15 June 2012
EMA/CAT/GTWP/155212/2011
Committee for Advanced Therapies (CAT)

Overview of comments received on 'Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells'

(EMA/CHMP/ GTWP/ 671639/2008)

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

Stakeholder no.	Name of organisation or individual
1	ActoGeniX N.V.
2	Clinigene EC-FP6 Network of Excellence for the Advancement of Clinical Gene Transfer and Therapy
3	Regulatory Research Party (RRG) of the Association for Cancer Immunotherapy (CIMT)

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
1.	**COMMENT #1:** ActoGeniX N.V. (AGX) welcomes the EMA's undertakings with regards to setting scientific guidance on standards to reach for sponsors wishing to build clinical trials applications (CTA) for investigational medicinal products (IMP) containing genetically modified organisms (GMO) cells. In view of the specificity of AGX' technology (i.e.; genetically modified (GM) *L. lactis* (non-commensal, non-colonising lactic acid bacteria) intended to synthetise and secrete therapeutic protein(s), and neither the GM bacteria nor the expressed proteins(s) enter the systemic circulation), one may wonder whether Genetically Modified bacteria may fall within the Scope of this Guideline. Since no such insurance is provided to AGX, AGX has undertaken commenting on this guideline as if reference to bacterial GMOs will be made for the next versions of this document. Hereby, AGX wishes to bring the experience gained with its technology platform to the comments made for this guideline. AGX foremost major comment is that reference to such GMO investigational medicinal product (GMO-IMP) should either be made throughout the document as appropriate or in a specific section. A special focus on the bacteria should highlight the specificity of the strategy. AGX does not intend to refer to bacteria entering systemic circulation such as those developed by other companies).	GTWP would like to thank AGX for their comments, and for sharing their views on medicinal products containing genetically modified bacteria. GTWP would like to clarify that this guideline is aimed at GTMP containing human and animal cells (ref: scope, lines 77-77). Therefore, bacterial cells are out of the scope of the guideline. However, AGX comments are valuable for the current revision of the "Note for Guidance on quality, preclinical, clinical aspects of gene transfer medicinal products", and will be given due attention by the GTWP. GTWP would like to clarify that this guideline aimes at MAA level. Investigational GTMP are out of the scope of this guideline.

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	Furthermore, in order to best support its position, AGX wishes to share its experience with EMA by providing the IMPD of a completed Phase 2a study (Protocol AG011-MDUC-201 EudraCT n° 2008-000967-40) which was approved by 3 EU-Competent Authorities (i.e.; Belgium, The Netherlands and Sweden).	GTWP welcomes the possibility to share the IMPD.
1	**COMMENT #2** While AGX welcomes EMA's proposal for requirements for quality information on GMO-IMP, AGX would have hoped that the document be the setting stage for a comprehensive roadmap on the amount of quality-related information to be generated and presented to support the different stages of development of a GMO-IMP. Such document would not deter the need for Scientific Advices as relevant. While acknowledging the incremental gain of knowledge in the quality aspects of the GMO-IMP during its development, such document would have been a landmark opportunity to address the means by which reporting to the regulatory stakeholders (i.e.; EU-MS NCA/EC and others) of such information should be organised within the context of the other development aspects (i.e.; safety, efficacy) in order to better serve the community (i.e.; participating subjects, regulatory stakeholders (NCA/EC/others), drug development community, sponsors). A good example lies with the concept of 5.2.5. Process Validation and issues related to viral contamination (comment page 7-8/16 related to different	As stated above, investigational GTMP are out of the scope of this guideline, which is limited to MAA level.

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	lines 200-221 and lines 146-161 respectively). Such incremental approaches are proposed by other regulatory bodies (i.e.; FDA (+) which combines these requirements along with those set by the ""Dear Gene Therapy IND or Master File Sponsor Letter point 5" http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm105882.htm" see with a special emphasis on section 5. : EMA comment: In the original comments the document found in the above link was copied in as PDF file and has been taken out for technical reasons. (+) See presentation on "The FDA Phase 1 GMP Guidance" http://www.bcg-usa.com/regulatory/docs/FDA_Presentations_Publications/SP8B06.pdf AND Guidance for Industry INDs — Approaches to Complying with CGMP During Phase 1 - January 2006 http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070273.pdf The latter guidance clearly addresses Gene Therapy products in its scope (p. 7/20) EMA comment: In the original comments the document found in the above link was copied in as PDF file and has been taken out for technical reasons. Guidance for Industry Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-	GTWP would like to remark that comparison with FDA holds only at MAA, because EMA has no remit on approval of clinical trials, while FDA does.

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	Characterized, Therapeutic, Biotechnology-derived Products http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071597.pdf	
2. An important foreword: architecture of the guideline	The CliniGene-NoE has communicated critical remarks on the concept paper preceeding this Guideline (GDL) currently open for comments, with the same title. Without any intent for provocation and according to our former contribution, this guideline was not believed to be relevant, which can be justified as follows: In fact, this GM-cells GDL does not provide any new concept or point to consider and is likely to be confusing. This is because it surprisingly covers within the same alinea, in many instances, both the end-product intended to reach the patient (following ex-vivo gene-manipulation) and the biotechnology cell-factory, intended for vector-production (VPCs: Vector Producing Cells). In our view, such an assimilation is likely to preclude the appropriate vision of this complicated hi-tech field, both in terms of regulatory requirements on the one hand and of marketing authorisation on the other: how can one compare the own endogenous patient's genetically modified cell intended for re-infusion and the GM cell-line used to release vectors, intended for the genetic modification of the former ? In addtion, the summary (now only three lines if correctly understood) should include the most relevant and most important new aspects compared to previous regulations, directories and guidelines referred to. Much of the information is redundant and cumbersome to read considering the reference	GTWP would like to thank Clinigene –NoE for their comments and criticisms. GTWP has already taken on board some of them and has started to work on a tool to help stakeholders in navigating among the guidelines. This comment is not accepted. The guideline does not mention VPC at all, because they are not in the scope of the guideline. In fact VPC are GTMP only if they are used in vivo, i.e. in the patient, in which case they are not “biotechnology cell-factory” but a medicinal product, and as such would fall under the scope of this guideline. This comment is accepted: the executive summary will be made more informative on the content of the guideline.

