European Medicines Agency

London, 21 September 2006
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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN PREVENTION AND TREATMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME

Table 1: Organisations that commented on the draft Guideline as released for consultation

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	MSD/Brussels	Belgium
2	Irish Medicines Board	Ireland

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW		
1 INTRODUCTION / Background		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Page 5/9 top of page	MSD agrees that standards of and approaches to critical care in ARDS are very variable.	In particular, it may be useful to point out that standard of care in academic centres versus community hospitals also vary considerably.
		RAPP comment: This fact has been already mentioned in the section "INTRODUCTION as follows: "Standards of and approaches to critical care (e.g. drugs, care, ventilation) in ALI/ARDS may vary between individual physicians, referral centers, and geographical regions. Because many aspects of management of critically ill patients lack a robust evidence base (due to the difficulties in studying this heterogeneous group of patients as mentioned above), differences in patient management also based on personal opinion and regional custom are common. This all adds to the high degree of heterogeneity within the ALI/ARDS population. "ventilation) in ALI/ARDS may vary between individual physicians, referral centers, and geographical regions. Because many aspects of management of critically ill patients lack a robust evidence base (due to the difficulties in studying this heterogeneous group of patients as mentioned above), differences in patient management also based on personal opinion and regional custom are common. This all adds to the high degree of heterogeneity within the ALI/ARDS population. "

PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS		
Line no + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Page 6/9 Section 2.3 §1	MSD agrees that for the protocol, the goal is to standardize best practice on concomitant treatment and care.	However, it should be recognized that in reality, it would be difficult to control the standardization all of the aspects outlined in this section.
		RAPP comment: We agree to this comment, but a full standardisation is not required in the current guideline. It is only mentioned that "a minimum standardisation for the following aspects should be discussed in the study protocol: …". However for a better clarification of this aspect we suggest that aforementioned sentence will be changed as follows: "A minimum standardisation for the following aspects should be discussed in the study protocol and an implementation should be considered as far as possible."

STRATEGY AND DESIGN OF CLINICAL TRIALS		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Page 7/9 Section 4.1	MSD has a question as to what "primary" and "secondary" pharmacodynamic studies refer to.	We would also like to clarify that these Early Studies would be in patient populations.
	RAPP comment: Primary and secondary pharmacodynamic studies are defined as follows:	**RAPP comment:** Thank you for this comment. We consider it important to note that early studies can not be conducted in all cases in healthy volunteers (e.g. drugs which are administered via tube). Therefore, we suggest that following

	Studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target are primary pharmacodynamic studies. Studies on the mode of action and/or effects of a substance not related to its desired therapeutic target are secondary pharmacodynamic studies (these have sometimes been referred to as part of general pharmacology studies). (Guidance for Industry; S7A Safety Pharmacology Studies for Human Pharmaceuticals; U.S. Department of Health and Human Services; Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) ICH; July 2001)	wording will be added in section "III.1 EARLY STUDIES" "A conduct of early studies in patient populations should be considered in some cases for ethical reasons."
Page 8/9 Section 4.3 "Children"	MSD acknowledges that ARDS in neonates is a special situation.	However, in children other that neonates, we would like to propose that based on the difficulty in recruitment and in demonstrating efficacy in children, extrapolation of demonstrated efficacy in adults should be acceptable. Safety would need to be demonstrated in paediatric patients.
		RAPP comment: We see your point, but on the other hand, if safety data has to be shown, efficacy data could also be provided. It is not explicitly required a presentation of a separate children in the revised guideline. An extrapolation of demonstrated efficacy in adults in phase II studies is possible. However, children should be included in main therapeutic studies and then a separate subgroup-analysis has to be provided.

Line no + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Page 2 Line 42-43	In the Introduction section paragraph 6 reads; "*Estimates of the annual incidence of Ali/ARDS vary but are rare in the region of 1.5-75 per 100,000 populations per year"* However since the guidance was originally drafted there has been a publication by Luhr et al. (Am J Resp Crit Care Med 1999 159:1849) on the prevalence of ARDS/ALI in Europe. They evaluated admissions to ICU over an eight week period (Oct/Nov 1997) in Sweden Denmark and Iceland and showed that the incidence of acute respiratory failure from any cause is 77.6/100,000/year. Of these 17.9/100,000/year satisfy the ATS/ERS criteria for acute lung injury, and 13.5/100,000/year for ARDS. The study was prospective and is probably the best publication to-date. The combined prevalence is well under the top end of the range 75/100,000 cited in the guidance (page 2 line 42).	**RAPP comment:** We endorse the comment of Ireland. Recent research has confirmed the fact that ARDS incidence was overestimated. This might be based on the extrapolation of US-data to the European region (MaCallum NS et al.: Epidemiology of acute lung injury; Curr Opin Crit Care 2005 Feb;11(1):43-9; Frutos-Vivar F et al.: Epidemiology of acute lung injury and acute respiratory distress syndrome; Curr Opin Crit Care 2004 Feb;10(1):1-6) We propose to replace the sentence (page 2, line 42-43) "Estimates of the annual incidence of ALI/ARDS vary, but are in the region of 1.5-75 per 100,000 populations per year." by "Estimates of the annual incidence of ALI/ARDS vary, but are in the region of 1.5-**34** per 100,000 populations per year."