European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 26 May 2009
Doc. Ref. EMEA/211762/2007

OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON CARCINOGENICITY EVALUATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF HIV INFECTION; EMEA/CHMP/SWP/194898/2006

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

	Name of Organisation or individual	Country
1	EFPIA	
2	Merck Sharp & Dohme	
3	Bristol Myers-Squibb (BMS)	
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Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW
EFPIA: The proposed guideline should not place more stringent requirements on the assessment of carcinogenic risk on compounds to treat HIV infection compared to non-HIV products; specifically, follow up mechanistic studies should not be required, but encouraged only under some instances.
Merck believes that the proposed guideline places more stringent requirements on the assessment of carcinogenic risk on compounds to treat HIV infection compared to non-HIV products. Specifically, the requirement for follow up mechanistic studies does not appear to consider risk vs. benefit to the patient. Although medical advances have improved the life expectancy of HIV infected individuals, there still remains a need for novel therapies to improve treatment of the constant emergence of drug resistant isolates.
BMS: We commend the EMEA for proposing the draft guidance. There are, however, several aspects of the draft guidance where clarification would be useful or that appear contrary to the EMEA's stated objectives. Detailed comments are cited below in the Section for "SPECIFIC COMMENTS ON TEXT". BMS has one general comment on text in Section 5 TIMING OF THE EVALUATION OF CARCINOGENICITY, 5.1 Carcinogenicity, (lines 1-11) which is also reflected in the EXECUTIVE SUMMARY text. Within Section 5.1 of the draft guidance it states, "…it is in principle expected that, as for any product for which the expected clinical use is continuous for at least 6 months, the results of the carcinogenicity studies are submitted before granting marketing authorization" and later states, "However, according to the Note for Guidance on the need for Carcinogenicity Studies of Pharmaceuticals (CPMP/ICH/140/95), for products intended for the treatment of patients with limited treatment options or of clearly demonstrable added value, the submission of the results of carcinogenicity studies as a post-approval commitment may be accepted". BMS concurs that the benefit-to-risk profile of a medicinal product be considered when determining if carcinogenicity studies need to be submitted prior to granting the marketing authorization. Based upon the benefit-to-risk profile, it is generally anticipated that the results of the carcinogenicity studies for new HIV medicinal products, whose expected clinical use is continuous for at least 6 months, can be submitted as a post-approval commitment.

SPECIFIC COMMENTS ON TEXT

1. INTRODUCTION

Line no. + paragraph no.	Comment and Rationale	OUTCOME
Paragraph 1 p. 3/8	**EFPIA:** This section reads as if all anti-retroviral therapies (ART) have toxicities similar to that of the NRTIs. This is not the case, since the mechanism of toxicity for NRTIs is incorporation of drug into host DNA, which in turn leads to genotoxicity and tumorigenicity that have been well described in the scientific literature. Not all ARTs act in this manner and it is inappropriate to suggest they do. Since biotechnology-derived pharmaceuticals are currently in use as medicinal products for HIV, clarifying statements	Not supported. It is clearly stated that different classes of medicinal products for the treatment of the Human Immunodeficiency Virus (HIV-1) infection, with different modes of action and toxic profiles have been and are being developed. Agreed and mentioned in Guideline.

	indicating that the carcinogenicity and genotoxicity testing may not be applicable for those types of products (see ICH 1a and 6) should be added.	
2 Scope, Lines 1-2	**BMS:** In Section 2 SCOPE (lines 1 - 2), the draft guideline states that the guideline is to apply "mainly to the development of new medicinal products for the treatment of HIV infection". Elsewhere in the document (e.g., Executive Summary, Section 1 INTRODUCTION) the draft guideline refers to the reconsideration of "available products". Clarification is needed to indicate that the guidance applies only to new medicinal products, not existing or available medicinal products. Proposed change: In order to clearly define the scope of this guideline, BMS recommends that the guideline clarify that it applies only to new medicinal products for the treatment of HIV infection.	Agreed, the Scope of the Guideline has been modified to indicate that it *'applies to the development of new medicinal products for the treatment of HIV infection.'*

5. TIMING OF THE EVALUATION OF CARCINOGENICITY		
Line no. + paragraph no.	**Comment and Rationale**	**OUTCOME**
5.1 Paragraph 1 p. 4/8	**EFPIA:** The meaning of the following **highlighted** text should be clarified: …. carcinogenicity studies (**but the relevancy of these tumors to humans is unknown**, especially liver tumours induced by NNRTIs), it is in principle expected that, as …..	Now Section 6.1: the text has been modified.
5.1 p. 4/8	The sentence implies that, in the case of positive findings, a mechanistic explanation is always required. However, in some cases this will not be possible or should not be necessary (i.e. ≥ 10-fold safety margin is established for the tumorigenic response, well established causes of tumorigenesis, or tumorigenesis due to a genotoxic mechanism).	Now Section 6.1: the text has been modified.

