Request for exemption from Authorisation for the use of N,N-Dimethylformamide (DMF) CAS 68-12-2 as a solvent in the production of Medicinal Products

With ECHA's public consultation, the substance N,N-Dimethylformamide (DMF) is proposed in draft for "the 5th prioritization for authorisation". This solvent has an important role for the production of and as an analytical standard for medicinal products

Version 01
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General comments on the Draft proposal to include DMF in Annex XIV, including the prioritisation of the substance

Introduction:

The EU Pharmaceutical Industry's Chemical Legislative (ChemLeg) Working Group[1] (each of them are members of EFPIA) requests that the use of DMF in the manufacturing of pharmaceutical products as defined in Art. 1(2) of the Directive 2001/83/EC relating to medicinal products for human use and in the production of veterinary products as defined in Art. 1(2) Directive 2001/82/EC for medicinal products for animal use is exempted from REACH authorisation requirements. This exemption would also include all PPORD uses of DMF (up to 50ts/pa) in the production of medicinal and veterinary products.

We believe this exemption should be granted because of the following key reasons:

- Community Legislation relating to the Health, Safety and Environmental (HSE) control of DMF already exists in particular community legislation relating to Occupational Exposure Levels. ChemLeg members have DMF OEL monitoring data taken from various Active Pharmaceutical Ingredient (API) Manufacturing facilities across various Member States which can be shared with ECHA on request from ECHA;
- Community Legislation covering substitution/replacement of DMF already exists under the Industrial Emissions Directive;
- Use of DMF in pharmaceutical manufacturing is not wide dispersive
- If technically possible at all (see reasoning below), DMF can only be substituted by other Aprotic Solvents with similar health hazards;
- Substituting a solvent used in the manufacture of a commercially available Pharmaceutical Product may require additional human and animal testing (contrary to the principles of REACh);
- Substituting a solvent used in the manufacture of a commercially available Pharmaceutical Product requires the current Marketing Authorisations (granted by the European Medicines Agency (EMA)) to be amended leading to excessive costs (3M – 12M EUR per product) and time delays;

[1] Abbott/Abbvie, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, Eli Lilly, GSK, Janssen Pharmaceuticals (Companies of Johnson and Johnson), Merck, MSD, Novartis, Novonordisk, Pfizer, Roche, Sanofi, Sandoz.

- REACH article 62(5)(b)(i) suggests that an Annex XIV listed substance handled in a facility that is permitted by Directive 96/61/EC doesn't need to consider risks from Human Health or the Environment when submitting an application for an Authorisation Use of that Substance

The amount of DMF manufactured and/or imported into the EU is, according to registration data, in the range of 10,000 – 100,000 t/y. No information on exports is provided. According to registration information complemented by information from industry consultations performed in 2011 and 2012 (Annex XV report, 2012; RCOM, 2012), 50% of the total volume (5,000-50,000 t/y) is used in the production of APIs or crop protection ingredients. The majority of the uses take place at industrial settings. There is no registered use for consumer products[2].

Within the EU Pharma Industry, DMF is used at Bulk API Manufacturing Sites (there will be some use at small R&D facilities but these volumes of DMF are limited). According to the DG ENTR website, there are approx. 900 Bulk API Manufacturing sites across the EU-27[3]. In creating this consultation response, the Pharmaceutical Industry's Chemical Legislative Working Group accounted for 60 Bulk API Manufacturing sites of which 30 use DMF; extrapolating that data to the data on DG ENTRs website and we get a maximum of 450 individual Bulk Manufacturing Sites using DMF (or approx. 15 sites per Member State).

DMF is used within the ChemLeg Group of companies under highly controlled conditions in batch production processes (which typically are run a few times per year/month at most pharmaceutical plants) and is therefore not considered as wide dispersive use nor is there a continuous potential for exposure.

Benefits of Aprotic Solvents (such as DMF) in the Production of Medicinal Products

DMF is an aprotic solvent used to manufacture Active Pharmaceutical Ingredients (APIs) for pharmaceutical products which treat potentially life threatening or debilitating conditions such as, Small Cell Lung Cancer, Cervical Cancer, Herpes Simplex virus, Varicella Zoster viruse, asthma, eczema and psoriasis. DMF is also used in Pharmaceutical lab R&D and as an analytical standard for a number of medicinal products.

