29 NOVEMBER 2012

Responses to Comments Document (RCOM) on ECHA's Draft 4th Recommendation for Bis(2-methoxyethyl) ether (EC number: 203-924-4)

This document provides ECHA's responses to the comments received during the public consultation on the draft 4th recommendation for inclusion of substances in Annex XIV of REACH. In addition to this Response to Comments table, on ECHA's website there is available a zip-file including all attachments to the individual comments (as far as not confidential): http://echa.europa.eu/documents/10162/13640/axiv_rcom_diglyme_attachments_en.7z

PUBLIC VERSION

CONTENT

I - General comments on the recommendation to include the substance in Annex XIV, including the prioritisation of the substance:

#	Date	Submitted by (name, Organisation/ MSCA)	Comment	Response
13	2012/09/19 22:22	ChemSec International NGO Sweden	We support the recommendation to include this substance in Annex XIV.	Thank you for providing your opinion
12	2012/09/19 22:08 See attachment *12_TUI List REACH.pdf*	European Environmental Bureau (EEB) International NGO Belgium	The EEB supports the inclusion of this substance in Annex XIV due to its hazardous properties, high production volumes and wide spread uses. It is also a substance that is included in both the SIN List (http://www.sinlist.org/) and the Trade Union Priority List (http://www.etuc.org/a/6023) and cause occupational diseases. The use of this substance in the market is having adverse consequences for public health and environment and should be banned or severely restricted at European level.	Thank you for the information, and for providing your opinion.
11	2012/09/19 19:13 See attachment *11_BASF comn DEGDME.doc*	BASF SE Company Germany	Please refer to the attachment (s)....	Thank you for your comment regarding the overall pattern of use of the substance in the EU, as well as the information on your specific application. For Diglyme there is no conclusive information available about the allocation of the EU tonnage per use. Your and some other comments (e.g. comment #6) reflect that the great majority of Diglyme (>90%) is known to be used by chemical and pharmaceutical industry for large scale industrial processes (synthesis, extraction/distillation) in closed systems. Further applications have also been identified based on registration data or information from the Annex XV Dossier and the public consultations. These include uses claimed to be performed in close-loop applications, such as in the production batteries (as solvent of electrolytes; no process description available) and in the activation of PTFE sealants (comment # 8); as well as further uses for which no details are available, such as production of binding agents and production of plastic and rubber products. Potential other uses such as in coatings, adhesives, and in syntactic foam for filling composite materials

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				appear not be covered by the generic exposure scenario in registration, while they have not been confirmed by the industry as uses occurring in the EU. ECHA considers that the potential for uncontrolled occupational exposure may indeed in many cases be relatively limited. However, at the same time there are also aspects which indicate that control of risks may not be obvious in all cases, and that the proper implementation of Risk Management Measures (RMM) such as suitable gloves and LEV is very often essential. One of such indications is the RCRs calculated in the Registration's CSR for several of the associated processes / tasks, which are close to indicate risk, especially taking into account the uncertainties expressed in the Annex XV Dossier on the values of the derived DNELs (see also RCOM for the SVHC identification, response to comment # 2 therein: http://echa.europa.eu/documents/10162/8432b580-d238-4001-ad21-c561fbf73e10). Dermal exposure is a factor of concern for use of Diglyme in non-automated tasks/processes, and although the use of couplings of transfer pipes, the short operation time and the proper use of suitable gloves would probably ensure adequate control of risk, proper implementation in particular of "low hierarchy" measures (e.g. PPE and work practices) - which are dependent on individual workers, adequate training and continuous supervision - throughout the supply chain is not guaranteed, and therefore their effectiveness is questionable. There is also uncertainty regarding potential exposure during some of the applications as solvent / process chemical, as overall the information on actual applications in the EU (or the involved processes) is somewhat vague. Finally, although the PROCs included in the registration are linked with low inhalation exposure for relatively low volatility substances such as Diglyme, many processes seem to be

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				performed at high temperature (Diglyme an ideal solvent for such reactions; need for recovery by distillation). In your comment you note that especially in high-temperature applications closed systems are essential, for avoiding losses of diglyme and manufactured substances. However, it should be kept in mind that in particular systems/processes (mainly in smaller scale applications) not designed to recycle diglyme effectively may be subject to potential dermal or inhalation occupational exposure, e.g. due to handling of unrecovered solvent or due to vapour emissions from not effectively enclosed systems. Therefore, ECHA considers that inclusion into Annex XIV would still be beneficial to address the identified potential for uncontrolled exposure, ensuring that risks are controlled and to promote substitution.
10	2012/09/19 18:47	European Trade Union Confederation Trade union Belgium	ETUC supports the inclusion of this substance in the Authorisation list. This substance is also included in the Trade Union Priority List for Reach authorisation. see: http://www.etuc.org/a/6023	Thank you for the information, and for providing your opinion.
9	2012/09/19 18:30	Company Germany	SR&D and precursor uses like filling and packaging of R&D chemicals are threatened by authorization. We would recommend an inclusion into annex XVII with restriction of the uses that have an impact on health and environment. We do not recommend to include this substance in Annex XIV. We have further strong doubt of the number of sites that are using this substance.	Thank you for providing your opinion. Please note that in the process of assessing whether a substance on the Candidate List has priority for inclusion in Annex XIV and therefore should be recommended for inclusion in this annex we are not in the position to assess the pertinence of alternative regulatory risk management options for the substance or some of its particular uses. Note also that authorisation is not comparable to a ban or restriction of a substance but rather to a requirement to request authorisation for carrying out particular uses with the substance. Recognised substances of very high concern maybe granted an authorisation if the applicant can show adequate

