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PIC/S Focused Stakeholders Consultation on Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use and Annex 2B Manufacture of Biological Medicinal Substances and Products for Human Use

Table 1.0: PIC/S Consultation Questions

Contact Information (Name, position, and full contact details):
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ISPE wishes to thank PIC/S for recognising ISPE as a stakeholder to make comments on the draft revisions, Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use and Annex 2B Manufacture of Biological Medicinal Substances and Products for Human Use of Annex 2 of the current PIC/S GMP Guide Annex 2 Manufacture of biological medicinal substances and products for human use. This important work will be valuable for all industry stakeholders and will help clarify GMP expectations for manufacture of ATMP's giving more guidance on appropriate GMPs for these innovating products, which require some flexibility. This document will be an advancement in the field of new therapies.

Question #1: Scope of Guidance Document	
PIC/S Question	What are your views on ATMP guidance applying to the manufacture of ATMP products as described in the following illustrations (line 58 of the consultation document)? As an alternative, should plasmid manufacturing and/or virus manufacturing be in scope of this document, if yes in what form? **Illustration 2-1 Type and source of Material: Human and or animal sources**

Example product	Application of this guide to manufacturing steps shown in grey

Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue / cells[1]	Vector manufacturing; cell isolation, culture and purification	Ex-vivo genetic modification of cells, Establishment of MCB, WCB or primary cell lot	Formulation, filling
Somatic cell therapy	Donation, procurement and testing of starting tissue / cells[1]	Establishment of MCB, WCB or primary cell lot or cell pool	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, fill
Tissue engineered products	Donation, procurement and testing of starting tissue / cells[1]	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, fill

Illustration 2-2 Type and source of Material: Non Human and/or animal sources

Gene Therapy: in Vivo Viral Vectors by stable producer cell lines	Plasmid manufacturing[1]	Producer cell lines manufacturing	Vector Manufacturing	Formulation, filling
Gene Therapy: in Vivo Viral Vectors by transient production system	Virus manufacturing[1]	Cell system manufacturing	Vector Manufacturing	Formulation, filling

[1] Separate GMP requirements may apply where required under national law.

ISPE

As ATMP's materials are not covered by the ICH Q7 Guide, the EU GMP Part II or the PIC/S GMP Guide Part II, we consider these materials need to be part of revised Annex 2 PIC/S Part A. We suggest the proposed extension to virus and plasmid could be incorporated, as well as mRNA.

The document should, however, address these materials (virus, plasmid, mRNA manufacturing) in a flexible way to allow for new starting materials that emerge in the future to be included in the scope without requiring a new revision of the document.
The increase of GMP requirements as the production steps come closer to the finished product is good and need to be retained as a principle.

We suggest to split the table in a different way with one part dedicated to Drug Substances and another part dedicated to final product manufacturing, formulation and filling. This could incorporate different levels of requirement of GMP.

We suggest adding an arrow below the table to show the increase of GMP requirements following the processes steps coming closer to the final steps.

We suggest as well to have Annex 2A linked with PIC/S GMP Part II (ICH Q7A).

We propose having a separate Establishment of MCB and WCB with appropriate level of GMP requirements box and not positioned as they are in the table.

Question #2: Product Quality Review in Clinical Trial Phases

PIC/S Question	Considering the length of time that some advanced therapy investigational medicinal products (ATIMP) could be in clinical trial phase; is there a need to include requirements to periodically perform a Product Quality Review proportionate to the development stage? Currently, product quality reviews are not required for medicinal products in a clinical trial phase. Expectations for a Product Quality Review for ATIMP could consider aspects found in Section 1.10 of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part I Chapter 1 Product Quality Review. This could include: 1.10 Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least: (i) A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances; (ii) A review of critical in-process controls and finished product results; (iii) A review of all batches that failed to meet established specification(s) and their investigation; (iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken; (v) A review of all changes carried out to the processes or analytical methods; (vi) A review of Marketing Authorisation variations submitted, granted or refused, including those for third country (export only) dossiers; (vii) A review of the results of the stability monitoring programme and any adverse trends; (viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time; (ix) A review of adequacy of any other previous product process or equipment corrective actions; (x) For new Marketing Authorisations and variations to Marketing Authorisations, a review of post-marketing commitments; (xi) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc; (xii) A review of any contractual arrangements as defined in Chapter 7 to ensure that they are up to date.

