31 August 2015

Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)

Comments from:

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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The Biotechnology Industry Organization (BIO) thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the "Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products." BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products. This first draft is a helpful attempt by EMA at creating a unifying guideline supporting gene therapy medicinal products (GTMP) that also pulls together previous EMA guidelines that address specific aspects of gene therapy development. However, the guideline is not harmonized with other regions and BIO recommends that established regulatory authorities align on guidance as much as possible to facilitate global development programs. This is especially important as gene therapies are often being developed for the treatment of rare genetic diseases which by necessity typically feature trials that are inclusive of global patient populations. Additionally, there are areas of the guideline that need to be simplified and checked for redundancy. For example in the "Nonclinical	

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	Development" section there appear to be two different sections both addressing the aspects of genomic integration (in 5.4.1 and 5.5.2). Also, EMA should consider employing some of the methods used by the U.S. Food and Drug Administration (FDA) in their unifying gene therapy guidance published in 2013, such as outlining considerations for when a Sponsor would need to conduct a nonclinical biodistribution study. It would provide Sponsor's with greater clarity if the FDA and EMA guidance documents were clear about the similarities and differences between the two organizations' expectations (*i.e.,* the requirement for nonclinical shedding studies by EMA, whereas there is no mention of a requirement in the FDA guidance). Additionally, BIO suggests that the EMA provide a list of abbreviations and definitions in the guidelines in order to provide clarity for readers. Lastly, on a content-related note, BIO believes that the guideline allow accumulated data to guide the level of testing that is required. For example, if a vector design/backbone has shown the same bio-distribution multiple times with different genes, and has shown no vector backbone-related toxicity in humans, then minimal animal work should be required to assess these characteristics. Likewise, if a viral vector capsid has shown a biodistribution and circulation half-life that are essentially the same independent of the gene inserted, then analysis of effects of capsid function should be limited.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
87-102		**Comment:** Based on the first paragraph in the Executive Summary it seems the scope of the guideline is clarifying requirements for marketing authorization. BIO finds third paragraph which refers to "dose selection for the clinical trials" appears confusing. Consider replacing "for the clinical trials" by "from the clinical trials". In this case "dose selection" would be understood to refer to the dose for marketing authorization. **Proposed Change:** "The non-clinical section addresses the non-clinical studies required to support a marketing authorisation application with the aim of ~~at~~ maximising the information obtained on dose selection ~~for~~ from the clinical trials, to support the route of administration and the application schedule. Non-clinical studies should also allow determining whether the observed effect is attributable to the GTMP."	
133-143		**Proposed Change:** BIO recommends stating that the scope of the guideline is to clarify marketing authorization application (MAA) requirements or expectations by discipline for GTMPs. It is understood that this guideline will be helpful to Sponsors throughout the development of GTMPs.	
144-165		**Comment:** The guideline points out that if a GTMP is considered a Genetically Modified Organism (GMO) it would need to comply with applicable Directives regarding GMOs. BIO notes that a number of GMO regulatory requirements in the EU are not adapted for GTMPs. Often such directives have been created for genetically modified plants and as such, a large number of requirements are not applicable to GTMPs thus	

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		causing unnecessary burden for companies developing GTMPs, particularly Micro-, small- and medium-sized-enterprises (SMEs).	
234		**Comment:** The section heading is "4.1.2 Development genetics" **Proposed Change:** BIO suggests renaming this section "4.1.2 Vector genetics"	
240-241 and 247		**Comment:** Line 247 should be combined with lines 240-241 as it is referencing plasmid DNA. **Proposed Change:** "For plasmid DNA (including plasmids delivered via bacterial vectors): the plasmid backbone, transgene and selection gene full sequence and any other regulatory sequences should be described."	
256-257		**Proposed Change: "**~~F~~ The use of antibiotic resistance genes (or other elements used for selection) in the final GTMP should be avoided if possible and where not possible, justified."	
806-808		**Comment:** BIO finds this section of the text to be unclear. **Proposed Change:** "Generally, the use of the same animal model in both the toxicology investigations and the pharmacokinetic studies is ~~recommended~~ should be considered, in particular ~~in case~~ when vector-related toxicity signals are observed but should take into account the relevant biological response, pathophysiology, and anatomy."	