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				control of risks arising from the applied for uses or if there is no suitable alternative available to the substance available and the socio economic benefits of a use outweigh the associated risks for health and environment.
8	2012/09/19 12:51	Company Germany	Diglyme spielt bei der Herstellung von PTFE-Dichtungen eine große Rolle. Im beigefügten Dokument sind der Verarbeitungsprozess, die Arbeitsschritte sowie die Maßnahmen zum Schutz der Beschäftigten genau beschrieben. Dieser Prozess wurde von der Dichtungstechnik BRUSS entwickelt und dementsprechend wurden umfangreiche notwendige Anlagen geplant und erstellt. Leider gibt es keinen Ersatzstoff, der die Anforderungen an Diglyme in diesem Herstellungsprozess erfüllt. Im Vorwege wurden unterschiedliche Möglichkeiten der Aktivierung von PTFE hinsichtlich ihr Tauglichkeit und Wirtschaftlichkeit hin untersucht. Bei dem beschriebenen Aktivierungsverfahren und somit bei der Verwendung des selbst hergestellten Aktivierungsmittels wurden die besten Ergebnisse erzielt.	Thank you for your comment and the information provided on your specific application in the activation of PTFE sealants. As regards the availability of alternatives, please see response to comment # 6 in this section (first two paragraphs therein). On your request for exemption, please see section III of this document. See also response to comment # 11 (above) in the current section.
7	2012/09/19 11:11	MSCA Sweden	We support the prioritisation of bis(2-methoxyethyl) ether (Diglyme)for inclusion in Annex XIV. The substance has moderate to relatively high priority due to relatively high volume and moderate to high dispersiveness.	Thank you for providing your opinion.
6	2012/09/18 17:05	Company Germany	Bis(2-methoxyethyl)ether (Diglyme, DEGDME) has highly desirable properties as a polar aprotic solvent (e.g. sufficient solubility of many inorganic reagents, enhanced reactions due to the solvent polarity, water miscibility, etc.). It is therefore frequently used in the chemical synthesis of Active Pharmaceutical Ingredients (API´s), associated intermediates and in the synthesis of fine chemicals. The lack of reactive functional groups makes it inert towards a broad range of reactants (e. g. Grignard reagents, organo-lithium compounds, etc.). Under this aspect DEGDME is superior to many other aprotic polar solvents. Alternative feasible solvents with comparable properties have not been found so far. As a consequence, the interdiction of use of DEGDME in industrial processes would significantly limit the number of chemical reactions and would make the manufacturing of some active ingredients for pharmaceutical applications virtually impossible. In addition, the introduction of alternatives requires extensive redevelopment of the	Thank you for your comment and the information provided. Topics such as the availability and suitability of alternatives, socio-economic considerations regarding the benefits of a use or the (adverse) impacts of ceasing a use as well as information on the low level of risk associated to a use are important. Information regarding these topics should be provided as part of the application for authorisation (e.g. in the analysis of alternatives, the chemical safety report or the socio-economic analysis). This information will be taken into account by the Risk Assessment and Socio-Economic Analysis Committees when forming their opinions and by the Commission when taking the final decision. It may impact the decision on granting the applied for authorisation and the conditions applicable to the authorisation, such as e.g. the length of the time limited

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			synthesis processes for APIs and associated efforts for the renewal of the (drug) authorization. Worker exposure: The great majority of uses of bis(2-methoxyethyl)ether (Diglyme, DEGDME) are industrial and are performed in industries where control of exposure and contamination is well-understood and practiced. Good industrial hygiene and air quality are essential in these industries and we are not aware of any applications where there is a need for direct contact with DEGDME. Risks associated with the uses of DEGDME are therefore adequately controlled. Consumer exposure: Based on the OSPA Charter on Glycolethers inappropriate end-use applications are not supported by the OSPA member companies. To enforce this, member companies request annual declarations from all customers that DEGDME will not be used for products placed on the market for sale to the general public (e.g. household & consumer products, cosmetics etc.). The return of the completed and signed declaration form is a prerequisite for the future supply of DEGDME. Consequently, the REACH registration dossier does not include use scenarios for consumer applications as these are not supported. In addition to that DEGDME is listed in Annex XVII of REACH regulation (entry 30). According to this restriction DEGDME shall not be used in substances and preparations placed on the market for sale to the general public above the concentration limit of 0.3%. Prioritization: It is our opinion that the draft background document for bis(2-methoxyethyl)ether (Diglyme, DEGDME) (Ref. 1) overestimates the wide dispersiveness of uses of DEGDME by far. To the best of our knowledge the number of use sites is considered as small (< 10) and a prioritization score of 1(-2) for the "number of use sites" seems to be appropriate in our view. We do not agree with the perception of the draft background document (Ref. 1) that exposure to workers may be significant for some operations. The generic exposure scenarios of the REACH registration dossier demonstrate that the registered uses do not indicate risks and	review period of the authorisation. However, it is to be stressed that the prioritisation for the inclusion in Annex XIV is based on the criteria set out in Art 58(3) and follows the agreed approach described in the general approach document (http://echa.europa.eu/documents/10162/17232/axiv_priority_setting_gen_approach_20100701_en.pdf). Consequently information on topics such as the availability and suitability of alternatives, socio-economic considerations regarding the benefits of a use or the (adverse) impacts of ceasing a use as well as information on the low level of risk associated to a particular use are not considered in the prioritisation for recommending substances for inclusion Annex XIV. As regards your reference to the alternative regulatory option of imposing restrictions for particular uses, please see response to comment # 9 in this section. Regarding your request for exemption for the use in the synthesis of fine chemicals or API, please see responses to comments #8 and #2 in section III of this document. In relation to your comment on the pattern of use of the substance and the potential for exposure / assessment of wide-dispersiveness, please see response to comment # 11 in this section. In addition, please note that we haven't assumed use in consumer products in assessing the priority of the substance.