The powerful solvating properties of Polar Aprotic Solvents (such as DMF) facilitate organic synthesis reactions which often, cannot be achieved in less polar solvents. Polar Aprotic Solvents offer general high solubility of many APIs and intermediates which often have poor solubility in less polar solvents. This also facilitates processes that require minimal solvent quantities, compared with the much larger volumes of other solvents that may be required. Rates and selectivity of certain reactions (e.g.

[2] ECHA Draft Background Document for DMF June 2013

[3] http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/importance/facts-figures_en.htm

nucleophilic substitutions) are substantially enhanced due to the solvent polarity and other properties. Polar Aprotic Solvents such as DMF are essential for these reactions, since (a) they prevent unreacted materials from being carried forward in the process stream and (b) they minimise the formation of side products, thereby producing intermediates and APIs of the highest quality.

There are other Polar Aprotic Solvents with similar physical or chemical properties (albeit of lower polarity) that **could potentially** be used in place of DMF in some API manufacturing syntheses. The most common 'direct' alternative may be DMAC. Others include formamide, N-methylformamide, NMP, NEP and N-methylacetamide. However, these alternatives carry essentially the same health hazard as DMF. Some of these solvents are already on the REACh Candidate List or have been proposed to Annex XIV or Restriction. In addition, these solvents may have different reactivity and so the replacement of DMF with such solvents could lead to incomplete reactions and side products that impact the safety, quality and yield of the API. Moreover, this may result in additional animal and human testing and waste streams. In other cases, the properties of DMF are so unique in effecting a desired reaction reactivity, selectivity, solubility, or purification that no comparable performance with any other solvent is known or the alternative solvents pose a greater environmental, occupational health, or other concern.

Scoping work to identify alternatives to DMF in the manufacture of pharmaceutical products within the EU has been undertaken in the past with very limited success. Significant development work would be required to identify and validate viable alternatives involving major changes to the manufacturing processes and the Marketing Authorisation (see below). Given the complexity of global supply chains, the ability of the pharmaceutical industry to secure a continuous supply of medicines to the market could be at risk if DMF was not available for use.

Description of the Use of DMF in the Production of Medicinal Products

The manufacture of APIs and associated intermediates are performed in enclosed reactor trains in accordance with Good Manufacturing Practices (GMP). DMF (and other solvents) are introduced into the reactors via transfer systems designed to minimize environmental release, by trained personnel using appropriate engineering controls and/or protective equipment, and are thus contained within the process stream. Occupational exposure is also controlled through compliance with the Chemical Agents Directive (98/24/EC). Residual amounts of DMF in the eventual pharmaceutical product are safety-limited by the ICH Q3C (Guideline for Residual Solvents). So in practice, virtually all the DMF used during manufacture would be present in the waste streams (other than that lost through evaporation) which is primarily disposed of via incineration (some recycling of DMF will occur). Altogether, the risks of environmental exposure of DMF in the pharmaceutical manufacturing environment are minimized by the equipment design and operational controls.

Uses (or categories of uses) to be exempted from the authorisation requirement:

The use of DMF in the manufacturing of pharmaceutical products as defined in Art. 1(2) of the Directive 2001/83/EC relating to medicinal products for human use and in the production of veterinary products as defined in Art. 1(2) Directive 2001/82/EC for medicinal products for animal use is exempted from REACH authorisation requirements. This exemption would also include all PPORD uses of DMF (up to 50ts/pa) in the production of medicinal and veterinary products.

Rationale for the Request for an Exemption as per Art 58(2)

As we are all aware, a directive is a legal instrument provided for in the EU Treaty and to date the majority of Community HSE legislation is based on the choice of the directive as the most appropriate legal instrument. It is binding in its entirety and obliges Member States to transpose it into national law within the deadlines clearly set out in the directive. A directive enters into force once it is published in the Official Journal of the EU.

EU directives on safety and health at work have their legal foundation in Article 153 of the Treaty on the Functioning of the European Union (ex Article 137 TEC), which gives the EU the authority to adopt directives in this field. A wide variety of EU directives setting out minimum health and safety requirements for the protection of workers have since been adopted. Member States are free to adopt stricter (but not less strict) rules for the protection of workers when transposing EU directives into national law, and so legislative requirements in the field of safety and health at work can vary across EU Member States.

