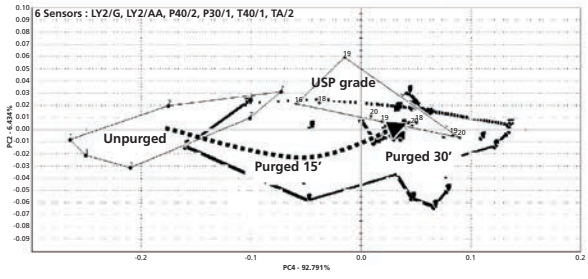
The history of abuse of DMSO in the hands of the public during the 1960s and 1970s is well documented elsewhere (11). In recent years, however, DMSO has matured as a useful and recognized excipient in regulated and some lightly controlled pharmaceutical applications. In 2011, Health Canada added DMSO to its Natural Health Products Ingredient Database (NHPID). NHPID-listed materials can be freely used in natural health products without a prescription. These are products "used in traditional medicine and in Western natural health product formulations to maintain and improve health" (12). There has been notable movement against purveyors of unregulated DMSO-based therapies by FDA in recent years; one envisions that this enforcement activity will continue. A modern review of all manner of DMSO therapies was published in 2015, coauthored by the late Dr. Stanley Jacob (13). The passing of Dr. Jacob—perhaps the earliest and most devoted champion of the pharmaceutical development of DMSO—in 2015 was a noteworthy event in the history of this unusual substance. **Table II** summarizes the various regulatory filings associated with DMSO.

Product attributes

Odor. Historically, DMSO products have suffered from malodor and color problems. Interestingly, DMSO is essentially odorless in a highly purified state. Odor and color problems are largely attributable to trace levels of thiochemical impurities, which can include dimethyl sulfide, dimethyl disulfide, and bis-(methylthio)methane. The human nose is extremely sensitive to these substances, which have odor thresholds in the single-digit, part per billion range (14).

A patented process used to manufacture Dimethyl Sulfoxide *USP, Ph.Eur.* produces a liquid that is odorless and water-white. These attributes are desirable features for topical dosage forms. Although odor is a subjective measure and the perception of odor varies between individuals, modern organoleptic analytical methods demonstrate clear differences between the odor profile of non-GMP produced DMSO products and a product suitable for use in finished dosage forms. **Figure 1** provides principal component analysis data generated by Alpha M.O.S. using their α-Fox "e-nose" instrument. Compared were a Procipient (DMSO *USP Ph.Eur.*) sample—labeled 'USP grade'—and a series

Figure 1: Odor profile comparison: industrial-grade dimethyl sulfoxide (DMSO) product samples to Dimethyl Sulfoxide *USP, Ph.Eur.* sample (manufactured by Gaylord Chemical Company) (15).



of technical grade DMSO products that had been purged for various times to remove traces of odorous impurities. The method was capable of measuring odor quality differences between the Procipient sample and the technical DMSO samples, as shown by the areas and location of the sample data on the principal components analysis (PCA) representation map. The data further support the idea that volatile, low molecular weight impurities are the principle source of malodor associated with inferior DMSO products: purge treatment caused the odor profile of the technical grade DMSO product to approach that of the Procipient sample. It is worthwhile to note that these odor differences are apparent despite the fact that the nominal purity of the technical grade DMSO samples was quite high—approximately 99.98 % by gas chromatography–flame ionization detector (GC–FID).

Sterility. As growth in injectable and other parenteral dosages develops, appropriate sterilization methods for DMSO are needed. The manufacturer of Procipient (Dimethyl Sulfoxide *USP, Ph.Eur.*) makes no claims regarding product sterility but does support the product with representative biological endotoxin testing (BET) and bioburden assay data as a courtesy. DMSO is not amenable to heat sterilization as some product decomposition occurs. Chemical sterilization using ethylene oxide (EO) and other oxidizing agents is also not practical as DMSO itself is susceptible to oxidation. Radiation sterilization methods (X-ray, E-beam, γ-ray) are not well developed for DMSO and apparently also lead to decomposition.

The preferred sterilization for DMSO method has become sterile filtration using 0.22 µ filters and, importantly, in DMSO compatible housings. A difficulty arises during the sterilization of viscous DMSO formulations, such as devices based on solutions of medical polymers. This issue may require the manufacturer to compound separately sterilized components (i.e., DMSO and polymer powder), which are aseptically filled into a sterile container. Vendors who provide filtration media that they recommend for use with DMSO include EMD Millipore and Pall. The use of DMSO as a cryoprotectant for cells and living tissue has grown steadily over time. Supplies of Dimethyl Sulfoxide *USP, Ph.Eur.* have been sterilized and repackaged into smaller volumes. Smaller packages better suit the needs of cord blood banks and researchers; such products are available from cell media companies.

Novel formulation technology

A literature search for the period from 2007 to January 2014 produced many hundreds of relevant papers. A few highlights from this search, categorized by dosage form type, are discussed in the following.

Topical products. It has been long recognized that DMSO is amenable to gel preparation using established thickening excipients, such as carbomer or methylcellulose. An exciting topical drug-delivery system capable of producing DMSO-based pharmaceutical foam formulations has been developed by Foamix Pharmaceuticals (Rehovat, Israel). Foam-based delivery systems offer advantages over semi-solids (ointments, gels, and creams), including a more appealing residual feel after product use (16).

Parenterals. Stable DMSO formulations have been developed for the parenteral injection of peptide drugs (17). Options for nonaqueous storage and delivery of hydrolytically sensitive active ingredients are a valuable aspect of such inventions.

Medical devices. Patented uses for DMSO as a safe vehicle for medical polymers have proliferated. Polymers such as ethylene-vinyl alcohol (EVOH) copolymer or PLGA form *in-situ* implant devices, which can provide structural benefits. BIOS2 Medical reported an EVOH composition that cures when applied to bone, thereby improving load-bearing capacity (18).

A polymer-drug mixture so implanted may also be designed to deliver an active ingredient in a controlled manner. A sustained-release implant that releases a breast cancer drug has been invented. The innovators describe the use of DMSO to deliver the polymer/drug formulation into the body (19).

Use as a processing aid. DMSO has been reported as a processing solvent for polymer/drug compositions applied to implantable medical devices. A recent example discloses its use as a purifying agent to remove impurities from EVOH copolymer. This purification step is intended to produce polymer suitable for use in drug-eluting stents (20).

Conclusion

Since the last published review on this subject, significant new registrations have occurred for DMSO-based pharmaceutical products. The use of DMSO as an excipient is diversifying to include examples in both topical and parenteral products. Regulatory acceptance of DMSO products manufactured under GMPs has broadened to the EU, with the establishment of a CEP in 2014. These advances, in combination with a growing appreciation of the performance properties of DMSO, suggest that interest in this substance persists.

FIGURE 1 IS COURTESY OF THE AUTHORS

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