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			the exposure of workers is controlled. The prioritization score for "Release" should therefore rather be set at 1 ("controlled"). Currently workplace exposure measurements are being performed to support this assessment and the REACH registration dossier will be updated subsequently. Conclusion: We suggest to exempt industrial uses of DEGDME as synthesis solvent in the fine chemical and pharmaceutical industry (e.g. for synthesis of active pharmaceutical ingredients (API) or precursors thereof) in case of inclusion of DEGDME in Annex XIV or to evaluate the alternative of the restriction procedure for this substance for uses identified as dangerous for workers and consumers. Ref. 1: ECHA, Draft background document for bis(2-methoxyethyl)ether (Diglyme, DEGDME); Document developed in the context of ECHA's fourth Recommendation for the inclusion of substances in Annex XIV; 20 June 2012	
4	2012/09/17 19:49	Company Sweden	As a consequence of the inclusion of bis(2-methoxyethyl)ether on the 4th draft recommendation of priority substances to be included in Annex XIV of the REACH Regulation that was published on June, 20th 2012, we would like to ensure that ECHA is familiar with certain critical uses of bis(2-methoxyethyl)ether. We encourage ECHA to exempt from the authorization requirement the vital use of bis(2-methoxyethyl)ether as a solvent in the manufacture of sensors for protein interaction analysis and for the manufacture of fine chemicals used for purification of Active Pharmaceutical Ingredients. Information on our use: Bis(2-methoxyethyl)ether is used as a solvent in the manufacture of sensors for protein interaction analysis and for the manufacture of fine chemicals used for purification of Active Pharmaceutical Ingredients. Bis(2-methoxyethyl)ether is not part of the final products. There are currently no known technically equivalent substitutes for this use. Use descriptors for our use of bis(2-methoxyethyl)ether: • SU3 Industrial uses: Uses of substances as such or in preparations at industrial sites	Thank you for your comment and the information provided in both consultations on your specific applications. On your request for exemption, please see section III of this document. See also responses to comments #6 and #11 in the current section.

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			• SU9 Manufacture of fine chemicals - C20.5.9 Manufacture of other chemical products n.e.c. • PC0 Other – UCN code O15000 Solvents • SU24 Scientific research and development • PC21 Laboratory chemicals • PROC 9 Transfer of substance or preparation into small containers (dedicated filling line, including weighing) • PROC 3 Use in closed batch process (synthesis or formulation) • ERC4 Industrial use of processing aids in processes and products, not becoming part of articles. No release of the substance to water, air or soil. 100 % of the substance is handled as hazardous waste and handled by authorized waste vendor. We always handle bis(2-methoxyethyl)ether in small quantities under controlled conditions. Qualitative industrial hygiene risk assessments IHRA are performed for the handling of bis(2-methoxyethyl)ether and exposure of workers is minimized through the whole process. Occupational exposure is monitored by qualitative exposure assessments (IHRA), to recognize and use site-specific information to develop an index of criteria to rank the potential risks in the facility. The exposure assessment examines the three key risk components, sources of risk, exposure pathways (inhalation, dermal, ingestion). The risk assessment lends itself to developing mitigation or exposure control measures. All used bis(2-methoxyethyl)ether is handled as hazardous waste and treated by authorized waste vendors. According to Regulation (EC) No 1272/2008 bis(2-methoxyethyl)ether is classified as toxic for reproduction category 1B, H360FD. In the comments submitted confidentially we describe our uses in more detail together with the controls used to protect the health and safety of employees in accordance with EU directives. Refer also to our previous comment during the consultation period before the inclusion of bis(2-methoxyethyl)ether on the Candidate list, reference number ff9a5937-f0bc-4942-b339-4b0f0adb3869.	
3	2012/09/17 14:25	MSCA United Kingdom	We note there are many uncertainties in the assessment with respect to uses and the level to which workers are exposed therefore, substance evaluation may be a better approach to clarify if there are real risks.	Thank you for providing your opinion.