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	to eleven other documents.	
2. **The reference should be the Note for Guidance**	The CliniGene-NoE has always viewed the so-called "mother" GT-NfG as THE major one, internationally recognised as a reference. In providing comments to what we believe to be minor documents, the CliniGene-NoE has systematically quoted that the GT-NfG is: **(i)** user-friendly and comprehensive **(ii)** adequately organised: the overall hierarchy ought to be maintained **(iii)** cross-indexed from one section to the next: a feature which makes it both accurate and user-friendly **(iv)** so far, there has been no essential issue found to be missing in this mother GT-NfG document when proceeding to side to side comparison with additional minor guidelines, which overall organisation and architecture was missing to follow the GT-NfG's.	GTWP would like to thank Clinigene-NoE for the positive comment.
2. **Scope of the guideline: the biotech cell-factory (VPCs) versus personalised medicine**	It is recognized that the guideline is primary aimed at defining the requirements for product quality and to guide on non-clinical and clinical issues related to market authorization application. In many aspects, VPCs and GT vectors obtained from them, are likely to fit the scheme of biotechnology products, whether concerning their: (i) GMP manufacture; (ii) the necessary QA-QC; (iii) cryopreservation; (iv) potential shipment; (v) attempts toward standardisation and (vi) ultimately commercialisation which will address a group of patients. Conversely, the own patient's endogenous genetically modified cells follow a distinct rationale which essentially relates to personalised medicine. While this ex-vivo GM cells based treatments need to be prepared according to the	GTWP agrees on this view. As stated above. VPC are out of the scope of guideline. This comment is not accepted. A discussion on GMP requirements for production of

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	best quality and safety standards [*which need to be more precisely established as experience will grow but are quite similar to provisions implemented as GLP for Bone marrow transplantation (BMT), or alternatives such as PBMCs or Cord Blood*], it does not fit the usual scheme for GMP production; nor a clear rationale toward marketing authorisation and commercialisation, as a product derived from a single patient and intended to be re-injected to the same recipient after genetic modification. In addition and in some instances, those GM-cells are believed to be too fragile to sustain cryopreservation and are thus intended to be re-infused shortly after their take and subsequent manipulation. There will be attempts at rationalising personalised medicine to a group of matched HLA-recipients from banked HLA-compatible (stem) cells; but we are not there yet. So, when addressing primary ex-vivo GM (stem) cells this guideline is mostly pertaining to each patient's GM cells. A requirement for GMP at this stage of the procedure is surprising, while it is not deemed necessary for BMT.	genetically modified cells is not in the scope of this guideline.
2. **First-in-Human versus marketing authorisation stage**	However, since principles may apply also to products at earlier development stages, we believe helpful if guidance is given to manufacturers providing more details on expected requirements at different developmental stages. Areas of process and analytical method validation could be of particular interest and information on the expected extent of validation in the course of product development would better guide manufacturers during product development. Critical features of products or processes involving the use of integrating vectors like transduction efficiency, transgene expression, MOI or VCN are required to be justified or related to clinical efficacy data. However, since the principles of the guideline may also apply to products under development,	This comment is not accepted. As stated above, investigational GTMP are out of the scope of this guideline. This comment is not accepted Since the guideline is aimed at MAA level, reference to clinical data is considered appropriate.

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	we believe appropriate referring not only to clinical results, but also to proof of principle, non clinical data. This is particularly relevant for those products which have never been administered in humans beforehand [First-in-Human (FIH)]. Some of the requirements may simply not be feasible. This may preclude promising therapies for patients who are in urgent need of novel therapies.	
2. **In summary**	1. According to the "Guideline on human cell-based medicinal products" these products are heterogeneous with regard to origin and type of cells. Cells may be self-renewing stem cells, more committed progenitor cells or terminally differentiated cells exerting a specific defined physiological function. Cells may be of autologous or allogeneic origin. In addition, the cells may also be modified genetically. This guideline (EMA/CHMP/GTWP/671639/2008) refers to all genetically modified cell-products. 0ur suggestion is to separate these requirements according to the different types of ATMPs, e.g. gene therapy medicinal products, somatic cell therapy products and tissue engineered products and the VPCs biotechnology-related cell-factory. 2. The guideline refers to a lot of other guidelines. This makes it not user-friendly nor likely to have the reader understand the content of the guideline. 3. Therefore we come back to our suggestion to prepare one guideline for the whole development of e.g. gene therapy medicinal products in taking advantage of the ongoing revision of the NfG. With this last suggestion, indeed the effort and time would be invested in building up a document likely to represent an international reference and help support innovation-based initiatives in providing user-friendly guidance.	This comment is not accepted. 1) This guideline is focussed on genetically modified cells, whatever the classification is 2) as stated above, a navigating tool is in preparation 3) GTWP does not share the view that such a wholly comprehensive document will be user-friendly.

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	The CliniGene-NoE is prepared to provide help in consolidating a comprehensive GT-Note for Guidance but rather not going on commenting documents which miss: (i) a general structure in keeping with the specifics of GT-ATMPs; (ii) a cross-indexation and (iii) sends the user back to an additional set of over 13 other guidance documents which are mostly redundant and do not follow a similar structure.	
3.	The content of the guideline will have to be harmonized with the Pharmacopoeia Europea.	GTWP would like to thank RRG for their comments. This comment is accepted, the content of the guideline will be checked for consistency with E.P.5.14.

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)*
59-67 AND 61	1.	Comment: This non exhaustive list of examples does not contain any reference to AGX' products such as but not limited "genetically modified bacteria (i.e.; lactic acid bacteria)". The examples of this list are part of the EMA-CAT's ATMP classification procedure as follows "products consisting of prokaryotic cells (bacteria), genetically modified to contain a recombinant nucleic acid, which express the product (protein) encoded by the inserted genetic sequence using the secretion machinery of the modified prokaryotic cells." Proposed change (if any): - genetically modified prokaryotic cells for in situ, local, non-systemic delivery of therapeutic proteins, allergens or antigens or combinations thereof (i.e.; Genetically modified *Lactococcus lactis* secreting human interleukin-10, intended for the treatment of inflammatory bowel disease.)	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria. The scope is limited to human and animal cells.
61	2.	Comment: Genetically modified cells for treatment of monogenic diseases. To better define the scope of application, this paragraph should exclude certain types of genetically-modified cells i.e. virus packaging	This comment is accepted. Scope can be better clarified.

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		cells for manufacture, which should be constrained to additional controls in terms of viral safety and stability. In addition, and although iPS cells have been considered in separate reflection paper, issues pertaining to their genetic manipulation need to be taken into account. Proposed change (if any): Genetically modified stem cells for treatment of monogenic diseases.	GTWP believes that such issues are discussed in the guideline (e.g. see par 5.2.3 lines 190-194). Proposed change is not accepted.
67-68	1	Comment: AGX thinks that considerations with regard to: • The summary or local expected action, • The persistence of the GMO, • The genetic material transfer. should be addressed in the proposed guideline. Proposed change (if any):	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.
76-77 The genetically modified cells can be of human origin (autologous or allogeneic) or animal origin (xenogeneic cells), either primary or established cell lines.	1	Comment: With reference to AGX's general comment, it would be worthwhile adding bacteria as origin of GMOs. Proposed change (if any): (Proposed insert and grammatical alignment: "of…") The genetically modified cells can be of human origin (autologous or allogeneic) or of animal origin (xenogeneic cells), either primary or	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells. Proposed change is not accepted.