	Proposed Change: **"…, Companies are <u>encouraged</u> to provide data (obtained either by experimentation or from public literature)…"**	
5.2 Line 5 p. 4/8	**EFPIA:** There is a word missing "if knowledge of possible ? are available" Proposed Change: "if knowledge of possible <u>interactions</u> are available"	Now Section 6.2: the text has been modified.
5.2 Line 5 p. 5/8	**EFPIA:** A word has been omitted. Proposed Change: Deviations from this approach might be needed if knowledge of possible **<u>interactions</u>** are available suggesting a potential to synergistically enhance adverse effects	See above
Section 5.1	**Merck** The draft guideline states that "In case of positive findings in the results of carcinogenicity studies conducted, Companies are required to provide mechanistic data to support the possible explanations of the tumour findings that would help clarify the clinical relevance". Proposed Change: Generation of mechanistic data which will explain the clinical relevance or a positive tumor response is an extremely challenging endeavour. Such data will likely require extensive experimentation and considerable time and resource. Merck has the following comments on this requirement: • Proposed modification to the text cited in the draft Guideline is as follows: **"In case of positive findings in the results of carcinogenicity studies conducted, Companies are required to provide ~~mechanistic data to support the possible explanations~~ supportive evidence of mode of action (such as established data in published literature) of the tumour findings that**	Now Section 6.1: the text has been modified.

	would help clarify the clinical relevance". Results of these investigative studies should be provided in a timely manor and submitted in a supplemental filing as appropriate". • Positive tumorigenic responses determined to be caused by established modes of tumorigenesis should not require follow up mechanistic studies. • Follow up mechanistic studies should not be required when a ≥ 10-fold safety margin is established for the tumorigenic response. • Follow up mechanistic studies should not be required when evidence suggests the cause of tumorigenesis to be due to a genotoxic mechanism.	
5.1 Carcinogenicity, Lines 12 - 14	**BMS:** In Section 5 TIMING OF THE EVALUATION OF CARCINOGENICITY, 5.1 Carcinogenicity (lines 12 - 14)**,** the draft guideline states that "Companies are required to provide mechanistic data to support the possible explanations of the tumour findings that would help to clarify the clinical relevance". Mechanistic data that provides possible explanations may not be possible in all cases. Further, tumour findings, if present, may occur at such high multiples of clinical exposure that mechanistic studies are not warranted. Accordingly, the submission of mechanistic data should be on a case-by-case approach. Proposed Change: In order to provide a science-based approach to the submission of mechanistic data which recognizes that mechanistic data may not provide possible explanations in all cases, BMS recommends the guideline state "Where feasible, companies *should* provide mechanistic data to support the possible explanations of the tumour findings that would help to clarify the clinical relevance. *Mechanistic data is typically not needed in cases where tumour findings are known to be not relevant to humans (e.g., rodent*	Now Section 6.1: the text has been modified.

	liver tumours induced by NNRTIs) or where tumour findings occur at high multiples of human therapeutic exposure. Tumour findings, if present, may occur at such high multiples of clinical response that mechanistic studies are not warranted. Accordingly, the submission of mechanistic data should be evaluated on a case-by-case basis."	
5.3 Paediatric use, Lines 2-4	**BMS:** In Section 5.3 TIMING OF THE EVALUATION OF CARCINOGENICITY, Paediatric Use (lines 2 - 4)**,** the draft guideline states "The need for carcinogenicity testing should be addressed prior to long term exposure in paediatric clinical trials considering the length of treatment (or cause for concern) (CPMP/ICH/286/95)." The present draft language does not address the definition of "long term exposure" or provide guidance where the clinical benefit of a new medicinal product could exceed the risk of its use in paediatric clinical trials. Proposed Change: BMS recommends that "long term exposure" in the paediatric population be defined as at least 6 months for consistency with the prior statement (Section 4 GENERAL CONSIDERATIONS, line 10) in the draft guidance, and include a statement such as "*Typically, carcinogenicity studies are not needed prior to conducting paediatric clinical trials where clinical benefit exceeds risk of using a new medicinal product for HIV or where there are no other treatment options.*"	Now Section 6.3: this sentence is already mentioned in (CPMP/ICH/286/95) and has been included to maintain consistency between guidelines.
5.4 use in Pregnant Women, Lines 9-13	**BMS:** In Section 5 TIMING OF THE EVALUATION OF CARCINOGENICITY, 5.4 Use in Pregnant Women (lines 9 - 13), the draft guideline states "Carcinogenicity studies should be completed before marketing authorisation submission if it is possible that the new product may be used in pregnant women." BMS does not agree with the requirement that carcinogenicity studies be required before the marketing authorization	Now Section 6.4: the sentence has been modified.

	submission if it is possible that this product may be used in HIV-infected pregnant women. Moreover, standard rodent carcinogenicity tests do not address the issue of transplacental carcinogenesis. Instead, BMS suggests that the standard battery of reproductive toxicity studies be conducted as with any other drug. As for all medications, HIV medicinal products should be given to pregnant women where therapeutic benefit to the mother and foetus exceeds risk. Should post-marketing studies on new HIV agents indicate the potential for carcinogenicity, the continued use of these new agents would still be determined based on the benefit-to-risk relationship. Proposed Change: BMS recommends revising lines 9-13 in Section 5.4 to be consistent with lines 1-11 in Section 5.1 TIMING OF THE EVALUATION OF CARCINOGENICITY, Carcinogenicity.	

6. NON-CLINICAL DATA IN THE SPC		
Line no. + paragraph no.	**Comment and Rationale**	**OUTCOME**
p. 5/8	**EFPIA:** It should be clarified that other statements are also possible for describing Carcinogenicity, in the same way as is indicated for Mutagenicity. Proposed Change: Carcinogenicity studies showed an increased incidence in (organ tumour) in (animal species). The mechanism of tumour formation and the potential clinical relevance is not known. Carcinogenicity studies in (animal species) were negative. While the carcinogenic potential is unknown, these data suggest that the clinical benefit of [Active substance] outweighs the potential carcinogenic risk to humans **(not exhaustive list of possibilities)**	Now Section 7; agreed and added in the paragraph above the example statements.