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				In the process of assessing whether bis(2-methoxyethyl) ether has priority for inclusion in Annex XIV (and therefore should be recommended for inclusion in this annex) we have taken into account the information available in the registrations and the Annex XV dossier, including any further relevant information submitted during the public consultation on identification of the substance as SVHC. In this context, please consider also response to comment #11 in this section. Nevertheless in this process we are not in the position to assess whether substance evaluation would be needed prior to take a decision on including the substance in Annex XIV. In addition, please note that the prioritisation approach which was agreed and applied here to prioritise and recommend substances from the Candidate List for inclusion in Annex XIV is not intended to assess the risks arising from the uses but to provide a very basic and general assessment of the use pattern and exposure potential a substance may have for humans (workers, consumers) or/and the environment. If a substance is included in Annex XIV it is then the obligation of the applicant for authorisation to demonstrate that the risks arising from the applied for uses are properly controlled or that there are no alternatives available and the socio economic benefits of the use outweigh its risks. Consider please also that beside proper control of risks substitution of SVHCs, where technically and economically viable, and good functioning of the internal market are objectives of the authorisation title.
2	2012/09/17 11:47	Company Switzerland	With ECHA's 4th recommendation published on 20th June 2012, the substance Bis(2-methoxyethyl)ether (Diglyme) was recommended for "prioritization for authorisation". This solvent has an important role for the production of medicinal products. General comments on the recommendation to include Bis(2-methoxyethyl)ether (Diglyme) in Annex XIV, including the prioritisation of the substance	Thank you for your comment and the information provided. As regards your request for exemption from the authorisation requirement, please see response to your comment in section III of this document. See also response to comment # 6 in the current section.

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			Bis(2-methoxyethyl)ether (Diglyme) It is classified in Annex VI, part 3, table 3.1 of Regulation (EC) 1272/2008 as toxic for reproduction 1B, H360FD ("May damage fertility. May damage the unborn child." and was therefore included in the Candidate List for Authoristion on 19.12.2011. Bis(2-methoxyethyl)ether (Diglyme) is mainly used as an solvent in industrial manufacturing and production processes. It exhibits a high boiling point and excellent chemical stability even at elevated temperatures. Thus, it is an ideal candidate for any reactios at elevated temperatures (e.g. above 100°C) where the majority of other solvents is not suitable due to their lower boiling points and missing chemical alternatives. It shows excellent results with regards to yield and ease of workup during pharmaceutical manufacturing processes. Additionally the application of existing EU regulations to the use of Bis(2-methoxyethyl)ether as a solvent in pharmaceutical production guarantees a high level of protection of human health and environment. Therefore, the use Bis(2-methoxyethyl)ether as solvent in pharmaceutical production be exempted from authorisation. Bis(2-methoxyethyl)ether is used as a solvent in a closed batch process, during the syntheses of active pharmaceutical ingredients. The manufacture of active pharmaceutical ingredients is performed within enclosed equipment in accordance with Good Manufacturing Practices (GMP). Bis(2-methoxyethyl)ether (and other solvents) are introduced into the reactors via transfer systems designed to minimise environmental release, by trained personnel using appropriate protective equipment, and are thus contained within the process stream. 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 by, not only by 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	

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			for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency… 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 that Bis(2-methoxyethyl)ether, (CAS 111-96-6) to be exempted from Authorisation) in the production and analytics of medicinal products.	
1	2012/09/12 15:22	MSCA Norway	The Norwegian CA supports the prioritization of Bis(2-methoxyethyl) ether (Diglyme) for inclusion in Annex XIV.	Thank you for providing your opinion.

II - Transitional arrangements. Comments on the proposed dates:

#	Date	Submitted by (name, Organisation/MSCA)	Comment	Response
12	2012/09/19 22:08	European Environmental Bureau (EEB) International NGO Belgium	As soon as possible	Thank you for your comment. ECHA made its proposals for the latest application dates on the basis of discussions by the stakeholder expert group that was following the development of the Guidance for including substances in Annex XIV. This expert group estimated that the time needed for preparation of an authorisation application of sufficient quality might in standard cases require 18 months (roughly 12 months worktime for drafting the application plus an additional buffer of 6 months for consulting required external expertise). As there is yet no reliable information available that would suggest shortening or prolonging this time interval, we consider that a period of 18 months should normally be given to allow for the preparation of a well documented application for authorisation. The anticipated workload of the Agency with regard to processing of authorisation applications was accounted for by grouping the proposed substances in 3 groups and spreading the application and sunset dates over a period of six months – see comment #7 in this section (below).
7	2012/09/19 11:11	MSCA Sweden	We agree with the proposed dates	Thank you for your comment. Please note that the REACH Committee agreed in its meeting of 21/22 November 2012 that the latest application dates for the chromium(VI) substances included in the 3rd Recommendation should be set to 35 months after EiF of the inclusion of these substances into Annex XIV (anticipated to be in March 2013). In order to allow consistency amongst all chromium(VI) substances recommended for inclusion in the Authorisation List, the latest application dates for the chromium(VI) substances of the 4th Recommendation are therefore set to 24 months after EiF of their inclusion in Annex XIV (anticipated to be in February 2014). The latest application date for all chromium(VI) substances of the 3rd and 4th Recommendation