ISPE	For this section we consider that clause 1.4 of Part 1 of GMP PIC/S is more appropriate, rather than clause 1.10. A full quality review as per marketed products seems not to be desirable, which is consistent with the approach for clinical products. Nevertheless, based on QRM principles a review of quality information from previous batches and previous steps would be useful. Trend analysis requiring more data information should not be required. This review should consider points i, ii, iii, iv, v, vii, ix, xi, & xii of section 1.10 of the PIC/S GMP Guide Part I as these points need to be part of the manufacturing preparation to keep production under control. We suggest to remove from the new section 1.10 for ATMP's at the clinical stage points vi, viii, x, which are not relevant for these products at the clinical stage of development. The following steps under QRM should be adapted to the stage of product development: The premises and equipment used for clinical trials should be qualified. Due to potential low manufacturing activity, inspection or checking of facilities and equipment should be performed at appropriate intervals. Production should be verified in a continual way by examination of increasing amounts of in-process data to keep the process under control without having a full process validation.
Question #3: Working environment requirements when processing is not performed in a closed system	

PIC/S Question	What are your views on the expectation for the working environment requirements when processing is not performed in a closed system? Section 3.13 of the attached consultation document for Annex 2A presents a PIC/S proposal. These expectations align the same requirements expected for the manufacture of sterile medicinal products but allow for an exception based system if authorised by the competent authority. You may need to make reference PIC/S PE 009-14 PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 1 Section 1 to 35. Please note that Annex 1 has recently concluded a consultation and is currently being revised. 3.12 Where processes are not closed and there is exposure of the product to the immediate room environment without a subsequent microbial inactivation process, (e.g. during additions of supplements, media, buffers, gasses, manipulations) then this must be in a working environment with air particle counts and microbial colony counts and other clean room parameters equivalent to those defined in Annex 1. The appropriate level of air classification should be determined having regard to the specific risks taking into account the nature of the product and the manufacturing process. (Replaces PICS GMP Guide Part I Section 3.1) 3.13 A less stringent environment than specified in 3.12 above may be acceptable where approved by the competent authority. This should be considered only when a product is intended to treat a life-threatening condition where circumstances necessitate a less stringent environment and manufacturing alternatives do not exist or are not suitable. In this case, the environment must be specified and justified to provide patient benefit that outweighs the significant risk created by manufacturing under less stringent environments. It must be demonstrated that the chosen environment is suitable for maintaining critical quality and safety attributes, taking into account the intended purpose, the mode of application and the health status of the recipient. (Replaces PICS GMP Guide Part I Section 3.1)

ISPE	It is not necessary for all ATMP's to be manufactured under sterile conditions. If the products can be sterilized after a process step, less stringent conditions can be applied. If the product cannot be sterilized then more environmental verification should be carried out at the most critical parts of the process. When processes are made in a non-closed system, it is appropriate to refer to Annex 1 GMP's for the parts relevant for ATMP's with respect to particle count, bacteria count, air flow checking. Air classification should be defined following QRM and CCS (Contamination Control Strategy) principles. Based on CCS the appropriate level of air classification should be determined having regard to the specific risks, taking into account the nature of the product, its relevant critical quality and safety attributes,and the manufacturing process step. We suggest keeping reference to Annex 1 parts relevant to ATMP's even with the future release of the revision of this document. When a product is intended for a life-threatened product, with no manufacturing alternatives, then with NCA's agreement less stringent conditions should be acceptable based on QRM reviews and CCS principles. These production conditions need to be defined before approval, and additional environmental verification at the most critical point should be made during production to demonstrate that the product and the patient are not at risk.
Question #4: Equipment use when manufacturing extends into hospitals	
PIC/S Question	What are your views on the expectations to address facilities and equipment used in a hospital ward or theatre? Section 3.14 of the attached consultation document on Annex 2A presents a PIC/S proposal when certain manufacturing activities must be extended into hospitals as part of decentralized or point of care manufacturing. You may need to make reference PIC/S PE 009-14 PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 15 on Qualification and Validation or Annex 20 on Quality Risk Management. 3.14 Performing a manufacturing step in premises that are not under direct control of the MAH or Sponsor, (including for example placing equipment used to perform manufacturing steps in an hospital wards or theatre), is permissible provided that the MAH or Sponsor demonstrates that the process maintains its validated status utilising the provisions of Annex 15 and any derogation from the mandated standards in this Annex are justified utilising QRM principles described Annex 20, and subject to approval by the competent authority.

