European Medicines Agency

COMMENTS ON USER GUIDE FOR MICRO, SMALL AND MEDIUM-SIZED ENTERPRISES (SMES) EMEA/206798/2006

Draft, 21 December 2006

COMMENTS FROM CATS CONSULTANTS GMBH/ADRIAAN FRUIJTIER
GENERAL COMMENTS
This is a very well written, comprehensive overview.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE: 1. INTRODUCTION

Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
1.2.1 Community marketing authorisation – the centralised procedure, paragraph 2 See also section 6.1.	Current text: "Medicinal products made of recombinant proteins, veterinary medicinal products intended primarily for use as performance enhancers, human medicinal products containing a new active substance for treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorders or diabetes, and designated orphan medicinal products fall within the mandatory scope and must be filed centrally at the EMEA". The text is completely correct, but it may be useful to state that on 20 May 2008 the Centralised Procedure will also become mandatory for products intended to treat auto-immune diseases and other immune dysfunctions and products to treat viral diseases. This is important information for companies that are currently developing products in these indications.	"Medicinal products made of recombinant proteins, veterinary medicinal products intended primarily for use as performance enhancers, human medicinal products containing a new active substance for treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorders or diabetes, and designated orphan medicinal products fall within the mandatory scope and must be filed centrally at the EMEA. ***On 20 May 2008 the mandatory scope will be extended to include human medicinal products containing a new active substance for treatment of auto-immune diseases and other immune dysfunctions and human medicinal products to treat viral diseases***".

[1] Where available

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

GUIDELINE SECTION TITLE: 4. MEDICINAL PRODUCT DEVELOPMENT (HUMAN)		
Line no[2]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Subsection 4.1.1 Active substance (drug substance): Paragraph 3	Current text: "For new active substances, applicants are encouraged to apply for an International Non-proprietary Name (INN) as early in the development stage as possible". However, the WHO has stated that a substance should have entered the clinical phase when applying for an INN (see www.ops.org.bo/medicamentos/essential_medicines/3-quality/**inn**.ppt). Furthermore, the Regulatory Affairs Journal reported in its article "Revisiting the Biosimilar Debate" (December 2006) that companies should not apply for an INN before their product reach Phase II. It might be worthwhile to check with the WHO what the preferred timing is for the submission of an INN application: Depending on the outcome of the consultation with the WHO; either: "For new active substances, applicants are encouraged to apply for an International Non-proprietary Name (INN) as early ***as possible*** in the ***clinical*** development ~~stage as possible~~", or "For new active substances, applicants are encouraged to apply for an International Non-proprietary Name (INN) as early in the development stage as possible, ***but not before Phase II***".	Depending on the outcome of the consultation with the WHO; either: "For new active substances, applicants are encouraged to apply for an International Non-proprietary Name (INN) as early ***as possible*** in the ***clinical*** development ~~stage as possible~~"
Under «Characterisation	In the text reference is made to the V(ICH) Guidelines. It might be useful to include a link to the website (www.ich.org)	Not applicable. All ICH Guidelines are available on EMEA web-site see section 3.2 of the User Guide.

[2] Where available

Subsection 4.2.2 Toxicology Paragraph 4	Current text: "For pharmaceuticals administered infrequently or for a short duration of exposure (e.g., anaesthetics and radiolabelled imaging agents) carcinogenicity studies are not needed unless there is cause for concern" It might be useful to also include a reference to anti-cancer medicinal products, in accordance with the Note for Guidance on the pre-clinical evaluation of anti- cancer medicinal products. As many small companies develop anti-cancer medicinal products this is relevant information: For pharmaceuticals administered infrequently or for a short duration of exposure (e.g., anaesthetics and radiolabelled imaging agents) carcinogenicity studies are not needed unless there is cause for concern. ***For anticancer medicinal products carcinogenicity studies are normally also not required***." Text for footnote: ***See Note For Guidance On The Pre-Clinical Evaluation of Anticancer Medicinal Products (CPMP/SWP/997/96)"***	For pharmaceuticals administered infrequently or for a short duration of exposure (e.g., anaesthetics and radiolabelled imaging agents) carcinogenicity studies are not needed unless there is cause for concern. ***For anticancer medicinal products carcinogenicity studies are normally also not required***."
4.5.2 Paediatric Initiative	Current text: "The legislative process is being finalised and it is anticipated that the regulation will become law by the end of 2006." This text can now be updated: The legislative process ***has been*** ~~is being~~ finalised and ~~it is anticipated that~~ the regulation ***has*** ~~will~~ become law ***on 26 January 2007.***~~by the end of 2006.~~	Section 4.5.2 has been completely revised and updated.