				will then consistently be February 2016. This adjustment of the LAD for the chromium(VI) substances requires a re-organisation of the LADs of the other substances of the 4th Recommendation in order to account for an appropriate distribution of the workload in the time provided for. Therefore, it is suggested to change the LADs for Diglyme to 18 months after EiF.
4	2012/09/17 19:49	Company Sweden	Considering that our use of bis(2-methoxyethyl)ether is as process chemical (solvent) for the manufacture of sensors for protein interaction analysis and the manufacture of fine chemicals used for purification of Active Pharmaceutical Ingredients used in the Pharmaceutical and Biopharmaceutical industries, we would like the period for application for authorization set to 60 months after date of inclusion in Annex XIV, instead of the proposed 21 months, in case our use of bis(2-methoxyethyl)ether as process chemical for the manufacture of sensors for protein interaction analysis and for the manufacture of fine chemicals used in the Pharmaceutical and Biopharmaceutical industries would not be exempt from the authorization requirement. Difficulty to develop alternatives for these very specific applications, is the reason why we would like a longer period for application for authorization to be able to explore and validate less hazardous alternatives to bis(2-methoxyethyl)ether in both individual manufacturing processes.	Thank you for your comment. Please note that authorisation, inter alia, is a means to promote the development of alternatives. Article 55 explicitly stipulates that applicants for authorisation shall analyse the availability of alternatives and consider their risks, and the technical and economic feasibility of substitution (this has to be included in the analysis of alternatives to be submitted as part of the authorisation application in accordance with Art. 62 (4e)). Therefore, the present lack of alternatives to (some of) the uses of a substance and the need to complete R&D programmes to get qualified alternatives to it is no viable reason for adjourning the subjection of a substance or some of its uses to authorisation. Information regarding lack of alternatives is however important information for inclusion in an authorisation application. This information will be taken into account by the Risk Assessment and Socio-Economic Analysis Committees when forming their opinions and by the Commission when taking the final decision. It may impact the decision on granting the applied for authorisation and the conditions applicable to the authorisation, such as e.g. the length of the time limited review period of the authorisation.

III - Comments on uses that should be exempted from authorisation, including reasons for that:

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13	2012/09/19 22:22	ChemSec International NGO Sweden	Being such a hazardous substance, no use should be granted a generic exemption from authorisation.	Thank you for providing your opinion.
8	2012/09/19 12:51	Company Germany	Der Beschreibung können Sie entnehmen, dass Diglyme in einem geschlossenen System verarbeitet wird und somit die Gefahr für die Verarbeiter sehr gering gehalten wird. Evtl. Restgefahren werden durch organisatorische Maßnahmen sowie persönliche Schutzausrüstung beseitigt. Durch regelmäßige Messungen wird die Einhaltung der erforderlichen Grenzwerte am Arbeitsplatz überwacht. Wir bitten Sie daher zu prüfen, ob es für die Verwendung von Diglyme in einer derartigen geschlossenen Anlage, wie die Fa. Dichtungstechnik G. BRUSS sie entwickelt hat, eine Ausnahmeregelung von Annex XIV geben kann und Diglyme auch zukünftig verwendet werden kann.	Thank you for your comment. Regarding the request for exemption from authorisation, please note that industry's voluntary actions in reducing releases or related to the availability of alternatives cannot be considered as such as a reason to propose an exemption (see also response to comment #2 in this section). Information on the low level of risk associated to a use or related to the availability and suitability of alternatives, socio-economic considerations regarding the benefits of a use, as well as the (adverse) impacts of ceasing a use are important. Information regarding these topics should be provided as part of the application for authorisation. This information will be taken into account by the Risk Assessment and Socio-Economic Analysis Committees when forming their opinions and by the Commission when taking the final decision. It may impact the decision on granting the applied for authorisation and the conditions applicable to the authorisation, such as e.g. the length of the time limited review period of the authorisation.
5	2012/09/18 15:13	Company Germany	We request an exemption for the filling of diglyme into small packages for lab use. The industrial packaging/filling for the lab use is done by well trained personnel. Ethylene glycol dimethyl ether is used as solvent in scientific research and development, especially in organometallic synthesis like Grignard reactions and palladium-catalyzed reactions. Usually the volumes used are low. Competitors importing the substance in small bottles for lab use would have a	Thank you for your comment. Please see response to comments #8 and #2 (last part on use for analytical purposes) in this section. Although uses for scientific research and development of a substance are exempted from the authorisation requirement in