ISPE	Performing production steps, in premises that are not under direct control of the MAH or Sponsor environment should be approved by Competent Authorities as part of the process. The MAH needs to keep under control those process steps for which it has direct control, and ensure equipment has been verified using Annex 15 recommendation as support (PIC/S Annex 15 will be considered a support documentation). Responsibility for assuring the quality of the manufacturing supply chain remains with the MAH. Manufacturing steps performed in premises that are not under direct control of the MAH or Sponsor environment such as a Hospital ward or theatre should be carried out under a recognized Quality System. Premises and Equipment if not qualified should be verified following Hospital equipment and premises verification rules bringing to the installations the appropriate level of confidence for the intend use. We suggest making GMP Annex 15 a non-mandatory document, and used only as a support document.
Question #5: Batch release when product does not comply with specification	
PIC/S Question	What are your views on the expectations specified when release of a batch may be in a patient best interest but it does not comply with specification? Section 5.45 and 5.46 of the attached consultation document on Annex 2A present a PIC/S proposal. 5.45 Batches of medicinal products should only be released for sale or supply to the market after certification by an Authorised Person. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site which has been approved for that purpose by the relevant national competent authority. Generally, a finished product that does not meet release specification should not be administered to a patient unless the provisions given below in 5.46 are met; 5.46 Where authorised by national law, the administration of a product that does not meet the release specification, might be performed in exceptional circumstances (such as when there is no alternative treatment available that would provide the same therapeutic outcome and the administration of the failed products could be lifesaving). The responsibility and the decision of the patient treatment are solely on the treating physician and are beyond the remit of this GMP guide. The Authorised Person, the marketing authorisation holder (MAH) and or the Sponsor of clinical trial should consider the following in making the product available:

	a) The batch manufacturing records and the documentation provided to the treating physician should clearly state that the batch has failed the release specifications and describe the parameters that have not been met; b) The Authorised Person may provide a less technical description of the failed parameters upon request to the treating physician and where possible a description of potential consequences; and c) The Authorised Person (or delegate) should report within 48 hours the supply of the product to the relevant competent authorities, on behalf of the MAH or Sponsor in accordance with their legal obligations.
ISPE	As indicated in the proposed text, connection between the treating physician, and Authorised Person of MAH or manufacturer is a critical point especially when a batch not compying with its release specification is proposed for administration. The Authorised Person should be consulted to provide input to the treating physician's risk assessment. However, the sole responsibility for administering the treatment rests with the treating physician. Even in a PIC/S document, we suggest clarifying the Notification to the Comptetent authorities in Europe which requires 3 Authorities to be informed, (Supervisory Authority in EU and EMA + National Competent Authority). This could be a note in the document.
Question #6: Batch release in cases of decentralized or point of care manufacturing	
PIC/S Question	What are your views on the expectations to address batch release when certain steps of manufacturing are decentralized or occur at the point of care? Section 5.47 and 5.48 of the attached consultation document on Annex 2A present a PIC/S proposal. 5.47 There may be cases where manufacturing of the ATMP takes place in sites close to the patient (e.g. ATMPs with short shelf-life, clinical advantage of using fresh cells as opposed to freezing the starting materials/finished product, advantages of using automated equipment, etc.). This includes manufacturing models where partial manufacturing occurs at a central site and finishing occurs at a local site. It also includes manufacturing models where there are no steps occurring at a central site and the active substance is provided to a number of local sites where full manufacture occurs. In such cases, steps in the manufacturing of the ATMPs may occur in multiple sites that may be also located in treatment centres (point of care) including hospitals. 5.48 The batch certification and release process become particularly important in the case of ATMPs manufactured under a decentralised system as manufacturing in multiple sites increases the risk of variability for the product. In particular, through the batch certification and release process it must be ensured that each batch released at any of the sites has been manufactured and checked in accordance with the requirements of the CTA or MA and other relevant regulatory requirements including compliance with GMP. The steps of the batch certification and release process should be laid down in a standard operating procedure (SOP). The following conditions need to be respected:

(a) A "responsible site", should be identified. The responsible site is responsible for the oversight of the decentralised sites. The responsible site:

i. must have availability of an Authorised Person,
ii. must ensure that those involved in the batch certification and release process are adequately qualified and trained for their tasks,
iii. should perform audits to confirm compliance with the batch certification and release process (as descripted in SOP),
iv. must ensure that there is a written contract/technical agreement between the responsible site and the decentralised sites establishing the responsibilities of each party, and
v. must ensure that there are written arrangements to:
- timely report quality defects, deviations or non-conformity to the central site,
- ensure deviations are investigated to identity root causes and implement corrective and preventive measures as appropriate, and
- ensure deviations are approved by a responsible person (after having assessed the impact on quality, safety and efficacy), with the involvement of the Authorised Person as appropriate.

(b) The Authorised Person should have ultimate responsibility for the batch certification (responsibility cannot be delegated). However, it should be possible for the Authorised Person of the responsible site to rely on data/information that is transmitted to him by qualified and trained personnel at the decentralised sites. In certain exceptional cases (for example, different time zones or unexpected release that has to occur at night time) and when permissible according to national law, when the release of the product is needed to address life threatening conditions, the Authorised Person may delegate the release to personnel at the decentralised site that act under the direction of the authorised person, under the following conditions:

i. There is a detailed algorithm that determines the cases when the product can be released at the local site without the preliminary approval of the Authorised Person, including deviations that do not require the intervention of the Authorised Person. If technology permits this step can be performed by a validated computer system;
ii. The Authorised Person reviews all releases that have occurred at the sites within an appropriate timeframe (i.e. no longer than a monthly interval) to confirm the adequacy of the releases including:
- determining that the local sites can continue release
- if any product needs to be recalled or going through hazard alert
- if any provision in the release procedure and /or technical agreement needs modification; and
- the product has not been released without Authorised Person authorisation when required.

ISPE	Data collection, Data Management, Data Integrity and delegation of responsibilities related to batch release for such a complicated supply chain, is a critical point. Batch release processes and responsibilities need to be fully explained, understood and documented particularly as batch released may be carried out under electronically shared data. For such products if there is a short shelflife, the release review should be done in a shorter time frame than one month as proposed as exemple based on QRM if many other batches have to be produced and released in the organization. All listed items in 5.48 seems acceptable and cover all activities under Authtorised Person and MAH responsibilities. All Quality assessments and contracts need to be ready before starting such a batch certification and release process.
Question #7: Starting Materials	
PIC/S Question	What are your views on the control of starting materials? Is the approach to control of starting materials sufficiently described in the draft PIC/S *Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use* (Sections 5.24 to 5.33, B1.3 to B1.4, B2.1 to B2.2, and B3.3) when read with other applicable sections of PIC/S Guides or are there any requirements or positions that need to be accounted for with particular reference to critical starting materials, raw materials and active substances?
ISPE	Some active ATMP materials are coming from patients or donors; it needs to be emphasised that the sampling of these materials should be undertaken in a way that will not contaminate the material. Also, the supply chain must allow product transfer without damage to the product. Application of QRM to the total supply chain QRM is a critical part of the process to understand the risks to raw material quality. The guidance could be enhanced with a short explanatory paragraph of the importance of QRM across the whole supply chain. We suggest adding a definition of “Raw Materials for ATMP’s” in the glossary.
Question #8: Outsourcing to non GMP licensed third party in exceptional circumstances	