COMMENTS FROM EUROPEAN BIOPHARMACEUTICAL ENTERPRISES (EBE)		
GENERAL COMMENTS		
None		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE: 1. INTRODUCTION		
Line no[3]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Page 3, second paragraph	Innovative medicine. Isn't it for all medicines?	The aim of Commission Regulation (EC) No 2049/2005 is to promote innovation and the development of new medicinal products by SMEs. The scope of the Guide may be broadened at a later stage to include other aspects of interest to SMEs, such as generics.
Page 4, six paragraph	Decision has to be taken of whether veterinary medicines should be included in the guide. Incentives are there for veterinary medicines however the guide is more thorough with regard to human medicinal products. This is also relevant on page 23, paragraph 4.	The Guide has been updated to include section 5 on 'Medicinal Product Development (Veterinary).
GUIDELINE SECTION TITLE: 3. SCIENTIFIC ADVICE		
Page 11, paragraph 8	Maybe include typical topics that advice is sought for? From the SME annual report?	This information will continue to be published in an annual report from the SME office.
GUIDELINE SECTION TITLE: 3. MEDICINAL PRODUCT DEVELOPMENT (HUMAN0		
Page 15, paragraph 3	The active substance should also be manufactured according to GMP.	Not applicable. This is covered in section 4.4.1 on Good Manufacturing Practice (GMP).

[3] Where available

Page 15, paragraph 6	Supply for Phase III clinical trials should be manufactured by a final production process so few changes are made (preferably none) to the final product to be launched on the market. Maybe refer to impurities in new drug substances ICH?	Not applicable. This is covered in section 4.3.5 on Clinical Trials – Notice to Applicants.
Page 16, paragraph 4 and 5	Characterisation. Please list the ICH guideline referred to.	A link to the Guidelines section of the EMEA web-site has been inserted.
Page 16, paragraph 6	Stability. Maybe add that typical post approval commitments include submission of real time stability data (reference to EU guideline on this?)	Not applicable. Post approval commitments are not encouraged.
Page 17, paragraph 9	Maybe cross refer to the ICH guideline Q8 on “specification justification reports”? Specification justification reports are made of stability data, analytical methods and process validation data	Not applicable. Quality by Design is covered at the end of section 4.1.3.
Page 18, paragraph 3	Cross refer to ICH M2 guideline. Very important guideline for preclinical and clinical development.	ICH M2 relates to electronic standards for transmission of regulatory information, the ICH guideline relating to timing of preclinical studies in relation to clinical trials is ICH M3. A cross-reference to ICH M3 has been included at the beginning of section 4.2.
Page 19, paragraph 2	Cross refer to ICH M2 guideline	As above.
Page 21, paragraph 3	Mention the EU guideline on acceptance of foreign clinical data?	A link to section 3.2 has been inserted.
Page 22, paragraph 5	Maybe this section is better under page 15 under quality? Maybe refer to comparability guidelines	Not applicable. This point has been addressed in section 4.3.5 because the section on Quality is a joint section covering medicinal products for both human and veterinary use.
Page 25, Paragraph 3	"If the designation of the drug is based on significant benefit a report demonstrating the significant benefit of the product with references to protocol assistance, clinical results obtained and the initial arguments at the time of designation submission should be sent separately from the MAA to the Scientific Advice and Orphan Drug section. This report should be sent in parallel with the application. "	Section 4.5.1 has been revised accordingly.