#	Date	Submitted by (name, Organisation/ MSCA)	Comment	Response
			competitive advantage due to the fact that they would not need an authorisation.	accordance with Article 56(3) this appears to only apply to its final use for SRD purposes under the conditions defined in Article 3(23). However, use of a CMR substance included in Annex XIV, on its own or in a mixture (above the lowest of the concentration limits specified in Directive 1999/45/EC or in Part 3 of Annex VI to Regulation (EC) No1272/2008) with the intention to supply them for SRD purposes, would probably require authorisation. As bis(2-methoxyethyl) ether is toxic for reproduction, there is a strong societal interest to protect humans, in particular workers handling the substance, from risks potentially arising from its uses. An authorisation requirement for bis(2-methoxyethyl) ether will accordingly ensure that the health of workers in the EU involved in the uses of this substance is protected.
4	2012/09/17 19:49	Company Sweden	Although our uses of bis(2-methoxyethyl)ether are in small volumes, the uses are vital in the manufacture of sensors for protein interaction analysis and for the manufacture of fine chemicals used for purification of Active Pharmaceutical Ingredients. The sensors for protein interaction analysis and the fine chemicals manufactured using bis(2-methoxyethyl)ether as process chemical are not used and classified as medicinal products. There are currently no known technically equivalent substitutes for this uses. The inability to use bis(2-methoxyethyl)ether in the manufacturing processes of the fine chemicals and the sensors for protein interaction analysis will adversely impact drug discovery and development, the Pharmaceutical and Biopharmaceutical industries. We therefore request ECHA's consideration to exempt from the authorization requirement the use of bis(2-methoxyethyl)ether as process chemical during the manufacture of fine chemicals and sensors for protein interaction analysis used in the development, manufacture and purification of Active Pharmaceutical Ingredients. This exemption is necessary to avoid serious disruption to the discovery and manufacture of Active Pharmaceutical Ingredients and medicinal products by the Pharmaceutical and Biopharmaceutical	Please see response to comment # 8 in this section.

#	Date	Submitted by (name, Organisation/ MSCA)	Comment	Response
			industries and to ensure that innovation in the field of drug discovery in the European Union is allowed to continue.	
2	2012/09/17 11:47	Company Switzerland	Exemption from authorisation is requested for the use of Bis(2-methoxyethyl)ether in the production of medicinal 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, as outlined in REACH Art. 58(1)e. Rationale for the Request for an Exemption as per Article 58(2) REACh Art 58(2) confirms the following: Uses or categories of uses may be exempted from the authorisation requirement provided that, on the basis of the existing specific Community legislation imposing minimum requirements relating to the protection of human health or the environment for the use of the substance, the risk is properly controlled. In the establishment of such exemptions, account shall be taken, in particular, of the proportionality of risk to human health and the environment related to the nature of the substance, such as where the risk is modified by the physical form. EU authorities (and other regulatory bodies throughout the world) evaluate the final medicinal product in conjunction with its entire production cycle. Thus these solvents are regulated by strict Pharmaceutical residual solvents guidelines. In addition, other existing EC regulation covers the risk management for solvents like Bis(2-methoxyethyl)ether. Hence, the use of Bis(2-methoxyethyl)ether in the production of API's or as analytical standards should be exempt from Authorisation. The relevant existing EC regulations are: Directive 2001/83/EC & Regulation (EC) No 726/2004 The use of Bis(2-methoxyethyl)ether in the manufacture of an active pharmaceutical ingredient(s) falls within the scope of Regulation (EC)	Thank you for your comment. As regards your request for exemption please note that uses (or categories of uses) can only be exempted from the authorisation requirement on the basis of Article 58(2) of REACH, unless they are already explicitly exempted in REACH Art. 2(5 or 8) or in Art. 56(3 – 6). According to Article 58(2) of REACH it is possible to exempt from the authorisation requirement uses or categories of uses 'provided that, on the basis of the existing specific Community legislation imposing minimum requirements relating to the protection of human health or the environment for the use of the substance, the risk is properly controlled'. ECHA considers the following elements when deciding whether to include an exemption of a use of a substance in its recommendation: - There is existing EU legislation addressing the use (or categories of use) that is proposed to be exempted. Special attention has to be paid to the definition of use in the legislation in question, compared to the REACH definitions in accordance with Art. 3(24). Furthermore, the reasons for and effect of any exemptions from the requirements set out in the legislation have to be assessed; - This EU legislation properly controls the risks to human health and/or the environment from the use of the substance arising from the intrinsic properties of the substance that are specified in Annex XIV; generally, the legislation in question should specifically refer to the substance to be included in Annex XIV either by naming the substance or by referring to the group the substance belongs to, e.g. by referring to the classification criteria or the Annex XIII criteria;

