13 March 2013
EMA/CHMP/BWP/151908/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on Quality of biological active substances produced by transgene expression in animals' (CHMP/BWP/151897/2013)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Synageva BioPharma Ltd.
2	BIA (UK Bioindustry Association)

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	It should be noted that beyond the specific controls requisite to monitor and assure the intra- and inter-generational stability of the transgene in a transgenic animal producing a protein therapeutic, additional controls should be established relative to the potential for microbial and viral contamination. These should be scientifically consistent with those required for other animal derived source materials for use in the production of medicinal products for human use.	No changes required, this point is sufficiently covered. For example, in section 2 (Scope), Section 5.2 (Generation and control strategy for the production animals).
2	Guideline endorsed	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
186-190	1	Comments: In section 5.2, the draft guidance proposes that, "*To maintain control of genetic variability, the breeding strategy to obtain production animals should be clearly defined and ideally the maximum number of generations between founder and production animals should be defined. In any case, the genetic stability of the transgenic animal line should be validated over the maximum number of generations between the MTB and animals constituting the production group*". It is unclear if the first sentence of the referenced section refers to the general genetic variability of the production line or to the specific transgene. If the former is the case, such control of the genetic variability of the animals used in the production of other animal derived medicinal products is not required (e.g. animal immunoglobulins and immunosera for human use, ref. CPMP/BWP/3354/99; eggs, ref. Ph.Eur. 5.2.2). It is not clear why such control of the genetic variability in transgenic animals is required in this draft. In the case of the latter for the specific transgene, in our experience, such changes have not been observed in established transgenic animal lines.	Partly accepted. Control of genetic variability refers to the production line and the transgene. The extent of genetic variability within the production group should be controlled to maintain as high a level of consistency of the matrix in which the transgene is expressed as possible, for example by ensuring the consistency in stain of the breeding partners. It is agreed that it is not necessary to pre-determine the genetic consistency of the animals throughout their entire generational span. Instead, adequate characterization may be provided for each generation on an on-going basis. However, the concept of continuous process verification was not designed for such a procedure and so an on-going monitoring of genotypic, phenotypic and process parameters should be performed.

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		It should be emphasized that transgenic approaches are distinct from cell culture using immortalised cell lines in that the gene of interest is inserted into normal cells, which are well recognised to differ favourably from immortalised lines in terms of genetic and epigenetic stability. In any case, it is possible to completely characterize the transgene in each generation of a transgenic animal line. Extensive genetic analyses of the G1 founders to definitively establish the precise sequence and chromosomal location of a complete transgene in a production line is quite feasible with currently available technologies. Because at each generation there is the opportunity to confirm the complete transgene and flanking genomic sequence, and there is no *a priori* reason that sequence transmission from GX to GX+1 would occur at any greater or lesser fidelity than G1 to G2, the absolute requirement for pre-determined generational limits and related validation should be clarified in cases where adequate genetic characterization is provided at each generation. In addition, given the generational time of most transgenic species, in the order of 6-months to years, validation of the maximal number of generations for a Product Line is not practicable on any reasonable time-scale. This scenario more	

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		appropriately lends itself to the concept of Continuous Process Verification (see the draft Guideline on Process Validation (EMA/CHMP/CVMP/QWP/70278/2012-Rev1). Proposed change (if any): "*To maintain control of genetic variability, the breeding strategy to obtain production animals should be clearly defined and ideally the maximum number of generations between founder and production animals should be defined. In any case, the genetic stability of the transgenic animal line should be validated over the maximum number of generations between the MTB and animals constituting the production group. In cases where sufficient genetic characterization is performed at each generation, validation of a generational limit need not be pre-established or may be performed as a Continuous Process Verification consistent with the principle as described in the draft guidance Guideline on Process Validation (EMA/CHMP/CVMP/QWP/70278/2012-Rev1). The methods used should be capable of identifying if critical genetic elements have undergone changes leading to an alteration in the intended product.*"	
198-201	1	Comments: In section 5.2, the draft guidance proposes that, "*The impact of the genetic variability, as derived by natural*	Partly accepted. Matrix constituents can be variable and in order to assure that

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		allelic differences or mutations, in those elements that are responsible for the matrix into which the recombinant product is generated, should be considered. Basic testing of the matrix itself should be introduced to assure consistency between transgenic animals and over generations." Matrix analyses, either genetic or expression related, are not presently required for other products derived from animal (e.g., animal immunoglobulins and immunosera for human use, ref. CPMP/BWP/3354/99; eggs, ref. Ph. Eur. 5.2.2) or human sources (e.g., plasma derived medicinal products, ref. CPMP/BWP/706271/2010). It is recognized in the draft guidance that the variability in the matrix constituents of the source material is addressed as part of the validation of a robust purification process. It would be expected that significant differences in matrix constituents would only be observed when source material is pooled from few individual animals. The company would prefer the guidance reflect that these analyses are most appropriate and feasible when only a limited number of transgenic animals comprise the production lines. In cases where "basic testing" would be appropriate, what types of analyses would be recommended? Are there any examples that might be useful to include in	the purification process is able to consistently achieve a specified level of purity, the variability in these constituents must be understood and documented. It is not intended that every animal should be monitored in this way however, a sufficient number of animals should be monitored to ensure the full range in variability in these constituents is known and accommodated for during purification. Where the production group is very small, this may involve all the animals. Where the group is large, a justified sample of animals may be sufficient.

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		the guidance? The guidance should provide emphasis on any matrix constituents that might influence the purification process and product quality. Proposed change (if any): "In cases where there are only a few transgenic animals contributing to the source material pool, t~~T~~*he impact of the genetic variability, as derived by natural allelic differences or mutations, in those elements that are responsible for the matrix into which the recombinant product is generated, should be considered.* B*asic testing of the matrix itself should be introduced to assure consistency between transgenic animals and over generations.*"	
209-212	1	Comments: In section 5.2, the draft guidance proposes that, "*The production group should be maintained in a well-controlled environment with restricted movement of animals, personnel, feed stuff and materials. The general principles of a Specified Pathogen Free flock are appropriate (e.g. Ph. Eur. 5.2.2 Chicken Flocks Free From Specified Pathogens for the Production and Quality Control of Vaccines) although additional measures may be necessary.*" We agree the general principles of SPF (housing, isolation, etc.) should be applied, even in situations	Partly accepted. It is accepted that the current wording is too vague regarding possible changes to the principles of SPF maintenance of production groups, and instead, the SPF procedure may be adapted with a proper justification.

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		where SPF is not formally applicable. The company believes the statement “although additional measures may be necessary” should be amended to “with modifications as appropriate”. The former implies that at least all the requirements outlined in Ph. Eur. 5.2.2 apply to production in Transgenic Eggs, which is not the intent given the “general principles” description. Proposed change (if any): “*The general principles of a Specified Pathogen Free flock are appropriate (e.g. Ph. Eur. 5.2.2 Chicken Flocks Free From Specified Pathogens for the Production and Quality Control of Vaccines)* ~~*although additional measures may be necessary*~~*with modifications as appropriate*.”	
254	1	Proposed change (if any): “*Strategy to maintain SPF status of the animal group where applicable*”	Not accepted. It is not envisioned that any production group of animals will be maintained under less stringent control that SPF (with properly justified adaption).