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829-848		**Comment:** BIO believes that the section on sensitivity is lacking in sufficient detail. **Proposed Change:** BIO asks EMA for more detail on the level of sensitivity that is expected.	
830-831		**Comment:** In early stages of nonclinical development, robust, qualified methods of analysis are commonly utilized. As a result, the proposed language would require development and validation of all methods in advance of initiation of the nonclinical development program. **Proposed Change:** "Methods of analysis used in the non-clinical programme should be technically validated with the test article in the appropriate tissue matrix; acceptance of robust, qualified assays in lieu of validated methods are considered acceptable for early stage non-clinical development studies."	
837-842		**Comment:** Per earlier language in this section, justification of the analytical methods used should be provided. As a result, although commonly utilized, sole use of a nucleic acid amplification (NAT) assay would be too restrictive thereby limiting alternative methods of analysis which may be deemed more appropriate. **Proposed Change:** "For example, ~~In~~ in the case of nucleic acid amplification (NAT), as the specificity of NAT methods depends on the choice and design of the primers and probes, as well as on the reaction conditions and the method of detection, the rationale for the selection of the primer and probe sequences should be carefully justified. Owing to its high sensitivity, NAT assays are prone to cross-	

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		contamination and false positive results unless proper precautions are taken.	
864-866		**Comment:** It is unclear if the guideline is suggesting that the Sponsor provide data detailing the pattern of viral receptors in the nonclinical species. Even if receptors are shown to be present, this may not necessarily lead to transduction. BIO believes it would be enough to simply show that the vector effectively transduces the tissue(s) in question. **Proposed Change:** "The expression and tissue distribution of cellular receptors for virus/bacteria in the animal model that might affect the efficiency of the uptake by the host and the cellular and tissue sequestration of the vector. Where such data are lacking it may be necessary to demonstrate transduction of target tissue(s) in the proposed animal model (*e.g.*, using RT-NAT, immunological-based assays and/or assays to detect functional protein)."	
866-868		**Comment:** BIO finds that the sentence: "Depending on the type of gene therapy vector, tissue tropism may occur or is intended via selective presence of the GTMP in tissues or organs, selective infection of cells/tissues or selective expression of the therapeutic gene(s)" is not entirely clear. **Proposed Change:** "Depending on the type of gene therapy vector~~, tissue tropism may occur or is intended via selective presence of the GTMP in tissues or organs,~~ selective infection of cells/tissues or selective expression of the therapeutic gene(s) may occur or be intended via tissue tropism or selective presence of the GTMP in tissues or organs."	

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883-885		**Comment:** It is unclear if the guideline is suggesting that if there is any possibility of humans possessing a pre-existing immunity to the viral vector that animals which also possess pre-existing immunity would be required in non-clinical testing. If this is the intent of the guideline, this would greatly increase the number of animals used in the non-clinical program, is likely to be of limited scientific value, and does not appear to be warranted. In clinical trials it is likely that patients with pre-existing immunity would be excluded anyway. **Proposed Change:** "~~Effects of pre-existing immunity against the vector vehicle and/or vector gene products in the patient may be mimicked by pre- treatment of the animals with the vector.~~ The animal's immune reaction to the parental virus or bacteria used to derive the GTMP should be taken into consideration, if applicable, and any potential impact on study outcomes or interpretation should be assessed. Effects of pre-existing immunity against the vector vehicle and/or vector gene products in the patient may be mimicked by pre-treatment of the animals with the vector, if warranted to support a particular patient population.	
892-893		**Comment:** BIO believes the word "xenografts" is out of place in this section. **Proposed Change:** "Transgenic animals are used to model different human diseases: infection, neurodegeneration, apoptosis, atherosclerosis, ageing, cancer, ~~xenografts~~, etc."	
900-903		**Comment:** Human delivery systems are not likely to be useable even in large animal models. BIO recommends keeping this language more flexible.	

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		Proposed Change: "Metabolism and other pharmacokinetic aspects, if needed. Use of large or disease animal models may be considered ~~needed~~ in order to mimic special ~~the~~ clinical conditions of ~~biodistribution of~~ the GTMP due to ~~depending on~~ the nature of the product and, its route of administration ~~and, optionally, the delivery system employed (e.g. intra-cerebral administration)~~."	
933-936		**Comment:** BIO believes the guideline is unclear regarding the kinds of assays expected to demonstrate "correct" transgene product and function.	
934-936		**Comment:** The definition of "aberrant gene" is not clear. **Proposed Change:** If synthesis of an aberrant (unintended) gene product from the GTMP cannot be excluded by quality data, the presence, and if so, the biological consequences of the aberrant gene product formation should be investigated.	
947-949		**Comment:** BIO believes the reference to determining the safety margin in this section would be better discussed in the toxicology section of the guideline with more context. **Proposed Change:** "Moreover, it is expected to determine the best effective dose without toxic effects of the product which exerts the desired pharmacological activity in the most suitable animal model. ~~Therefore, it will be useful to determine the safety margin~~."	