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		established cell lines or of bacterial origin.	
89 onwards **4. Introduction** AND all other relevant sections of the document	1	Comment: AGX considers that reference to GMO bacteria intended to secrete therapeutic proteins should also be made in the introduction and as relevant throughout the document. A special focus on the bacteria should highlight the specificity of the strategy. Proposed change (if any):	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.
90 For the purpose of this guideline, human and xenogeneic cells and tissues are referred to as “cells”.	1	Comment: In line with the general comment, please add reference to the bacterial origin of the cells Proposed change (if any): For the purpose of this guideline, human, xenogeneic and bacterial cells and tissues are referred to as “cells”.	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells. Proposed change is not accepted.
90	2	Comment: In this introduction, there is a full confusion between the end-products intended as a therapy and the biotech cell-factory intended as a by-substrate to manufacture the vector to be used toward the GM of the latter. Proposed change (if any): Clarify and rather change the architecture of the GDL and best consolidate all aspects of GT into a single	As stated above, VPC are not in the scope of guideline *per se*, but only if they are a medicinal product. Clarification will be made; the wording “VPC” will not be used in order to avoid

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		comprehensive GDL.	misunderstanding.
93-97 (4) the genetically modified cells are further processed, formulated and stored. AND Lines 122-145	1	Comment: AGX considers that the following step in the sequence proposed should be added “x) bacteria are purified through “reinculture”. As a matter of fact, AGX has developed the following strategy leading to the establishment of the Master Cell Banks which would subsequently be considered as Starting Material: • AGX internal laboratory work in order to 1/ genetically modify the MG1363 strain with the right chromosomal gene modification, 2/ isolate, and 3/ characterise the GM strain of interest (see section 2.1.S.1. General Information and more specifically under section 2.1.S.1.2. Structure (p. 23-35) and specific reports are available upon request. • Upon selection of the appropriate GM strain, AGX sends samples to Henogen for the establishment of the Master Cell Bank (MCB) as described in the IMPD section 2.1.S.2.1. Manufacturer(s) and 2.1.S.2.2.a. Cell banking: Master cell bank (MCB) p. 38 and p. 42-44 respectively. • Reports related to these steps are available upon request. Therefore, AGX’ approach is closer to the “traditional” biotechnology manufacturing strategies and departs form the the definition of starting material as proposed by the guideline in lines 122-145 with an emphasis on line 124.	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.
93-97 (4) the genetically modified cells are further processed, formulated and stored.		Proposed change (if any): The following steps are usually carried out to transfer genes into cells *ex vivo*: (1) cells are selected or isolated from a suitable donor (either human or animal) or sourced from a bank of primary cells or tissues	Change not accepted.

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AND Lines 122-145		(2) cells are prepared for gene transfer, e.g. by expansion in culture; (3) the target gene in a suitable vector is transferred into the cells; (4) bacteria are purified through "reinculture" (i.e. passage over a single colony stage) (5) the genetically modified cells are further processed, formulated and stored.	
98-105	1	Comment: AGX would like to highlight that taking its technology platform [(@)] as an example, none of the guidelines referred to in the introduction section address the following case: "no-genetic transfer" from the genetically engineered product. Therefore, AGX calls for the EMA's experts to introduce an option for gaining waivers to the existing guidelines. AGX wishes the EMA to explain in this document whether or not these waivers are obtained automatically or granted upon an appropriate plan is discussed/approved during specific Scientific Advices. [(@)] Which does not intend to transfer the genomically inserted gene coding for the therapeutic protein of interest from the bacteria (i.e.; prokaryote) to the recipient (i.e.; eukaryote) Proposed change (if any):	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells. GTWP would like to remark that GTMP definition as in Dir 120/2009 does not explicitly require such transfer to occur.
106-107	1	Comment: AGX considers that the risk assessment should also be expanded to the concepts developed in • Directive 2001/18/EC of the European Parliament and of the	Comment not accepted. The risk based approach referred to in the guideline is different from the environmental risk

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		Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. http://europa.eu/legislation_summaries/agriculture/food/l28130_en.htm • Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms http://europa.eu/legislation_summaries/other/l21157_en.htm • Aamending acts and national EU-member states specific legislations (if any – to be checked for by the EMA's experts) thereof. AGX refers to the Directive 2001/18/EC since its products are to be used in ambulatory treatment setting (i.e.; patients taking the products back home for treatment upon the schedule set forth in the clinical study protocol) Proposed change (if any): A risk analysis which may cover the entire development should be carried out according to part IV of the Annex I to Directive 2001/83/EC, Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC, Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms, their respective amending acts and national EU-member states specific legislations thereof.	assessment for GMO/ GMMO. Change not accepted.

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107-110	2	Comment: 107-110 and 114 – 118 are fully redundant Proposed change (if any): Consolidate.	Point taken. Lines 114-118 can be deleted.
114-118	2	Comment: The Concept paper "Development of a guideline on the risk-based approach according to annex I, part IV of directive 2001/83/EC applied to advanced therapy medicinal products" should be mentioned or even better the main requirements should be specified or even better all items under consideration consolidated in one unique guideline. The risk evaluation of the medicinal product should be placed under the responsibility of the manufacturer. The list of risks provided in this guideline can only be seen as examples. Proposed change (if any):	This comment is accepted. Reference to RBA can be made.
120-312 5. Quality Aspects	1	With regards to the section "5.Quality Aspects", AGX wishes to share its experience with EMA by providing the IMPD of a completed Phase 2a study (Protocol AG011-MDUC-201 EudraCT n° 2008-000967-40) which was approved by 3 EU-Competent Authorities (i.e.; Belgium, The Netherlands and Sweden).	As state above, bacterial cells are out of scope. Comment not accepted.
124	2	Comment: the end-product intended to reach the patient (following ex-vivo gene-manipulation) and the biotechnology cell-factory, intended for vector-production (VPCs: Vector Producing Cells) need to be distinguished as they are essentially different both in: **(i) nature**: one is a primary patient's autologous cells; the other a cell-line and	As stated above, VPC are not in the scope of the guideline. Comment is not accepted.

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		(ii) fate: one is meant to survive long-term into the body of the patient; the other shall be fully validated through biotech process, banked and eventually trashed after use. Proposed change (if any): Clarify and rather change the architecture of the GDL and best consolidate all aspects of GT into a single comprehensive GDL.	Change not accepted.
124 1) the cells to be genetically modified, AND Lines 93-97 124 1) the cells to be	1	Comment: AGX would like that a specific case for the bacterial origin GMO is made by the EMA. AGX understands that, according to the proposed guideline, this would mean that *L. lactis* MG1363 would be a starting material. Whereas, per AGX' point of view, the starting material should be the master cell bank (MCB) of genetically modified (GM) bacteria resulting from the combination of the non-GM strain with the intended insert. (See relevant sections of the IMPD section 2.1.S.2.1. Manufacturer(s) and 2.1.S.2.2.a. Cell banking: Master cell bank (MCB) p. 38 and p. 42-44 respectively.) Currently, AGX sets a full characterisation of the MCB to ensure that the expected characteristics are present. AGX would be happy to meet with EMA's experts in order to address all scientific concerns that might be expressed in order to have the GM bacterial strain set as starting material. Furthermore, AGX confirms that its position is in line with the definition of starting material in cGMP guidance GM strain cell bank (MCB) as a starting material as set forth by: • GMP Eudralex Part II, section 18 Specific Guidance for APIs	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.