The decision to recommend DMF for inclusion in Annex XIV is based solely on occupational health risks (DMF is classified as toxic for reproduction category 1b). Those risks are already properly controlled (as outlined below) by the application of Directive 98/24/EC (Chemical Agents Directive), Directive 2009/161/EU (IOEL for DMF), Directive 92/85/EC (Pregnant Workers), Directive 2010/75/EU (Industrial Emissions Directive) and 2001/83/EC (Medicinal Products Directive) which impose minimum requirements that

must be transposed into national legislation by EU Member States *(quotations from legislation is given below in italics)*

98/24/EC Chemical Agents Directive (CAD)

Article 1 of Directive 98/24/EC
This Directive ..... lays down minimum requirements for the protection of workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents that are present at the workplace or as a result of any work activity involving chemical agents.

Article 6(2) of Directive 98/24/EC
Substitution shall by preference be undertaken, whereby the employer shall avoid the use of a hazardous chemical agent by replacing it with a chemical agent or process which, under its condition of use, is not hazardous or less hazardous to workers' safety and health, as the case may be. Where the nature of the activity does not permit risk to be eliminated by substitution, having regard to the activity and risk assessment referred to in Article 4, the employer shall ensure that the risk is reduced to a minimum by application of protection and prevention measures, consistent with the assessment of the risk made pursuant to Article 4. These will include, in order of priority:

- *Design of appropriate work processes and engineering controls and use of adequate equipment and materials, so as to avoid or minimise the release of hazardous chemical agents which may present a risk to workers' safety and health at the place of work;*
- *Application of collective protection measures at the source of the risk, such as adequate ventilation and appropriate organizational measures;*

Where exposure cannot be prevented by other means, application of individual protection measures including personal protective equipment.

1. We believe ECHAs previous interpretation of the minimum requirements[4] as outlined in CAD is contrary to the principles of proportionality. The legal obligation on the employer to put in place specific protection and prevention measures **is** in keeping with the principles of proportionality. A technical feasibility assessment of control measures beyond what is recommended by a chemical agents risk assessment is disproportionate. Note the clear intentions of CAD: ***"To ensure not only the protection of the health and safety of each individual worker but also to provide a level of minimum protection of all workers in the Community which avoids any possible distortion in the area of competition" (Preamble 4 of Directive 98/24/EC)***

[4] RCOM DMAC

2009/161/EU Indicative OEL Values Directive

Article 2 of Directive 2009/161/EU
Member States shall establish national occupational exposure limit values for the chemical agents listed in the Annex, taking into account the Community values.

1. 98/24/EC (CAD) requires setting of indicative occupational exposure limit values (IOELVs) in all Member States (who are obligated to do transpose this and that their national limits must, at a minimum, be as stringent as the EU levels).

   DMF is referenced in Directive 2009/161/EU, establishing a third list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC and amending Commission Directive 2000/39/EC

   The following OEL has been set for DMF within EU law: 8 hour TWA: 5 ppm (15mg/m³), STEL (15 mins): 10 ppm (30mg/m³). Austria, Belgium, France, Germany, Ireland, Italy, Netherlands and UK are, to name but a few, Member States that have transposed this OEL into their National Legislation.

   ChemLeg members across various EU Member States have actual DMF monitoring data that can be shared with ECHA to show the controls used within our manufacturing facilities enables us to comply with the DMF OEL.

2. Furthermore, *"A registrant is allowed to use an IOEL as a DNEL for the same exposure route and duration, unless new scientific information that he has obtained in fulfilling his obligations under REACH does not support the use of the IOEL for this purpose."* [5]. **According to the ECHA guidance, IOEL values are valid DNELs to be accepted for occupational uses**. If the CMR properties were considered when deriving the IOEL, there is no scientific reason for ECHA not to accept the IOEL unless new experimental data has been generated.

In Summary:
DMF is referenced in 2009/161/EU and has been given a minimum OEL. Therefore 2009/161/EU should satisfy Art 58(2) Existing Community Legislation. Not accepting this Directive as satisfying the requirements for an exemption under Article 58(2) undermines the legal authority of Directive 2009/161/EU and creates a situation of double regulation which is against the principle of the EU Commission's approach to "Smart Regulation".

