**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**

To whom it may concern,

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) is pleased to announce a consultation to:

1. Invite comments to be provided on a draft of:
	* PIC/S GMP Guide *Annex 2A Manufacture of Advanced Therapy Medicinal Products (ATMP) for Human Use* (PS/INF 25/2019 (Rev. 1)) which is essentially based on the existing PIC/S Annex 2 with elements from other international standards that have been published;
	* PIC/S GMP Guide *Annex 2B Manufacture of Biological Medicinal Substances and Products for Human use* (PS/INF 26/2019 (Rev. 1)) which has been transposed to maintain harmonisation with the revised EU GMP Guide Annex 2 - *Manufacture of Biological active substances and Medicinal Products for Human Use* as published in EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines.
2. Collect feedback from stakeholders to help PIC/S develop its thinking in the area of ATMP recognising that this is a rapidly developing industry and that the PIC/S document being developed represents an intention of PIC/S to consider:
* issues that stakeholders (including academia, hospitals, subject matter experts or the pharmaceutical industry subject matter experts) are facing in the international context; and
* how harmonised international GMP standards can help to facilitate manufacturing of these products, especially in consideration of the increasing manufacturing that occur cross-border.

Since the current [PIC/S GMP Guide Annex 2 Manufacture of biological medicinal substances and products for human use](https://www.picscheme.org/layout/document.php?id=1407) entered into force, scientific progress has been made in the field. New technologies are now available impacting not only on manufacturing processes but also the location of manufacture which may be performed in non-traditional manufacturing settings. These new technologies and the non-traditional manufacturing settings call for a review of the good manufacturing practices applied to ATMP products including advance therapy investigational medicinal products (ATIMP). ATMP and ATIMP mean any of the following medicinal products for human use: gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered medicinal products.

With many of these products under development and approaching marketing authorisation specific quality issues may need to be incorporated into guidance. PIC/S has proposed two separate Annexes (2A and 2B) that will work together with other existing PIC/S Guides and Annexes to detail good manufacturing practices.

To facilitate development of a PIC/S thinking in the field of ATMP your feedback is welcomed on a number of aspects described in the following table (see questions 1 to 9). Line comments on Annex 2A and/or Annex 2B are to be included in the designated space. A draft version of the PIC/S Annex 2A and 2B are downloadable on the PIC/S website and have been formatted with prescribed line numbers.

The consultation period will last 3 months and run from **20 September 2019** to **20 December 2019**.

To submit feedback, please provide your feedback **exclusively** on this dedicated Consultation Notice **in Word format** (not PDF) and send by e-mail with subject line "PIC/S Focused Public Consultation – Revision Annex 2"to one of the following associations which have volunteered to collect and compile responses. **Stakeholders should only reply once**.

* [**ECA**](https://www.eca-foundation.org/) (European Compliance Academy) Foundation:
send to: heimes@gmp-compliance.org
* [**IFPMA**](https://www.ifpma.org/) (International Federation of Pharmaceutical Manufacturers & Associations):
send to: s.adam@ifpma.org
* **ISCT** (International Society for Cell & Gene Therapy)

send to: audrey@isctglobal.org

* [**ISPE**](https://ispe.org/) (International Society for Pharmaceutical Engineering):
send to: regulatorycomments@ispe.org
* [**PDA**](https://www.pda.org/) (Parenteral Drug Association):
send to: tmorris@pda.org
* **SQA** (Society of Quality Assurance)
send to: Megan.Callan@crl.com

Table 1.0: PIC/S Consultation Questions

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| Contact Information (Name, position, and full contact details): |
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| 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**

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| **Example product** | **Application of this guide to manufacturing steps shown in grey** |
| Gene therapy: genetically modified cells | Donation, procurement and testing of starting tissue / cells1 | 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 / cells1 | 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 / cells1 | 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**

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| Gene Therapy: in Vivo Viral Vectors by stable producer cell lines | Plasmid manufacturing1 | Producer cell lines manufacturing | Vector Manufacturing | Formulation, filling |
| Gene Therapy: in Vivo Viral Vectors by transient production system | Virus manufacturing1 | Cell system manufacturing | Vector Manufacturing | Formulation, filling |

1Separate GMP requirements may apply where required under national law. |
| Stakeholder Feedback | <insert feedback here> |
| 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](https://www.picscheme.org/layout/document.php?id=1408) 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. |
| Stakeholder Feedback | <Insert Feedback Here> |
| 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](https://www.picscheme.org/layout/document.php?id=1407) 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) |
| Stakeholder Feedback | <Insert Feedback Here> |
| 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](https://www.picscheme.org/layout/document.php?id=1407) 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. |
| Stakeholder Feedback | <Insert Feedback Here> |
| 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:1. 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;
2. 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
3. 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.

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| 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.* 1. 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.
	2. 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:
		1. A "responsible site", should be identified. The responsible site is responsible for the oversight of the decentralised sites. The responsible site:
			1. must have availability of an Authorised Person,
			2. must ensure that those involved in the batch certification and release process are adequately qualified and trained for their tasks,
			3. should perform audits to confirm compliance with the batch certification and release process (as descripted in SOP),
			4. 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
			5. 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.
		2. 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:

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; 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.
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| Stakeholder Feedback | <Insert Feedback Here> |
| 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? |
| Stakeholder Feedback | <Insert Feedback Here> |
| 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](https://www.picscheme.org/layout/document.php?id=1407) 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 systemb) 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 20c) 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. |
| Stakeholder Feedback | <Insert Feedback Here> |
| 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. |
| Stakeholder Feedback | <Insert Feedback Here> |

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| Line Comments on Draft Annex 2A (PS/INF 25/2019 (Rev. 1)) |
| **Line Number & Section** | **Current wording** | **Comment or proposed alternative wording** |
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| Line Comments on Draft Annex 2B (PS/INF 26/2019 (Rev. 1)) |
| **Line Number & Section** | **Current wording** | **Comment or proposed alternative wording** |
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