#	Date	Submitted by (name, Organisation/ MSCA)	Comment	Response
			No 726/2004 and Directive 2001/83/EC, relating to medicinal products for human use. The holder of a manufacturing authorisation of a medicinal product referred to in Article 40 of Directive 2001/83/EC is obliged "to comply with the principles and guidelines of GMP" as laid down by community law. Principles and guidelines of good manufacturing practice require impurity testing of pharmaceutical ingredients to ensure that specific threshold limits for residual solvents are met. EMA (European Medicines Agency) guidance on residual solvents (EMA/CHMP/ICH/82260/2006) contains a specific concentration limit for Bis(2-methoxyethyl)ether. Since the residual amount of Bis(2-methoxyethyl)ether in the eventual product (drug substance) is safety-limited by the EMA (Guideline for Residual Solvents), in practice virtually all the Bis(2-methoxyethyl)ether used during manufacture would be present in the waste streams that are then disposed in accordance with local environmental regulations. Thus, the risks of environmental exposure of Bis(2-methoxyethyl)ether in the pharmaceutical manufacturing environment are minimized by the equipment design and operational controls; disposal and record-keeping procedures exist within the oversight of the quality system. 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). 1999/13/EC Solvent Emissions Directive High Volume solvents (>50ts/yr) used in the Manufacture of Pharmaceutical Products are regulated under the Solvent Emissions Directive 1999/13/EC (as amended by 2004/42/EC) The purpose of	- This EU legislation imposes minimum requirements[1] for the control of risks of the use. Legislation setting only the aim of imposing measures or not clearly specifying the actual type and effectiveness of measures to be implemented is not regarded as sufficient to meet the requirements under Article 58(2). Furthermore, it can be implied from the REACH Regulation that attention should be paid as to whether and how the risks related to the life-cycle stages resulting from the uses in question (i.e. service-life of articles and waste stage(s) as relevant) are covered by the legislation. On the basis of the criteria above, we made the following observations on the argumentation brought forward by the commenting party: (i) Only existing EU legislation is relevant in the context to be assessed (no national legislation). (ii) Minimum requirements for controlling risks to human health or (and) the environment need to be imposed in a way that they cover the life cycle stages that are exerting the risks resulting from the uses in question. (iii)There need to be binding and enforceable minimum requirements in place for the substance(s) used. The relevant EU legislation referred to by the commenting party is assessed below. Regulation (EC) No 726/2004 establishes the operation of European authorisation procedures for the placing of medicinal products on the market in the European Union (EU). Each application for authorisation must be accompanied by the particulars and documents referred to in Directive 2001/83/EC on

[1] Legislation imposing minimum requirements means that:
- The Member States may establish more stringent but not less stringent requirements when implementing the specific EU legislation in question.
- The piece of legislation has to define the measures to be implemented by the actors and to be enforced by authorities in a way that ensures the same minimum level of control of risks throughout the EU and that this level can be regarded as appropriate.

#	Date	Submitted by (name, Organisation/ MSCA)	Comment	Response
			the Solvent Emissions Directive is to prevent or reduce the direct and indirect effects of emissions of volatile organic compounds into the environment, mainly into air, and the potential risks to human health, by providing measures and procedures to be implemented for certain activities. Manufacture of Pharmaceutical Products is covered under Annex I (Scope) and the volumes under Annex IIA (Thresholds and Emission Controls). 2004/37/EC Carcinogens and Mutagens Directive: The more stringent and/or specific provisions contained in the Carcinogens and Mutagens Directive (2004/37/EC) apply in addition to the requirements of the chemical agents directive 98/24/EC. Directive 2004/37/EC goes further, requiring an employer to use "existing appropriate procedures for the measurement of carcinogens", to assess the effectiveness of any preventative measures taken to protect the health and safety of workers. Downstream users are required by both community and national legislation not to exceed an exposure limit for a carcinogen. The Carcinogens and Mutagens Directive (2004/37/EC) requires that workplace exposures are avoided/minimised as far as technically possible. This legislation clearly specifies the actual type and effectiveness of measures to be implemented; of particular note is Article 5(2): Where it is not technically possible to replace the carcinogen or mutagen by a substance, preparation or process which, under its conditions of use, is not dangerous or is less dangerous to health or safety, the employer shall ensure that the carcinogen or mutagen is, in so far as is technically possible, manufactured and used in a closed system. Therefore, the use of Bis(2-methoxyethyl)ether as a solvent in pharmaceutical production meets the intent of Article 5(2) of Directive (2004/37/EC). As REACH does not overrule the Carcinogens and Mutagens Directive, this approach to controlling workplace exposure is regarded as the minimum requirement applied during the proposed use of Bis(2-methoxyethyl)ether to be exempted. In addition, there is existing regulation concerning the incineration of waste:	the Community code relating to medicinal products for human use or in Directive 2001/82/EC relating to the production, placing on the market, labelling, distribution and advertising of veterinary medicinal products. Whilst measures may be in place to control the residual amount of solvents in the final product, these pieces of legislation may not control risks to human health or the environment arising from the use of the substance at manufacturing stage of these products or, in particular, from the use and disposal of bis(2-methoxyethyl)ether. Therefore, they may be not regarded as a sufficient basis for exempting uses of bis(2-methoxyethyl)ether from authorisation in accordance with Article 58(2) of the REACH Regulation. (According to Art. 2(5) REACH, substances used in medicinal products for human and veterinary use within the scope of the relevant EU legislation are exempted from authorisation process. Please note that individual companies may benefit from the exemptions foreseen in Art. 2(5)(a) REACH if the conditions are met.) Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work (CAD) sets out a framework based on the determination and assessment of risk and general principles for the prevention of risk, associated with hazardous chemical agents. The Carcinogens or mutagens at work Directive 2004/37/EC (CMD) introduces a framework of general principles to protect workers against risks to their health (which includes prevention of risk) from exposure. The overriding principle is that the employer shall reduce the use of a carcinogen or mutagen (CM) at the place of work, in particular by replacing it, in so far as is technically possible, by a substance, preparation or process which, under its condition of use, is not dangerous or is less dangerous to workers' health and safety. Where substitution is not possible, CMs should be used in closed systems, where technically possible. Furthermore, a hierarchy of measures shall