PIC/S Question	What are your views on the expectations that provide flexibility to ensure that specialised testing and collection of human starting material is adapted to the particularities of ATMP while still maintaining the necessary quality of the product and reliability of testing as applicable? Section 7.1 of the attached consultation document on Annex 2A presents a PIC/S proposal. You may need to make reference PIC/S PE 009-14 PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 15 on Qualification and Validation or Annex 20 on Quality Risk Management. 7.1 Collection of starting materials and highly specialised testing in the jurisdictions that are subject to licensing (e.g. karyotype testing, exome sequencing) can be outsourced to non GMP licensed third party, as allowed by national law, provided that: a) There is a rationale and a justification in the quality system b) The contract giver takes responsibility to ensure that the contract acceptor demonstrates an appropriate level of GMP commensurate to the risk to the product and the activities performed using the principles of Annex 20 c) That proportionate qualifications/validations as appropriate are conducted (with reference to Annex 15 and Annex 20) to demonstrate that the activities are not detrimental to the quality of the product manufactured.
ISPE	We suggest not mixing starting materials collection and specialized testing. Both can be carried out in non-GMP environments. Nevertheless, special care has to be taken for material sampling as material will be processed in GMP environments and sampling must not bring contamination to patients. The human starting material collection should be performed according to the national laws on donation of cells and tissues for clinical purposes. A full traceability management needs to be developed. Even with non-GMP testing laboratories, the equipment and conditions should be commissioned and the laboratory should have procedures and a robust quality system, for example as per ISO 9000 standards. In any case, the MAH is responsible of the work done by its subcontractors. Release cannot be delegated.
Question #9: Other considerations	
PIC/S Question	Is there any other considerations related to GMP for the manufacture of ATMP that you deem important that is not covered by these questions? If so please provide feedback, limited to your top two priorities.

ISPE	1) We suggest clarifying in the scope of the document or in the Principle section the links between ATMP's GMP's and Annex 1 when revision is finalised. As ATMP's for some processes do not need to follow aseptic manufacturing, Annex 1 application should be considered based on QRM linked with the processes steps and not applicable as per aseptic processing given in the draft Annex 1. 2) QRM principles should be enhanced in the document, for example by including a paragraph in the Principles section to cover all the document even in the parts where it is not mentioned. It is recognized that QRM is mentioned in section 1.3. 3) Software validation should be addressed either in the Principles ot Validation section since some practices will require IT communication between production sites.

Line Comments on Draft Annex 2A (PS/INF 25/2019 (Rev. 1))		
Line Number & Section	**Current wording**	**Comment or proposed alternative wording**
128; 1.2	correct gene sequence	Not applicable for individualized products
141-145	As a result, Quality Risk Management (QRM) principles as detailed in Annex 20 are particularly important for this class of materials and should be used to develop their control strategy across all stages of manufacture so as to minimise variability and to reduce the opportunity for contamination and cross-contamination.	Add the word 'development' to read as follows: *QRM … should be used to develop their Control Strategy across all stages of development and manufacturing steps so as to minimize …..*
148	Chapter 2 Personnel	The training requirements as stated in draft Annex 2B (line 151 to 155) are also applicable to ATMP and thus, these requirements should be included: *"Personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological active substances and products are manufactured and tested should receive training, and periodic retraining, specific to the products manufactured and to their work, including any specific security measures to protect product, personnel and the environment."*
167 to 169 - 2.3	In general, personnel should not pass from areas where exposure to live micro-organisms, genetically modified organisms, toxins or animals to areas where other products, inactivated	Alternative suggested wording*: In general, personnel should not pass from areas where exposure to virus, cells, or animals to areas where other products, inactivated*