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genetically modified, AND Lines 93-97		Manufactured by Cell Culture/Fermentation with special emphasis on section 18.2 Cell Bank Maintenance and Record Keeping http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm • EU-GMP Annex 2 Manufacture of Biological Medicinal Products for Human Use http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/anx02en200408_en.pdf • ICH Guideline Q5D Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products for a more complete discussion of cell banking. http://www.ich.org/cache/compo/363-272-1.html#Q5D Proposed change (if any):	
126-131	2	Comment: The CTD was once developed for new chemical substances / medicinal products. Now it is effective for all kinds of medicinal products. Even the new group of ATMPs should be characterized according to the CTD format. The CTD format does not match the special character of ATMPs. Therefore our suggestion is to revise the CTD according to gene therapy medicinal products and cell therapy medicinal products. In this connection the IMPD should also be revised. Proposed change (if any):	The proposal is acknowledged. However, CTD is an ICH document, that is internationally agreed upon, and changing it is not in the remit of GTWP.
126-131	2	Comment: It is doubtful that this will be feasible for every cell therapy	The section referred to deals with

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		product. Concerning vectors this may apply; but is it doable for every supplement to culture media etc.? Proposed change (if any):	starting materials, i.e. those substances that end up into the final product. Thus supplements of culture media are not in the scope of this paragraph. Guidance concerning culture media and other raw materials for cell therapy products can be found in the Guideline on human cell-based medicinal products (CHMP/410869/06).
130-131 130-131	1	Comment: With regards to *"Vector characterisation and control data should be included in the Common Technical Document (CTD), either when the vector is internally produced or is supplied by another manufacturer"*, AGX wishes to highlight that due to its technology platform (i.e.; GM bacteria are not designed to deliver gene(s) but secrete therapeutic proteins) this concept does not apply. Alternatively, AGX confirms that both the genetic sequencing of both the insert and the full GM bacteria is performed to ensure identity to the predicted genomes. AGX hopes that EMA would adapt the text accordingly in the text of the guideline. Hereby, AGX confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.
132-140	1	Comment:	As stated in the general part, AGX

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		The whole section related to *"The type of delivery vector or vehicle used for ex vivo genetic modification should be justified based on the target cells, the clinical indication and other considerations."* Is not relevant for AGX' technology. AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline. Hereby, AGX confirms to be happy to further interact with EMA to best adapt the information in this proposed guideline. Proposed change (if any):	comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.
136-137	2	Comment: Packaging cell lines are stable virus producer cells: there is a contradiction as transient production is not obtained from packaging cells but instead from "producer" cell lines. Proposed change (if any): vectors from "producer" cell lines	This comment is accepted. Change accepted.
141-145	1	Comment: In addition to the fact that *"Prior to its use, the transfer vector should be shown to be free from any unwanted viral contamination, …"*, AGX considers that; in view of the features of its technology; the text should add that for GM bacteria, these, should be "free of vector used" to alter their genome. AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.

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)*
143-145	2	Comment: Again, confusion between primary cells to be re-infused into the patient and biotech cell-factory Proposed change (if any): unpurified vectors cannot be used on primary cells to be reinfused	This comment is not accepted: Cells intended for production of vectors are not within the scope of this section (starting materials), as they do not form part of the final product. Change not accepted.
147-149	2	Comment: " among other controls", is quite indefinite. "Other controls" should be more clearly defined. Proposed change (if any):	This comment is not accepted: The list is not exhaustive, as the requirements depend on each particular product. For further guidance, see GL on human cell-based medicinal products (CHMP/410869/06).
154-155	2	Comment: the reference of the guidelines is missing Proposed change (if any):	Both references can be found at the end of the GL.
146-161 5.1.2. Other materials, reagents and excipients	1	Comment: With regards to this specific section, AGX wishes to confirm that • The products under development are not of parenteral use, • Neither the GM bacteria nor the expressed proteins are expected to have systemic exposure, • Selected GM bacterial strains are purified over single culture before being sent to Henogen in order to establish the MCB, • At Henogen, the culture received from AGX is streaked three times to single colonies on vegetable-based agar plates. Thereby reducing the BSE/TSE risk.	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.

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)*
146-161 5.1.2. Other materials, reagents and excipients		• Moreover, AGX' best knowledge, *L. lactis* is not a carrier of human pathogen viruses, • The GMP principles apply to the manufacturing process starting from MCB to finished product and Section 2.1.S.2.3. Control of Materials (p. 53 of the IMPD) confirms that "No materials of human or animal origin are used during manufacture (TSE-free agents).". All these reasons advocate for an extremely low to no risk for either BSE/TSE or adventitious agents contamination. (see General Comment #2 with emphasis on information related to "Dear Gene Therapy IND or Master File Sponsor Letter point 5" http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm105882.htm) Finally, AGX has developed the following rational for its approved IMPD under section 2.1.S.3.2. Impurities (p. 69) and 2.1.P.5.5. Charactersation of impurities for capsules and enema (p. 168 and p. 179 respectively) and wishes to share it with EMA in order to adapt the section to GM bacteria. Proposed change (if any): Line 155: Add "The appropriate panel of testing should be applied to GM bacteria that are purified through reinculture subsequent to genetic modification"	Change not accepted.

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)*
170	2	Comment: Again, the genetic modification of primary cells to be re-infused into the patient cannot be merged with cell-lines engineering toward bioprocess as cell-factories. Proposed change (if any): reconsider architecture and concepts according to cells nature and fate (trash and re-infusion into the patients are essentially different)	Please see the comments above. Change not accepted.
170-181 5.2.2. Gene Transfer	1	Comment: Based on AGX' technology platform, this section is not deemed relevant to GM bacteria secreting therapeutic proteins and which are not designed to transfer genes to the recipients' genome (i.e.; human or animal). As a matter of fact, AGX considers that for GM bacteria, especially where chromosomal insertion is performed outside of mobile genetic elements, the risk of transfer is unlikely. Therefore, AGX hopes its proposal is reflected upon in the final version drawn up by EMA and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.
180-181	2	Comment: For First In Human (FIH) trials in which non-clinical data are available only, transduction conditions, namely multiplicity of infection, could be defined on the basis of non-clinical, proof of principle studies. Proposed change (if any): When using integrating vectors (e.g. LV	This comment is not accepted. Investigational GTMP are out of the scope of the guideline.

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)*
		and RV), multiplicity of infection should be kept at the minimum shown to be effective by transduction efficiency studies and non-clinical and/or clinical studies.	Change not accepted.
186	2	Comment: for the further manufacturing steps, the cryopreservation step should be specifically added. Proposed change (if any): cryopreservation requires specifications on the cryopreservative solutions, need of appropriate procedures, controls. Blood bank standards might usefully be referenced	This comment is not acceptable. Cryopreservation issues are not different from the storage issues for other GTMP or for non gm cells products. Change not accepted. Blood banks standards may not be relevant for cells derived from other tissues.
198-199	2	Comment: It is not clear, in the context of the in process controls section, whether the definition of intermediate is referred to production intermediates (e.g. primary cells stocked/on hold at specific stages of production) or to in line process samples for in process controls. Proposed change (if any):	This comment is not accepted. In the regulatory terminology, intermediates refer to drug substance/product intermediates which are under manufacturing but not yet the final DS or DP.
201-220	2	Comment: the product life cycle starts with the development, goes on with the transfer into commercial manufacturing and ends with the discontinuation of manufacturing the medicinal product. In the development phase and with the initiation of clinical trials such as FIH, there may be a lack of full process validation, which in fact might not be entirely required at this point. This assumption together with the requirements for IMPDs in particular should also be mentioned in	Comment not accepted: Investigational GTMP are not within the scope of this document.