ChemLeg members have data to show existing OEL for DMF is complied with at API Manufacturing facilities across various Member States.

[5] ECHA Guidance Chapter R.8: Characterization of dose [concentration]-response for human health p. 137

92/85/EC Pregnant Workers, Recently Given Birth or Breast Feeding

Article 5

- *If the results of the assessment referred to in Article 4 (1) reveal a risk to the safety or health or an effect on the pregnancy or breastfeeding of a worker within the meaning of Article 2, the employer shall take the necessary measures to ensure that, by temporarily adjusting the working conditions and/or the working hours of the worker concerned, the exposure of that worker to such risks is avoided.*
- *If the adjustment of her working conditions and/or working hours is not technically and/or objectively feasible, or cannot reasonably be required on duly substantiated grounds, the employer shall take the necessary measures to move the worker concerned to another job.*
- *If moving her to another job is not technically and/or objectively feasible or cannot reasonably be required on duly substantiated grounds, the worker concerned shall be granted leave in accordance with national legislation and/or national practice for the whole of the period necessary to protect her safety or health.*
- *The provisions of this Article shall apply mutatis mutandis to the case where a worker pursuing an activity which is forbidden pursuant to Article 6 becomes pregnant or starts breastfeeding and informs her employer thereof.*

1. Directive 92/85 provides for the necessary measures to be taken by the employer in case of risk or effect on the pregnancy or breastfeeding of a worker

In Summary:
Some active pharmaceutical ingredients by the very nature of their pharmacological action are Reprotoxins e.g. antimitotic drugs. Bulk API plants handling these substances (such as DMF) typically have reproductive hazard evaluation programmes in place covering APIs and solvents to protect the employee planning a pregnancy or recently become pregnant. Examples of risk reduction recommendations include additional PPE, delegating tasks to non-pregnant employees or banning such workers entering areas where DMF type substances are handled. Therefore 92/85/EC should satisfy Art 58(2) Existing Community Legislation

2010/75/EU Industrial Emissions Directive

IED Art 58: Substitution of Hazardous Substances
Substances or mixtures which, because of their content of volatile organic compounds classified as carcinogens, mutagens, or toxic to reproduction under Regulation (EC) No 1272/2008, are assigned or need to carry the hazard statements H340, H350, H350i, H360D or H360F, shall be replaced, as far as possible by less harmful substances or mixtures within the shortest possible time

IED Art 59(5) Control of Emissions:
The emissions of either volatile organic compounds which are assigned or need to carry the hazard statements H340, H350, H350i, H360D or H360F or halogenated volatile organic compounds which are assigned or need to carry the hazard statementsH341 or H351, shall be controlled under contained conditions as far as technically and economically feasible to safeguard public health and the environment and shall not exceed the relevant emission limit values set out in Part 4 of Annex VII[1].

1. DMF is used in Bulk Pharma manufacturing facilities to manufacture API; all Bulk Pharma API manufacturing facilities are required to have a PPC Permit (soon to be Industrial Emissions Permit under the Industrial Emissions Directive). This requirement is referenced in Annex I of the IED (section 4.5).

2. The IED (and the previous directives that have now been included within it including 2000/76/EC) requires permit holders who use H360D compounds to replace them, as far as possible, by less harmful substances within the shortest period of time. **DMF is a H360D substance**

3. The IED requires permit holders that emissions of H360D substances shall be controlled under contained conditions as far as technically and economically feasible to safeguard public health and the environment. **DMF is a H360D substance**.

4. DMF used in the API manufacturing stage is collected after use and (in the majority of cases) is incinerated (under the Waste Incineration Directive 2000/76/EC soon to be incorporated into the Industrial Emissions Directive). Where DMF is not incinerated, it is recycled.