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957-960		**Comment:** The guideline is unclear whether a Sponsor can show that in vitro transduction leads to effective transcription or the Sponsor needs to perform insertion site analysis in vitro on every integrating vector, even though the integration profile that occurs in vitro may be radically different than if the transduction occurred in vivo.	
966-986		**Comment:** No previous guidance refers to a safety pharmacology requirement. Therefore, BIO suggests removing the draft text as it is not harmonized with any other regulatory region, and suggest the following alternative text based on use of a scientific approach in defining whether safety pharmacology endpoints are needed in a GTMP program. **Proposed Change:** "~~Safety pharmacology studies are required in order to investigate the potential undesirable pharmacodynamic effects of the GTMP on physiological functions (central nervous system, cardiovascular system respiratory system and any other system based on the biodistribution of the product) in relation to exposure in the therapeutic range and above as recommend in ICH S7A, CPMP/ICH/539/00.~~ The inclusion of safety pharmacology endpoints in the nonclinical program should consider the potential effects of the transgene product's mechanism of action on the core physiological functions (i.e. cardiovascular, respiratory and central nervous system). In some cases, biodistribution may contribute to effects on specific physiologic systems and should be evaluated. Safety pharmacology endpoints may be combined with single-dose toxicity and biodistribution studies, if needed."	

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990-991		**Comment:** The definition of 'persistence' is needed. **Proposed Change:** "Pharmacokinetic studies should focus on the distribution, persistence (defined as the continued presence of genetic sequences in the host after acute exposure to a transfecting agent, whether due to integration of the genetic sequence into the host genome or to latent infection with the viral vector bearing the genetic sequence), clearance and mobilization of the GTMP and should address the risk of germline transmission."	
1002-1004		**Comment:** It is extremely limiting to state in a guideline that only one form of detection could be applied here. This also does not align with the principles of 3Rs, as nucleic acid amplification technology assays (NATs) could only be performed on tissues from sacrificed animals. As such, BIO recommends language be added to include use of other assays such as imaging or new technologies. This would be more in line with the 3Rs. **Proposed Change:** "For pharmacokinetic studies ~~only~~, validated nucleic acid amplification technology (NAT) assays have been ~~should be~~ used to investigate tissue distribution and persistence of the GTMP. Applicants should justify the selection of this or other assays and their specificity and sensitivity."	
1005		**Comment:** In FDA's 2015 "Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products", a number of considerations were listed that helped Sponsors determine whether biodistribution needed to be performed and if so, to what extent.	

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		Proposed Change: BIO recommends adding a similar section to this guideline.	
1007-1008		**Comment:** The ability to determine a safety margin of 10-fold for GTMP is not always feasible or possible given certain limitations such as volume of delivery restrictions and product concentration limitations. Please clarify that this is not the anticipated expectation of Sponsor companies. Additionally, it would be helpful to mention considerations that could help Sponsors determine whether biodistribution studies need to be performed and if so, to what extent. **Proposed Change:** "The dosing used for biodistribution studies should mimic the clinical use with appropriate safety margins~~, e.g., 10-fold the clinical dose~~ adjusted to the animal model used. Sponsors can leverage existing biodistribution data from the same vector but with a different transgene."	
1012-1013		**Proposed Change:** "Intravenous administration of the GTMP resulting in maximal systemic exposure may be included in the biodistribution studies as a worst-case-scenario. Depending on the nature of the GTMP, additional groups may be treated using a route of administration other than the proposed clinical route to assess the effect of widespread dissemination of the GTMP."	
1014-1018		**Comment:** BIO questions whether interim timepoints are necessary for biodistribution studies. The main aim of these studies is to demonstrate persistence or absence of persistence of vector. Multiple timepoints would potentially add significantly to animal numbers without adding value in terms of	