	products or different organisms are handled.	*products or different virus and cells are handled*.
228	Special precautions should be taken in the case of manufacturing activities involving infectious viral vectors (e.g. oncolytic viruses); these activities should take place in a segregated area.	For typical oncolytic viruses, segregation by area alone may not be sufficient to prevent cross contamination. We suggest for specific products, define the segregation level based on CCS and QRM, for dedicated facilities, dedicated areas or dedicated equipment.
392 to 393 – 5.3	Material of biological origin with unknown adventitious agent status should be treated in a way to avoid mix-up and cross-contamination.	The recommendation is redundant. Suggest delete (avoidance of mix-up and cross-contamination is a continous requirement throughout the process).
415 to 418 – 5.7	If closed systems are used for the production of ATMPs, checks should be carried out to ensure that all pieces of the equipment are connected in a correct manner to assure the closed state. Special attention should be given to apply these tests to automated systems. The integrity of single use equipment should be verified prior to every use. The integrity of reused equipment should be verified prior to and after cleaning and sterilisation.	For better understanding we suggest the following alternative wording. *If closed systems are used for the production of ATMPs, checks should be carried out to ensure that all pieces of the equipment are connected in a correct manner to assure the closed state. Special attention should be given to apply these tests to automated systems. If feasible and based on QRM principles, for example considering testing carried out by vendors, the integrity of single use equipment should be verified at adequate frequency prior to use and potentially post use, possibly automatically. The integrity of reused equipment should be verified before use after cleaning and sterilisation.*
421 – 5.8	When materials are added/withdrawn from the closed system without an aseptic connection (e.g. use of sterile connectors, use of filters), the system can no longer be considered closed.	Alternative wording proposed: *When materials are added/withdrawn from the closed system not aseptically (i.e. use of sterile connectors, sterile filters, appropriate equipment, or appropriate protection), the system can no longer be considered closed.*
427 – 5.9	The re-use of the same matrix at different stages of processing is discouraged.	Alternative wording proposed: *The re-use of the same matrix at different stages of processing* ***or for different products*** *is discouraged based on QRM.*
4.32 to 4.37 - 5.10	The use of technologies (e.g. processing inside sterile disposable kits, or processing using closed, automated, manufacturing platform or incubation in closed flasks, bags or fermenters) in a grade C environment may be acceptable if adequate control measures are implemented to avoid the risk of cross-contamination (e.g. appropriate control of materials, personnel flows and cleanness).	We suggest having the possibility of using grade D with in operation limits and based on QRM principles.

444	An evidence-based QRM process should……	Suggest modifying "evidence-based QRM process" to *"A QRM process"* as the use of evidence-based seems to suggest that other requirements with regard to QRM process can be non-evidence based.
527 Section 5.20(a)	All aseptic and sterilisation processes for investigational and authorized ATMPs are expected to be validated to the extent of routine production.	Suggest replacing by: *"validation of aseptic and sterilisation processes should be commensurate to the development stage using Risk Based Approach and taking into consideration the manufacturing environment"* Consideration should be given to providing some guidance on verification of processing at healthcare e.g. hospital sites
532 Section 5.20 (d)	For all aseptic processes, aseptic process simulations should be performed as part of initial validation and normally repeated every six months. See Annex 1 for more information. In the case of infrequent production (i.e. if the interval between the production of two batches is more than six months but less than a year), it is acceptable that the process simulation test is done just before the manufacturing of the next batch, provided that the results of the process simulation test are available prior to the start of production.	This subsection is considered to be too prescriptive. While it is agreed that aseptic process simulation are needed, the frequency and number of runs cannot be stated in the guidance at this stage. A Risk Based Analysis will be needed on a case by case basis and applicability of Annex 1 should not be quoted as there are many situations where deviations from Annex 1 will be justified by the site environment (Hospital ward etc..)
539 Section 5.20 (3)	If the ATMP is not produced on a routine basis (i.e. over a year) the aseptic process simulation should be conducted in triplicate prior to the start of manufacturing, involving all relevant operators.	*In 2017 draft Annex 1 it is stated that:* *"Typically 3 successful consecutive repeat APS would be expected; any differences to this expectation should be clearly justified prior to repeat performance."* Hence, it is suggested to rephrase it to: *"If the ATMP is not produced on a routine basis (i.e. over a year) the aseptic process simulation should be conducted in triplicate. Any difference to this expectation should be clearly justified."* Alternatively, this section can cross-reference to APS section in the revised Annex 1.
548 Section 5.21	ATMPs manufactured for early phase clinical trials (phase I and phase I/II), are not expected to be validated to the extent necessary for routine production	This section and requirement to not be validated <u>should be extended to phase III</u> or the <u>expectation for phase III</u> need to be added