In Summary:
All bulk API facilities using DMF must have an Industrial Permit to operate. That permit lays down minimum conditions to protect the environment as well as requiring substitution of H360D substances. The EU Commission does not need to implement further legislation to require the substitution of H360D substances (that are used in an IED permitted facility). All waste DMF is handled appropriately. Community Legislation (2010/75/EU) properly controls the emissions of DMF associated with the manufacture of APIs and the use of the API during drug manufacture. Therefore 2010/75/EU should satisfy Art 58(2) Existing Community Legislation

2010/75/EU Industrial Emissions Directive (Solvents)

IED Annex VII Technical Provisions relating to Installations and Activities using Organic Solvents Part 1(Activities): (8). Manufacturing of pharmaceutical products: The chemical synthesis, fermentation, extraction, formulation and finishing of pharmaceutical products and, where carried out at the same site, the manufacture of intermediate products

IED Annex VII Technical Provisions relating to Installations and Activities using Organic Solvents Part 2(Thresholds and Emission Limit Values): (20). Manufacturing of pharmaceutical products: >50ts/yr. of solvents; waste gases emission limit 20mg/m³; total ELV is 15% of solvent output

IED Art 59(1) Control of Emissions:
Member States shall take the necessary measures to ensure that each installation complies with either of the following: (a) the emission of volatile organic compounds from installations shall not exceed the emission limit values in waste gases and the fugitive emission limit values, or the total emission limit values, and other requirements laid down in Parts 2 and 3 of Annex VII are complied with

Existing Community Legislation (2010/75/EU) properly controls the emissions of DMF associated with the manufacture of APIs and the permitting/use/storage of the solvent during drug manufacture.

One objective of the IED is to prevent or reduce the direct and indirect effects of emissions of VOCs during the manufacture of pharmaceutical products into the

environment, mainly into air, and the potential risks to human health, by providing measures and procedures to be implemented for certain activities.

The IED already governs and manage the risks that the inclusion of Pharma uses of DMF in REACH Annex XIV seeks to manage. Article 62 (5b) of the REACH Regulation would suggest that this is also the case.

In Summary:
All bulk API facilities using >50ts/yr. of solvents (including DMF) must have an Industrial Permit to operate. That permit lays down maximum emission to air limits for solvents, therefore the IED provides minimum emission to air standards in API Bulk Manufacturing facilities using >50ts/yr. of solvents. This shows that DMF is properly controlled. Therefore 2010/75/EU should satisfy Art 58(2) Existing Community Legislation

Medicinal Products Directive: Directive 2001/83/EC & Regulation (EC) No 726/2004

1. The EU medicinal regulatory system protects public health and secures the availability of medicinal products for EU citizens by requiring all such products to have been granted a Marketing Authorisation (MA) of before they are placed on the EU market.[6] These MAs are granted only if the manufacturing process complies with the EU quality standards known as "good manufacturing practices." After a MA is issued, MA holders may not introduce any changes into the manufacturing process without the consent of the Member State competent authority.[7] Finally, once a medicinal product has been authorised and placed on the EU market, its safety is monitored throughout its entire lifespan to ensure that, in case of adverse reactions that present an unacceptable level of risk under normal conditions of use, it is rapidly withdrawn from the market.[8] This is done through the EU system of "Pharmacovigilance" set out in the Medicinal Products Directive (MPD).

2. We believe that the MPD does properly control the risks of the use of DMF within the manufacture of an API that falls within the scope of Regulation (EC) No 726/2004 and Directive 2001/83/EC, relating to medicinal products for human use. The holder of a MA of a medicinal product referred to in Article 40

[6] The rules on marketing authorization are found primarily in Directive 2001/83/EC of the European Parliament and of the Council Directive 2001/83/EC of 6 November 2001on the Community code relating to medicinal products for human use, *OJ L 311, 28.11.2001, p. 67–128* and Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, *OJ L 136, 30.4.2004,* p. 1–33 (together the "Medicinal Products Legislation").
[7] Directive 2001/83/EC, Article 23
[8] European Commission Website, DG Health & Consumers, Public health, Medicinal products for human use available at: http://ec.europa.eu/health/human-use/index_en.htm last visited on May 30, 2013

of Directive 2001/83/EC is obliged "to comply with the principles and guidelines of good manufacturing practice (GMP)" as laid down by community law. Principles and guidelines of GMP require impurity testing of pharmaceutical ingredients to ensure that specific threshold limits for residual solvents are met. All Pharmaceutical products that are impacted by such solvents have the information included in the MA which can be withdrawn if the pharmaceutical product does not meet the residual solvent specification. This concentration limit is enforced via the Member State relevant Health Regulator (e.g. MHRA in the UK). EMA guidance on residual solvents (EMA/CHMP/ICH/82260/2006) contains specific limits for DMF (PDE 8.8mg/day and 880ppm).