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		this paragraph (Eudralex, Vol. 4, Annex 13).	
201-202	2	Comment: "An acceptable number of consecutive production runs should be performed in order to validate the production process and to ensure consistency of the product." : How can this be implemented in practice other than with test cells or cell-lines ? this paragraph is likely to more specifically apply to the cell-factory Proposed change (if any):	This comment is not accepted. Process validation is a prerequisite for commercial manufacture of all medicinal products. In case autologous cells are transduced, the validation process can be performed also with other available, similar cells. See lines 215-217.
203	2	Comment: Fine identification of all impurities is a task that sometimes could not be completely accomplished taking into consideration the high complexity of this kind of production processes. Proposed change (if any): ...characterize and control the product as well as methods to detect and characterize impurities	The point is taken, however the change is not accepted. Characterisation is required only for product-related impurities.
206-213	2	Comment 1: It is recognized that the requirement of a validated process at the marketing authorization application stage falls under the scope of this guideline. In the light of what is reported in lines 212-213 for short shelf life products, it would be helpful if more details on validation requirements at the different stages of product development were outlined in a general strategy. Comment 2: How should this be implemented in cases where the cells need to be readministered to patients as early as possible? Will this requirement preclude possible treatments? Proposed change (if any):	This comment is not accepted. Investigational GTMP are not in the scope of guideline. For more detailed information on process validation of cell-based medicinal products, see GUIDELINE on human cell-based medicinal products (CHMP/410869/06) and guideline on process validation (CPMP/QWP/848/96) for basic principles.

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209	2	Comment: "Absence of adventitious virus": it is unclear whether it is required to be tested for on the product or if it would be possible to provide evidence that the materials used for genetically modifying cells are free from adventitious virus. Is it reasonable to require such test when the genetic modification is performed under short periods of time of culture ? Proposed change (if any):	This comment is not accepted. Indeed, the request is to address the viral safety as part of process validation, not at the time of batch release.
215-217	2	Comment 1: These measures obviously apply to the therapeutic GM-cells, in many instance likely autologous primary cells. Comment 2: We would like to underline that special cases might include e.g., **difficulties in obtaining a sufficient number of cells** so that validation can be performed at a reduced scale or using the same cell type obtained from a different source. Proposed change (if any): In special cases, if appropriately justified and supported by bridging data when applicable, it is possible that process validation be carried out at reduced scale, using the same type of cells obtained from a different source or on donated cells obtained from a healthy volunteer and on the same type of those to be used in the product, instead of using the product itself.	Comment 1 is unclear. Comment 2 is not accepted. The special cases referred to in the guideline text are those in which it is difficult to obtain patient's cells for a purpose different from clinical use. In such cases, validation can be performed using cells from a healthy donor. Reducing the scale of the validation exercise, as compared to production scale, will need to be justified by the applicant. Such justification will be handled on a case-by -case basis. Change is not accepted.

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218-220	2	Comment: This is not the appropriate place to quote such a general recommendation; again, it is important to distinguish primary cells (those most likely to be addressed here) and the biotech cell-factory. Proposed change (if any): move either to introductory part or in characterisation or potency sections; or at best restructure the guideline and merge it as a single consolidated one which separates the cell-factory and the manufactured product (quality) and that which is intended as a graft or infusion reaching the patient.	This comment is not accepted, The text belongs to process validation chapter, not to release of autologous cells. For definition of starting materials and final product, please see comments above. Change not accepted.
200-221 5.2.2. Process validation With more specific focus on 201-202 200-221 5.2.2. Process validation	1	Comment: AGX wishes the EMA to confirm how to organise the validation program according to the development stages. What would be the minimal requirements set for Phase 1, Phase 2, Phase 3? Would it be possible to introduce a possibility for Scientific Advice on these matters? At which stage of product development this is required? Would it be possible to have further clarifications on these matters? In view of AGX' technology platform and manufacturing process, it appears that further guidance is warranted with regards to how to address the process validation of the genetic modification, since the manufacturing process starts with an established MCB. (see General Comment #2) While AGX welcomes EMA's proposal for requirements for quality information on GMO-IMP, AGX would have hoped that the document be the setting stage for a comprehensive roadmap on the amount of quality-related information to be generated and presented to support	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells. Moreover, the guideline does not address Investigational GTMP.

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200-221 5.2.2. Process validation		the different stages of development of a GMO-IMP. Such document would not deter the need for Scientific Advices as relevant. While acknowledging the incremental gain of knowledge in the quality aspects of the GMO-IMP during its development, such document would have been a landmark opportunity to address the means by which reporting to the regulatory stakeholders (i.e.; EU-MS NCA/EC and others) of such information should be organised within the context of the other development aspects (i.e.; safety, efficacy) in order to better serve the community (i.e.; participating subjects, regulatory stakeholders (NCA/EC/others), drug development community, sponsors). A good example lies with the concept of 5.2.5. Process Validation (comment page 7-8/16 related to different lines in the document). Such incremental approaches are proposed by other regulatory bodies (i.e.; FDA (+) and with emphasis on information related to "Dear Gene Therapy IND or Master File Sponsor Letter point 5" http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm105882.htm) (+) See presentation on "The FDA Phase 1 GMP Guidance" http://www.bcg-usa.com/regulatory/docs/FDA_Presentations_Publications/SP8B06.pdf AND Guidance for Industry INDs — Approaches to Complying with CGMP During Phase 1 - January 2006 http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070273.pdf The latter guidance clearly addresses Gene Therapy products in its	

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		scope (p. 7/20) EMA comment: In the original comments the document found in the above link was copied in as PDF file and has been taken out for technical reasons. AND Guidance for Industry Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071597.pdf Proposed change (if any):	
207-214 process validation in the Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006), AND “Absence of viruses, vector copy number…”	1	Comment: With regards to this section due to the process by which the GM bacteria is obtained, AGX considers that this is not applicable. At best a statement should be mentioned in section 2.1.S.1. General Information and more specifically under 2.1.S.1.2. Structure (p. 23-35 of the IMPD). Proposed change (if any):	See comment above.
209	1	Comment:	As stated in the general part, AGX

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AND 292-293 209 AND 292-293		AGX believes that for bacterial GMO which do not intend to transfer genetic material, the absence of parts (i.e. outside of the recombination sites) of the (often non-viral) vector should be demonstrated. Therefore, AGX wishes EMA to include this requirement in the guideline as appropriate. Proposed change (if any): Add a sentences such as: “for GM bacteria the absence of parts (i.e.; outside of the recombination sites) of the (often non-viral) vector should be demonstrated”	comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells. Change is not accepted.
227	2	Comment: It is recognized that the requirement for appropriate validated methods in place at marketing authorization application falls under the scope of this guideline. However it would be helpful if guidance on method validation requirements at the different stages of product development were outlined in a general strategy. Proposed change (if any):	This comment is not accepted, the guideline does not address investigational GTMP.
227-242	2	Comment: one of the most important criteria which is omitted here is the product size, the number of viable cells constituting the product or the dose. The list in section 5.3 is too exhaustive considering that should all of these tests be performed, large amounts of the intended therapeutic product will be made unavailable for patients' treatment,	This comment is not accepted. The paragraph 5.3 Characterisation describes the requirements for overall characterisation of the medicinal product, not the requirements for batch release