619 Section 5.30	The quality requirements established by the manufacturer for the starting materials and materials, defined to be critical during QRM process, should be discussed and agreed with the suppliers.	We suggest this amendment: as initial quality requirements are often established by development with suppliers support. *The quality requirements established ~~by the manufacturer~~ in the MA or CTA for the starting materials and materials, defined to be critical during QRM process, should be discussed and agreed with the suppliers during the product life cycle.*
648	All material that comes in direct contact with the medicinal product should be of sufficient quality. The risk for cross-contamination due to microbiological contamination, extractable and leachable should be assessed especially for single use material (e.g. cell cultivation vessels, cryostorage containers).	Suggest to replace sufficient by appropriate: *"All material that comes in direct contact with the medicinal product should be of appropriate quality."*
707 Section 5.35	If the production of ATMP involves cell culture or propagation in embryos and animals, in order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, it should be based on a system of master and working virus seed lots and/or cell banks.	Suggestion to differentiate between autologous and allogeneic products. It should be considered that the establishment of seed lots/cell banks are not mandatory. *"It is recommended that the system of master and working seed lots/cell banks is used for allogeneic products which do not require a match between the donor and the patient. However, the establishment of seed lots/cell banks is not mandatory."*
793	The Authorised Person may provide a less technical description of the failed parameters upon request to the treating physician and where possible a description of potential consequences; and	Is the end of the sentence missing?
828 Section 5.58 (a)	The responsible site: should perform audits to confirm compliance with the batch certification and release process (as descriptive in SOP)	*During the product Life Cycle, the responsible site ……*
838 Section 5.48 (a)	Ensure deviations are approved by a responsible person with the involvement of the Authorised Person as appropriate.	"Authorised Person" should be defined in the Glossary and the document shecked to ensure that it is used correctly throughout. "Responsible Person" Is defined, however, this phrase in line 838 may not be that given in the Glossary. If different in line 838, an alternative should be considered and defined.

915 Section 6.7	A sample of a fully packaged unit (retention sample) should be kept per batch for at least two years after the expiry date.	This is challenging for individualized products, and may amount up to several thousand batches per year. Additionally there could be shelf life issues as well as availabiity of material if all of a batch is administered to a patient. This point is confusing. We suggest wording is amended to support more examples of ATMPs where only photographs and rention of labels are retained.
1070	There are potentially 2 types of gene therapy products (vectors and genetically modified cells) and both are within the scope of the guidance in this section.	Gene Therapy Products should include a broader scope than just 2 potential types. Instead, this should acknowledge that there are several types, including messenger RNA (mRNA)-based gene therapy products. We suggest incorporating m RNA in the table set in the scope.
1105 B2.2	Since the cells used in the manufacture of gene therapy products are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents.	This section must acknowledge that some gene therapy products are manufactured in cell-free biosynthetic reactions (e.g. mRNA products are produced enzymatically using purified enzymes).
1192 B3.2	Where devices, including custom-made devices, are incorporated as part of the products: (a) There should be a written agreement between the manufacturer of the medicinal product and the manufacturer of the medical device, which should provide enough information on the medical device to avoid alteration of its properties during manufacturing of the ATMP. This should include the requirement to control changes proposed for the medical device. (b) The technical agreement should also require the exchange of information on deviations in the manufacture of the medical device.	We suggest revising to: *During the life cycle of the product where devices, including custom-made devices, are incorporated as part of the product, an appropriate Quality Agreement should be made between manufacturer and device suppliers.* Quality Agreement may require definition in the Glossary or a reference given.
1231	Common Glossary To Annex 2A and 2B	Suggest to include “axenic” which can be found in the Glossary of current Annex 2.
1260 - Glossary	Antibodies may be divided into 2 main types based on key differences in their method of manufacture:	End of sentence appears to be missing
1262	Monoclonal Antibodies	This should be included under the category of alphabet M

Line Comments on Draft Annex 2B (PS/INF 26/2019 (Rev. 1))		
Line Number & Section	**Current wording**	**Comment or proposed alternative wording**
240	(g) Campaign based manufacturing	We suggest using the following text of this clause, *"Campaign-based manufacturing followed by validated cleaning and decontamination procedures."*
360	For autologous and donor-matched situations, the manufactured product should be viewed as a batch.	Suggest to transfer this requirement to draft Annex 2A since autologous and donor-matched situation is typically applicable to ATMP.
635	In the case of autologous products, the unique patient identifier…….	Suggest to transfer this requirement to draft Annex 2A since autologous product is typically applicable to ATMP.
804	The sequence of addition……in compliance with specifications.	Suggest to revert to the current requirement as stated in clause 4 (subsection B4) in Annex 2, i.e. "The sequence of addition…….in compliance with the manufacturing instructions or the batch records."