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		demonstration of persistence.	
1029		**Proposed Change:** BIO proposes changing the section header from "Genomic intended-integration" to "Intended genomic integration" for better clarity.	
1029-1032		**Comment:** The need for genomic intended integration studies should be based upon potential risk. As certain vectors do not have the ability to integrate or reactivate following latency genomic intended integration studies would not yield any additional data to identify/indicate a possible risk and therefore they should not be required. **Proposed Change:** "Plasmids, poxvirus, adenovirus, and adeno-associated virus-based vectors (AAV) are vectors that do not have a propensity to integrate or reactivate following latency, and in the absence of evidence to the contrary, present a low risk of gene therapy-related adverse events. Therefore, genomic integration studies are not warranted. In the cases where the whole vector (e.g. retroviruses or lentiviruses) or part of it (e.g. chimeric vectors with retroviral/lentiviral portions) is intended for integration in the host genome, this feature of the vector should be studied by integration studies (ex vivo tissue culture or in vivo)."	
1036-1037		**Comment:** It is unclear what is intended by "The spatial distribution can be studied also locally after injection into solid tissues." Is this for products that are intended to be injected into solid organs? Does spatial distribution here refer to	

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		within the organ or spread from the organ?	
1044-1045		**Comment:** It is unclear whether this is referring to the probability of targeted integration or off-target integration occurring.	
1051-1065		**Comment:** BIO believes that this discussion seems more appropriate in Sections on genotoxicity and tumorigenicity (5.5.2 and 5.5.3).	
1052-1053		**Comment:** The use of the word variety here suggests that multiple cell lines are required. It is unclear if this is actually the case.	
1056-1057		**Comment:** This is unclear and also not aligned with lines 1064-1065. **Proposed Change:** BIO recommends editing for clarity and alignment within the guideline. "When dealing with non-integrating vectors, applicants should investigate the potential for ~~if~~ unintended integration on a case by case basis ~~is occurring~~."	
1074-1087		**Comment:** Shedding is performed as part of clinical studies to understand the risk to both third parties as well as the environment. For non-replicating vectors that are non-infectious, the initial clinical data in the clinic should be sufficient to characterise the risk without the need for additional nonclinical studies, as it will supersede the nonclinical data. **Proposed Change:** "Shedding is defined as the dissemination of vector/virus through secretions and/or excreta and should be addressed in animal models. While	

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		shedding should not be confused with biodistribution (i.e. spread Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products EMA/CAT/80183/2014 Page 30/42 within the body from the site of administration), it is advised to integrate shedding studies into the design of biodistribution studies or other non-clinical studies, when feasible. Sponsor companies should consider shedding studies on a case-by-case basis depending on a number of factors including, but not limited to, planned route of administration, dose level and level of vector modification. For non-replicating vectors (e.g. Plasmids, poxvirus, adenovirus, and adeno-associated virus-based vectors (AAV)), shedding studies are not required."	
1079-1081		**Comment:** The translation of the preclinical shedding to humans is unclear. We suggest clarifying text after line 1081. **Proposed Change:** "For non-replicating vectors, sponsors should consider shedding analysis on a case by case basis depending on route of administration, vector modification, animal model, trophism alteration, etc."	
1081-1082		**Comment:** The need and timing for completion of shedding studies should be dependent upon the ability of the vector to replicate and its risk of potential viral infection following administration. **Proposed Change:** "For replicating vectors it is recommended to address shedding in non-clinical studies early in development. For non-replicating vectors non-clinical shedding studies should be conducted prior to filing a marketing authorization	

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		application. Non-infective vectors without significant systemic biodistribution following direct administration within a contained anatomical structure (e.g. direct administration to the eye or intraparenchymal brain administration) present no potential safety risk to non-target organs of patients or to the environment and therefore shedding studies are not required."	
1096		**Comment:** BIO suggests reiterating that the toxicology studies should only be conducted in species where the GMTP is biologically active and tissue distribution mimics the predicted profile in humans.	
1104-1105		**Comment:** BIO questions why the guideline points out "intravenous" as a worst-case scenario of exposure. In some cases, other routes, (*e.g.* intracerebroventricular (ICV)) might be the worst-case scenario. **Proposed Change:** "Depending on the nature of the GTMP, additional groups may additionally be treated ~~intravenously~~ by other routes as "worst case" scenario representing the effect of widespread dissemination of the GTMP."	
1110-1111		**Comment:** BIO suggests providing examples of instances in which extended follow-up might be required, and what criteria would be used to evaluate the relative appropriateness of proposed longer term follow-up studies. **Proposed Change:** "For GTMPs intended for single administration, the post-dose observation period in single dose toxicology studies ~~with an appropriate extended post-dose observation period shall be performed~~ should focus on peak expression time for acute and sub-acute toxicities for initiation of clinical trials. Longer term	