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		in particular in cases of paediatric samples. Most of the tests are not standardized therefore it does not make much sense to have too much expectation as many of these tests, such as “vector transfer “ only make sense if there is an indication of sensitivity. Proposed change (if any): **Essential changes requested as follows**: the evaluation criteria should be organised according to: (i) a list of essential characterisation parameters addressing the biology of the cell and the cell phenotype (dosage, identity, biopotency, integrity, phenotype); and (ii) a list of assays addressing molecular aspects pertaining to both the efficacy of genetic modification and the product safety (absence of replication, transfer of vector sequences etc….). A structured text arranged along these two main lines should replace the current draft.	testing. At MAA level, testing methods should be fully validated. Change is not accepted.
229	2	Comment: Cell viability should be considered as a relevant potency parameter for characterization. We propose to include cell viability in the list of functional parameters Proposed change (if any): - cell viability	The point is taken, cell viability can be added. Change accepted.
230	3	Comment: The sequence of the transgene cannot be assessed in non-clonal primary cells e.g. hematopoietic stem cells or T cells Proposed change (if any):	This comment is not acceptable. The scope is not limited to cells of haemopoietic origin; if cells e.g. from healthy donors are used for characterisation, it should be possible to analyse the transgene sequence by means of molecular methods;

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			assessment will be done on a case by case basis.
231-241	1	Comment: AGX wishes EMA to help understand whether all these characterisation tests are mandatory or only those specific to its technology should be selected and others to be added per the needs. Proposed change (if any):	Point unclear. All the requirements are feasible with human-animal cells.
233	2	Comment 1: How should this be implemented in cases where the cells need to be re-administered to patients as early as possible? Will this requirement preclude possible treatments? Comment 2: this point does not make much sense out of the context of long-term monitoring since there is no such evidence as a clone which would be likely to predominate just after transduction where hundreds to thousands of different integrations can be evidenced. **The issue of clonality and integration sites monitoring is adequately considered in the FDA-LTFU guideline.**	This comments is not accepted: Section 5.3. describes the requirements for characterisation of the medicinal product, not those for batch release testing (see 5.4.) GTWP believes that it will not be possible to appropriately evaluate the emergence of a population post therapy, if vector integration profile is not known in the product.
233 Vector Integration	1	Comment: AGX wonders whether this refers to the position of the genetic insert and calls for EMA's clarification. In such instance, specific information could be mentioned in section 2.1.S.1. General Information and more specifically under 2.1.S.1.2. Structure (p. 23-35 of the IMPD).	It refers only to integrating vectors such as lenti/retroviruses.

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		Proposed change (if any):	
233	3	Comment: The vector integration profile can be addressed in preclinical studies but not as release testing. For most integrating vectors data from the literature show a quite uniform pattern of each respective vector species (lentiviral, gamma-retroviral), so that there is no need to re-perform these studies for each individual vector Proposed change (if any):	This comment is not accepted. Integration studies are mentioned as part of product characterisation (paragraph 5.3.), not as part of release testing requirements (5.4.); vector integration profile is a critical feature of an individual GTMP and vector platform studies may help but not suffice, unless adequately justified.
236-238	2	Comment: Line 236 is somewhat redundant with line 230 and should be only “expression of insert”; Lines 237 and 238 are redundant	This comment is not accepted. Line 230 refers to the transgene itself (structural integrity), whereas line 236 is addressing the activity of the transgene (e.g. protein expression). Lines 237 and 238 are not considered redundant, as the genetic modification may significantly modify the cell phenotype and may lead to various subpopulations, which may need to be controlled.
239 Proliferation / Differentiation	1	Comment: In view of AGX’ technology, would this test refer to growth of the GM bacteria? In addition, per AGX’ understanding, no differentiation	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not

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		occurs with a bacteria. AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	include genetically modified bacteria but only human and animal cells.
240-241 Vector Release from cells Vector Replication/Reactivation AND 209 240-241 AND 209	1	Comment: AGX considers that this test is not relevant for GM bacteria using genomically integrated inserts technology, as the non-cargo part of the vector (see line 209) is absent. Therefore, it cannot be released from the bacteria. In conclusion, a specific waiver should be stipulated. AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.
243-245 Vector Release and/or Vector Replication	1	Comment: AGX considers that this test is not relevant for GM bacteria using genomically integrated inserts technology. In conclusion, a specific waiver should be stipulated. AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.

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		to best adapt the information. Proposed change (if any):	
245	2	Comment: Clarification of the significance of viral reactivation in the context of product characterization could be helpful Proposed change (if any):	To clarify the point, reference will be made to the risk based approach guideline.
247	2	Comment: For FIH trials in which only non-clinical data are available, transduction and transgene expression could be justified on the basis of non-clinical, proof of principle studies. Proposed change (if any): Transduction and transgene expression efficiency should be justified in relation to non-clinical and/or clinical efficacy data.	This comment is not acceptable. Investigational GTMP are out of the scope of guideline. Change not accepted.
248-252	2	Comment: This section mostly addresses the GM-cells reaching the patient's body. It is appropriate as part of the clinical safety section (section 7.5) of the present document; also please see 233, Comment #2. Proposed change (if any): clonality and chromosomal integrity of the cell population derived from the genetically modified cells could be studied when appropriate, as part of the clinical long-term follow-up.	This comment is partially accepted. Insertional mutagenesis cannot be addressed only during the clinical follow-up, but needs to be analysed from the cells during characterisation studies. Proposed change of wording not accepted.
253-259	2	Comment: this would be extremely difficult to perform on each short-shelf lived clinical batches of limited size which are meant to be re-	This comment is not accepted. The requirement still belongs on

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		infused into the patient shortly after the genetic manipulation. Should such controls be deemed necessary, then a threshold and time-lines should be quoted similarly to FDA-LTFU guideline. The current draft is too vague. Proposed change (if any): **pre-clinical evaluation on a limited fraction of the otherwise intended clinical sample can be performed as a bridging study toward pre-clinical characterisation.** Please, also see 215-217	characterisation studies, which are not expected to be performed on same cells going into the patient. Change not accepted.
264	2	Comment: "Purity": this section is misleading, as purity most often refers to molecular contaminants, not cells. Here in fact we are rather talking about transduction efficiency i.e. product biopotency.	This comment is not accepted. Purity can be related to the process and to the product. When considering purity of a cell population, it is important that those cells not contributing to the efficacy are identified and controlled, if necessary.
268-269 Purity criteria	1	Comment: With regards to “Level of contaminants of cellular origin, fragments”, AGX considers that this test is not relevant for GM bacteria using genomically integrated inserts technology. In conclusion, a specific waiver should be stipulated. Furthermore, AGX adopted the strategy described in section 2.1.S.3.2. Impurities (p. 69-72) of the IMPD. See introduction: *“The lyophilized DS has the following chemical composition (see*	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.

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268-269 Purity criteria		*Section 2.1.S.1.3.a):* • *L. lactis strain sAGX0037,* • *cryoprotectants: dextrin (from maize starch), sorbitol and sodium glutamate.* *Any components or molecules, which may be present in the DS, other than those described above, are defined as impurities. These could be either process-related or product (sAGX0037)–derived."* AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	
272-274	2	Comment: How can this be assessed? E.g. in the case of using nonviral vectors: How do we discriminate between what is attached to the outside of cells and what is effectively inside?	Comment not accepted. PCR-based techniques are available, the issue pertains to excision of vector from cell genome, eg. in iPS.
276-279	2	Comment: Is this expected to be done in patients or in animal models?	The point is taken; the sentence needs clarification.
277	2	Comment: see comment at line 247 Proposed change (if any):…, the minimal or optimal effective amount of genetically modified cells shown in non-clinical or clinical studies to	This comment is not acceptable. Investigational GTMP are out of the scope of guideline.