#	Date	Submitted by (name, Organisation/ MSCA)	Comment	Response
			2000/76/EC Waste Incineration Directive: Destruction of liquid waste solvents is by incineration, and is normally regulated by an IPPC licence. This requires the unit to be operated under the conditions of the Waste Incineration Directive (2000/76/EC) thus meeting all associated emission limit values to both air and water.	be applied when a CM is used. Both Directives outline a hierarchy of control and risk reduction measures (with substitution at the top), however, they leave the determination of the measures to be imposed to the employer and do not provide sufficient indicators to be used to assess whether a measure higher up in the hierarchy would have been technically possible. On this basis it is not considered that CAD or CMD impose binding minimum requirements for controlling risks to human health. Therefore, these Directives may not be regarded as a sufficient basis for exempting uses of bis(2-methoxyethyl)ether from authorisation in accordance with Article 58(2) REACH Regulation. In addition, it should be noted that as bis(2-methoxyethyl)ether is not classified as a carcinogen or mutagen, Directive 2004/37/EC does not apply. Directive 2010/75/EU on industrial emissions (IED), (which will replace a number of existing Directives, including the IPPC Directive (2008/1/EC), the Solvents Emissions Directive (1999/13/EC) and the Waste Incineration Directive (2000/76/EC) from 7 January 2014), includes the provision that installations using organic solvents and undertaking activities listed in Annex VII, where applicable reaching specified consumption thresholds, should operate only if they hold a permit or are registered. More generally, IED Directive requirements apply to facilities engaged in production on an industrial scale of pharmaceutical products including intermediates. The Directive encourages substitution/reduction in usage of organic solvents and sets down emission limit values for particular activities (including manufacturing of pharmaceutical products) to protect human health and the environment. Under Article 58 IED Directive, volatile organic compounds (VOCs) such as bis(2-methoxyethyl)ether which are assigned or need to carry the hazard statement H360D or H360F (i.e. toxic for reproduction 1B) '(…) shall be replaced, as far as possible by less harmful substances or mixtures within the shortest possible time'. Furthermore, according to Art 59(5) IED Directive, VOCs such as

#	Date	Submitted by (name, Organisation/ MSCA)	Comment	Response
				bis(2-methoxyethyl)ether which are assigned or need to carry the hazard statement H360D or H360F, '(…) 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 in Part 4 of Annex VII'. The emission limits stated in the IED Directive are by reference to activities using greater than certain tonnages/mass flow of solvent, while the authorisation requirement does not have a tonnage limit. In this respect, the provisions in this Directive may not cover all uses of this substance in pharmaceutical manufacturing subject to the authorisation requirement. The requirements relating to Waste Incineration under the IED Directive contribute to environmental protection at the waste life cycle stage. However, there does not appear to be sufficient protection of workers / man via the environment at other life cycle stages as outlined above. As regards the use of bis(2-methoxyethyl)ether for analytical purposes, this may fall under the exemption of the use of substances in scientific research and development from the authorisation requirement in accordance with Art. 56(3). We would suggest that you examine whether the mentioned use of your substance for analytical purposes can be regarded as SRD in accordance with the definition set out in Article 3(23). Article 3(23) defines SRD as "*any scientific experimentation, analysis or chemical research carried out under controlled conditions in a volume less than 1 tonne per year*". It is noted that • SRD activities can cover analysis for monitoring or quality controls purposes; • Therefore, in principle a substance may be exempt from authorisation if used, on its own or in a mixture, in analysis for monitoring and quality control purposes, for instance, in order to monitor the presence or concentration of that substance or

#	Date	Submitted by (name, Organisation/ MSCA)	Comment	Response
				other substances; • Nevertheless, this exemption only applies to the extent that the relevant operator uses that substance under controlled conditions[2] and in a volume less than 1 tonne per year. • Only substances used directly for research or analytical purpose, whether on their own, in mixture, or in conjunction with analytical equipments, can benefit from the SRD exemption. This excludes from the exemption any substances forming an integral part of an analytical device. If you conclude that your use for analytical purposes of bis(2-methoxyethyl)ether fulfil the above points, that use can benefit from the exemption of SRD from authorisation as set out in Article 56(3) and no authorisation would be required to continue the use after the sunset date. On the aspect of exemption of uses for the purpose of scientific research and development please see also response to comment #5 in this section.

IV - Comments on uses for which review periods should be included in Annex XIV, including reasons for that: **NONE**

[2] In the absence of explicit requirements set out by the competent authorities, the controlled conditions must be appreciated in relation to different elements including the intrinsic properties of the substance at stake, but also risk management standards. Although such standards may contribute to the determination of controlled conditions, there implementation may not alone be sufficient to meet this condition. Analytical activities that are not run under controlled conditions cannot benefit from the SRD exemption.