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		follow-up may be appropriate in some instances."	
1114		**Comment:** Interim timepoints can be evaluated through blood sample analysis. **Proposed Change:** "Inclusion of interim groups to be ~~sacrificed~~ evaluated at peak levels of biodisribution should be considered."	
1116-1117		**Comment:** BIO suggests editing the text for clarity. **Proposed Change:** "Per existing ICH nonclinical guidance, ~~Single~~ single dose toxicity studies for GTMPs should not be designed as acute toxicity studies with an endpoint of lethality ~~since the final endpoint should not be animal death~~."	
1128-1129		**Comment:** Whether to conduct DART studies could logically be assessed using previous nonclinical and clinical data. **Proposed Change:** "~~Studies on the effects on fertility and general reproductive function shall be provided according to ICH S5 (R2).~~ The potential for reproductive/developmental toxicity may need to be addressed depending on the product type, transgene mechanism of action, distribution and shedding profile and patient population. Studies on the effects on fertility and general reproductive function should be considered on a case by case basis using ICH S5 (R2) as a guide."	
1143		**Comment:** This whole section (5.5.2.1 Overall Safety Considerations) appears to	

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		be redundant to the genomic integration section in 5.4.1	
1163-1170		**Comment:** The first two paragraphs of Section 5.5.2.2 Vector-Specific Consideration, seem to be at odds with each other. The first seems to clearly state that insertion site analysis should be analysed for all vector types ("should be investigated"), while the second leaves the possibility more open depending on delivery. **Proposed Change:** BIO asks EMA to clarify - similar to Section 5.4.1 - whether the guideline is stating that insertion site analysis is required for adenoviral and adeno-associated viral vectors.	
1197-1201		**Comment:** The first two bullets overlap. BIO suggests they are combined for clarity. **Proposed Change:** "1. Knowledge of intended drug target and pathway related mechanistic/pharmacologic and known secondary pharmacologic characteristics relevant for the outcome of tumourogenicity studies and the prediction of potential human oncogenes pharmacology (e.g. issues with growth factor transgene)."	
1227-1240		**Comment:** It would be helpful to clarify that reproductive and developmental toxicity studies are not required for GTMPs that require use of full myeloablation prior to administration, such as for certain genetically modified hematopoietic stem cells. Additionally, the EMA anticipated timeline for conduction of such studies in relation to the overall development program should be provided.	

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		Proposed Change: "If required, studies on the effects on fertility and general reproductive function shall be conducted in accordance to ICH S5 (R2) with results available at the time of the MAA filing.	
1228-1229		**Comment:** The language on fertility should be the same as below in line 1236 for embryo-fetal and perinatal toxicity studies - "unless otherwise duly justified". **Proposed Change:** "Studies on the effects on fertility and general reproductive function shall be provided according to ICH1229 S5 (R2) unless otherwise duly justified in the application on the basis of the type of product concerned."	
1256		**Comment:** The guideline does not discuss how to justify the proposed dose or dosing regimen to include in the summaries of product characteristics for the MAA. If this is included in other guidelines, cross referencing would be useful.	
1285-1286		**Comment:** Long term monitoring of patients treated with a GTMP would benefit from a more precise timeline based on the type of vector used. **Proposed Change:** "Long term monitoring (1 year for non-viral therapies and adenoassociated-virus– based therapies, 2 years for adenovirus based therapies, 5 years for lentivirus or retrovirus based therapies) of patients treated with a GTMP is of particular importance, given also the legal requirement of long term efficacy and safety follow up (according to (EC) Regulation No 1394/2007)."	
1337-1338		**Comment:** There has never been any report or publication of a vertical transmission of a non retrovirus-based vector. The request for two means of contraception is therefore not justified for therapies not using vectors with a	

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		potential for integration. **Proposed Change:** "When there is a risk of shedding through the seminal fluid and the GTMP is a retrovirus-based vector, at least two means of contraception~~—including barrier contraception~~ should be recommended. Other GTMP will require one mean of contraception."	