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		achieve…	Change not accepted
282	2	Comment: Although potency is by definition a quantitative measure, it might be some special cases in which a well defined quantitative method for potency assessment cannot be performed. Proposed change (if any): The potency test(s) should provide, whenever possible, quantitative information on the newly acquired characteristics. Semi-quantitiative analytical method(s) for potency could be used if justified.	The point is taken. Change accepted.
289-290 Percentage of transduced cells	1	Comment: AGX considers that this is not relevant for GM bacteria using genomically integrated inserts technology and in view of the manufacturing strategy (i.e.; setting of MCB, etc) depicted in the IMPD. In conclusion, a specific waiver should be stipulated. AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells. See comments above.
291	3	Comment: Showing absence of replication deficient vectors in primary transduced cells is not always feasible. The FDA “Guidance for Industry” Document on testing for replication competent retroviruses states (from October 2000) that if cells are harvested less than 4 days after transduction RCR testing is not feasible. Also, sensitivity of 1	This comment is accepted. The paragraph will be amended as follows: For cells transduced with a replication defective integrating vector, in general

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		RCV per clinical batch is not possible for primary transduced cells, where there are patient specific batches, as this would destroy the clinical batch itself. Generally the commentators feel that tests for replication competent retroviruses on the final product (when the final product are gene modified primary cells) are not as essential as once thought. Due to the rigorous RCR testing during the production process of the retroviral vector itself it is extremely unlikely that patient cells can be transduced by an RCR. In the history of gene therapy with hundreds of patients having been treated such a case has never been reported. Given the low probability of detecting such a rare event (as discussed above it is impossible to have a sensitivity of one RCR per clinical batch in these kind of products) the increase in safety is rather marginal.	risk profiling and/or characterisation data should be sufficient to exclude the possibility of replication competent vector generation and the issue is more appropriately dealt with in the long term follow up studies. However, if this is not the case, the absence of replication competent vector generation from transduced cells should be demonstrated on each batch of final product. If RCV is detected, the transduced cell batch should be rejected.
291-297	2	Comment: this paragraph is repetitive in reference to 5.3	Comment not accepted: Paragraph 5.3. describes the requirements for product characterisation and 5.4 those for batch release. Some issues may need to be addressed in both circumstances.
292-293 AND 209 Vector/plasmid copy number per cell should be tested on each batch of final product. The result of RCV testing should be known before clinical	1	Comment: In line with the comment on line 209, AGX considers that for bacteria complying with its technology platform and since genetic stability has been demonstrated this batch to batch release requirement should not apply. AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells. See comments above.

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use.		to best adapt the information. Proposed change (if any):	
293	2	Comment 1: The absence of RCV is a paramount issue which essentially concerns the manufacture of the vectors and their characterisation. Based on a risk-analysis rationale, should the gene transfer vector be certified as RCV-free, it is most unlikely that RCV will breakout in target transduced cells meant to reach the patient in a time-frame which matches our technical reach. These improbable events would take time before there would be chances for them to occur. Therefore, we would emphasize the need to perform extensive RCV testing from the GT-vectors, banked as biotech products and not compromise the quantity and quality of the graft in performing tests which are irrelevant at this stage and belong to the long-term clinical follow-up. Comment 2: For cell products with short shelf life, completion of a cell based RCV testing might not be technically feasible, and, on the other hand, molecular based assay might be biased by carry over of viral genetic material. For such specific cases, we believe that alternative strategies could be adopted (e.g. based on risk approach and validation data consideration) to allow patient administration in absence of RCV result. A general policy could be added in the document to provide guidance to manufacturers.	This comment is accepted. The paragraph will be amended. (see above). (see above)
294	2	Comment: The guideline requires that the sensitivity limit of the test is related to a full clinical dose, but it does not specify the minimal	This comment is accepted. The paragraph will be amended.

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		dose of product to be tested for batch release. Such considerations are reported in the FDA guidance for RCR "Guidance for industry - Supplemental guidance on testing for RCR in retroviral vector gene therapy products and during follow up of patients in clinical trial using retroviral vector" in which a minimum of 1% (or $100x10^6$ cells, whichever is the less) of the final cell population is required for RCR testing. It should also be clarified if the test should be performed independently from the total length of the manufacturing process since for processes shorter than 4 days performance of cell-based RCV testing might not be necessary for specific type of viruses (e. g. retroviruses) as also reported in the above cited FDA guideline. Proposed change (if any): We propose the addition of a paragraph to address these issues.	(see above)
300-305	2	Comment: In general, for short shelf life product, we believe that the addition of a general policy could be added to the document to provide guidance for manufacturers when a complete QC program cannot be completed prior to the administration and a reduced release testing has to be carried out. This may include RCR testing but extended also to identity and potency assays. In our opinion a QC strategy in such cases, that is selection and timing for assay performance, should be based on consideration of both patients safety and possible therapeutic effects derived from the treatment ultimately balancing risks and benefits of the therapeutic approach. For these reasons we propose the following addition to the section:	This comment is not accepted. Guidance for the short shelf life products is specifically given in paragraph 5.4 lines 300-305; testing to be chosen will be product-specific.

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		Proposed change (if any): A reduced release testing program can be adopted by the applicant if justification are provided and based on risk based approach and on validation data obtained both during manufacturing and clinical development.	Change not accepted
307-311	2	Comment: as well as in other sections of this document here is a mix up between cell-based medicinal products and gene therapy medicinal products.	This comment is unclear. Indeed the scope of the guideline is genetically modified cells products, in most cases they will fall under the classification of both cell-based and gene therapy medicinal products.
314-318	2	Comment: The enumerations of clinical guidelines are only examples. It should be mentioned that there are much more guidelines that have to be fulfilled. In special those which relate to particular diseases.	This comment is unclear. Lines 314-318 belong to non clinical chapter of the guideline.
325-328	1	Comment: AGX wishes that the EMA qualifies this statement in a way so that the observed effect is also attributable to the GM bacteria. Proposed change (if any): They should also allow determining whether the observed effect is attributable to transduced gene, to transduced cells (of human, of animal or of bacterial origin) or to both, e.g. toxic effect due to over/under-expression of transgene by a correct number of cells as compared to normal expression by an abnormal number of cells.	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells. Change not acceptable.

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326-328	2	Comment: please clarify	
329-331	2	Comment 1: **At the time of non-clinical studies the production process is under development. Therefore it is not usual to have a fully validated production process at this stage of development. Analytical methods are also meant to be validated during this development phase;** then, there should be a qualification available for rooms and equipment. Comment 2: The guideline requirement of using for non-clinical studies batches of transduced cells produced and quality controlled according to the validated production method, may suggest, on one hand, that non-clinical studies should be conducted only at the very end of the CMC development, when both analytical method and manufacturing process are fully set up and, on the other hand, that the manufacturing process validation should be always performed before FIH. This requirement will result in a much longer timing needed for the development and clinical application of the product thus substantially delaying patient access to potentially beneficial investigation medicinal products under development. In the ICH 6 “Preclinical safety evaluation of biotechnology derived product” quality of materials for non clinical studies is mentioned also and it is defined as comparable to the one used for initial clinical studies provided potential impact of any manufacturing change could be extrapolated performing bridging animal studies. Definition of quality in the draft document may entail that material intended for non clinical studies should be higher in quality for genetically modified cells than for r-DNA biopharmaceuticals. We believe a clarification on the matter would be helpful as well as	The comment is partially accepted (see below).