3. Since the residual amount of DMF in the eventual pharmaceutical product is safety-limited by the EMA (Guideline for Residual Solvents in practice virtually all the DMF used during manufacture of the API would be present in the waste streams that are then disposed of via incineration as hazardous waste (under the Waste Incineration Directive 2000/76/EC soon to be incorporated into the Industrial Emissions Directive). Where DMF is not incinerated, it would be purified and recycled into DMF that can be used again.

4. Recital 111 of REACH cautions against mixing the policy aims of REACH with the policy aims of the European Medicines Agency (EMA). The legislative history of REACH reflects the special relationship between the chemical and medicinal regulatory regimes. The Commission expressly addressed the interaction between the two regimes when it proposed REACH, indicating how it would avoid potential overlaps (thereby showing that the Commission was (i) aware of the potential overlap between REACH and the medicines legislation and (ii) it aimed to avoid such overlap):

> *"Certain uses of substances are not subject to authorisation because their human health and environmental effects are considered to be addressed by equivalent Community legislation.* ***It would be unreasonable to subject such uses to two systems with the cost and resources this would imply.*** *The Commission will propose a modification of the legislation on medicinal products for human use and veterinary use respectively to address risks related to the environment. This will be part of the benefit/risk assessment which has to be positive as a prerequisite for approval of the medicinal product". [Emphasis added]*

In Summary:
Firstly, the REACH Regulation was not meant to overlap with or impede the functioning of this Medicinal regulatory regime. Indeed, substances used in medicinal products for human and veterinary use and falling under the scope of the Medicinal Products Legislation are specifically exempted from the REACH authorisation requirements.

Secondly, in line with the text of REACH, the history of the Regulation, and the proportionality principle, we believe that ECHA should avoid any conflict with the EMA's specific authority to approve the market placement of medicinal products.

Thirdly, as the use of solvents is covered specifically under the medical products legislation with specific limits for specific substances referring to that guideline, we claim the mentioned substance to be exempted from Authorisation in the production and analytics of medicinal products (including the production of intermediates to manufacture medicinal products).

Therefore 2001/83/EC and its associated Guidance should also help satisfy our compliance with the conditions for exemption set down in Art 58(2) with regard to existing Community Legislation.

Conclusions:

- In the comments above, we have cited various EU laws which, collectively and individually, meet the conditions imposed for the exemption under Article 58.2 of REACh
- It is not the intention of REACH to impact market availability of health care products that are adequately regulated through other European directives and regulations. This is underlined, not only by REACh Articles 2(5a) and 58(2) but also in Recital 111 stating:

  It is important to avoid confusion between the mission of the Agency and the respective missions of the European Medicines Agency (EMEA) established by Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency…

- Pharmaceutical manufacturing uses of DMF meet the requirements set out in Article 58 (2) of REACH and on this basis, should be exempted from REACH Authorisation requirements;
- Our uses of DMF as an aprotic solvent are already governed by existing EU legislation setting minimum requirements for the proper control of risks to human health or the environment;
- There will be no direct or net environmental benefit by including Pharma uses of DMF in Annex XIV;

- Use of DMF in pharmaceutical manufacturing is not widely dispersive, and the scoring system applied in Annex XV would not qualify DMF as used in Pharma for prioritization
- REACH article 62(5)(b)(i) suggests that an Annex XIV listed substance handled in a facility that is permitted by Directive 96/61/EC (soon to be incorporated into 2010/75/EU IED) doesn't need to consider risks from Human Health or the Environment when submitting an application for an Authorised Use of that Substance. This therefore exempts annex XIV listed substances from Authorisation if the substance is used in an IPPC Permitted facility and no economic or technically feasible substitution substances exist

NOTE:
DMF belongs to a class of "aprotic solvents" which also includes the solvent N,N-dimethylacetamide (DMAC). It should be noted that the proposed listing of DMAC on Annex XIV is currently subject to discussions between representatives of the pharmaceutical industry and the authorities, both on CA level in the Member States and on EC level. The arguments provided on DMAC from the EU Pharma ChemLeg Group are similar to the ones discussed in this consultation response.