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		consistency with ICH6 definitions, if feasible. Proposed change (if any): In general, the material to be used in the pharmacology and toxicology studies should be representative of the product proposed for initial clinical studies and produced with a manufacturing process comparable with the one in place for producing material for clinical use. However, it is appreciated that during the course of manufacturing development, changes normally occur in the manufacturing process in order to improve quality, yields or for scaling up. The potential impact of such changes should be considered and studies aimed at demonstrating comparability between pre and post change materials. When considered appropriate, along with product characterization studies (e.g. potency impurities, identity) performed for comparability purposes, supportive non clinical studies (e.g. pharmacodynamic, pharmacokinetic or toxicology) may be performed.	The text is amended as follows: The non clinical studies should be carried out with batches of transduced cells produced and quality controlled according to the production process in place for clinical studies and should use state-of-the art and adequately validated techniques.
337	2	Comment 1: in-vitro models should be mentioned Comment 2: Quality standards for non-clinical studies are not mentioned in the guideline. We believe that this point should be addressed. Non-clinical programmes may involve the use of non standard animal species like immunodeficient mice or disease animal models, therefore it might not be always feasible to conduct such studies, or part of these, in fully certified GLP laboratories. We propose to include in the guideline a specification on quality standard compliance for non clinical studies consistent with ICH 6 “Preclinical safety evaluation of Biotechnology derived product”, so that sufficient technical flexibility is allowed, while ensuring non	Comment 1 is accepted. The text is amended. Comment 2 is not accepted. GLP compliance is a legal requirement; any deviation from it should be justified on a case-by case-basis.

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		clinical studies conductance with high quality standards Proposed change (if any): Addition of the following paragraph: "Toxicity studies are expected to be performed in compliance with Good Laboratory Practice (GLP); however it is recognized that toxicology data could be obtained in the frame of PD and PK studies and that such studies often employing specialized test system may not be able to fully comply with GLP or be performed in GLP certified laboratories. In such cases, lack of full GLP compliance does not necessarily mean that the data from these studies cannot be used to support clinical trials and marketing authorization. In general, principles of GLP should be followed (including, but not limited to, raw data recording, traceability and reporting), areas of non compliance should be identified and their significance evaluated relative to overall safety assessment.	
340	2	Comment: This section is quite redundant with section 5.3, 5.4 and 5.5. Therefore a thorough thinking on a structure fitting the demands of GT-ATMPs would be welcome. Again consideration of the essentially different nature of the GT-vectors (biotech GMP-manufacture) and of primary cells to reach the patient would be essential in defining the round-robin of issues at stake. In that regard, provisions towards the marketing authorisation of GT-products appears straightforward and more than that of autologous GM-cells.	The comment is unclear. The chapter is about non clinical studies, some redundancy with quality issue may appear.
341-342	1	Comment: AGX wishes a clarification as to the EMA's expectations. Would "*the expected effects of genetic modification, such as cell differentiation*	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not

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341-342		*and/or proliferation induced by gene product or recovery of the intended physiological function*" need to be demonstrated towards the bacteria or the subject (human or animal) who receives the GM bacteria? Since AGX's technology platform is only secreting therapeutic proteins and cannot exchange genetic material with eukaryotic cells, AGX wishes a waiver is referred to in the guideline. AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	include genetically modified bacteria but only human and animal cells.
354	3	Comment: It is not always feasible to investigate the in vivo fate of genetically modified cells as non gene modified cells in other than murine systems often cannot be distinguished from host cells. Proposed change (if any): Rephrase to: "genetically modified cells should be investigated and, if technically feasible, be compared to non genetically modified counterparts."	Comment accepted. Change accepted.
354-355 The *in vivo* fate (biodistribution, homing, life span) of genetically modified cells should be investigated and	1	Comment: Per AGX's understanding such requirement would require that *L. lactis* MG1363 strain would be used as a counterpart in preclinical setting. Since AGX' technology is geared towards developing GM bacteria for local non-systemic administration of therapeutic proteins, AGX' views are that preclinical programmes should be designed towards evaluating the features (i.e.; safety and efficacy) of the GM bacteria	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.

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compared to non genetically modified counterparts.		only. AGX would appreciate EMA's input as to why such comparison should be developed and what would be the expected study/ies design, outcomes and timing in the overall development programme timelines. AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	
356-358 Germline transmission aspects should be investigated according to the Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005).	1	Comment: In view of AGX' technology platform targeting the delivery of non-systemic GM bacteria secreting therapeutic proteins, it is hoped that EMA would highlight that a waiver can be granted in the guideline. AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.
379 Integrating vector "When cells are	1	Comment: AGX wishes to clearly highlight and remind that its technology platform does not integrate genetic vector into the tested subject	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not

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transduced with integrating vectors (e.g. retroviral or lentiviral),…"		(i.e.; human or animal). Therefore, AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	include genetically modified bacteria but only human and animal cells.
381 Special attention should be paid to activation of oncogenes and/or inactivation of tumour suppressing genes and risk of insertional mutagenesis.	1	Comment: In view of AGX' technology, the mechanisms devised in this section are deemed to be non relevant for local delivery of GM bacteria secreting therapeutic proteins locally. Therefore, AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.
383-384	2	Comment: The definition of "clonal" integration profile is ambiguous. Integrating vectors generate after short term culture a mixture of millions of different clones among which it is unlikely that one emerges before long-term follow-up is secured. Conversely, a single clone may be generated and selected on purpose under certain circumstances. Proposed Change (if any): We propose to include oncogenesis in the general consideration under line 368-372	The comment is noted.
395	2	Comment: clear requirements for each group of the ATMPs should be listed.	The comment is unclear. The guideline scope is limited to genetically modified cell products.

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428	2	Comment: Section 7.3, Pharmacokinetics should be structured and hierarchised along the different issues under consideration: 429-433 address the protein product and so do 440-445; 434-436 address monitoring of GM-cells; 437-439: nucleic acid and genetic modification related issues. Proposed Change (if any): organise along three abovementioned topics.	The comment is accepted. The section is reorganised.
434-436 Viability, proliferation/differentiation, body distribution, migration, functionality…	1	Comment: In view of AGX' technology (i.e.; 1/ AGX' technology is not designed to transducer/modify host (i.e.; eukaryotic system) cells, 2/ use of non-colonising, non-commensal GM bacteria, 3/ neither bacteria nor expressed proteins are intended to systemic administration and of the expressed proteins), AGX believes that this requirement should be waived for IMPs using such GMOs. AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.
491-492	1	Comment: In view AGX' technology using a non-colonising, non-commensal bacteria, the following statement does not apply: "*Genetically modified cells may need specific long-term studies to monitor safety issues including lack of efficacy and risk of vector dissemination or*	As stated in the general part, AGX comments cannot be taken on board because the guideline scope does not include genetically modified bacteria but only human and animal cells.

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		reactivation." and an exemption should be granted and highlighted. Therefore, AGX hopes that the EMA finds an appropriate way to reflect upon this in the guideline and confirms to be happy to further interact with EMA to best adapt the information. Proposed change (if any):	

Please add more rows if needed.