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Science and Risk-based Approaches for the Classification of Post-approval Changes for ATMPs in the EU

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Executive Summary

Regulatory efficiency, as a prerequisite for a modern regulatory system, is recognised in the Pharmaceutical Strategy for Europe and the need to revise the variation framework through changes in legislation and guidelines is listed as a flagship initiative.

Due to the unique properties of ATMPs and the rapid evolution of technologies, even with the current revisions, the variation guideline still creates a rigid framework that may block innovation, continuous improvements and potentially patient access for ATMPs.

The European Commission is in the process of revising the variation framework for medicines for human use to establish more efficiency during life cycle management and to reduce the administrative burden for both marketing authorisation holders and the regulatory authorities. The initial revisions to the variations guideline has resulted in the reclassification of specific variations into lower categories, adding flexibility for biological medicinal products, including Advanced Therapy Medicinal Products (ATMPs). These initial changes to the variations classification guideline are providing some simplification and helping towards efficient life-cycle management, but further simplification could be made for ATMPs.

The European Commission Competitiveness Compass was launched in January 2025 and was intended to help manufacturers by simplifying legislation across the EU. ATMP stakeholders (regulators, manufacturers, and patients) would benefit from appropriate use of a risk-based framework (similar to the thought process shared by the EMA in their investigational ATMP guideline EMA/CAT/22473/2025) supporting the management of life cycle variations of ATMP products. The upcoming second revision of the variation regulation is therefore a good opportunity to simplify the legislation appropriately for the lifecycle of ATMPs. This would include enabling the use of ICH Q12 concepts for ATMPs, including the use of Established Conditions (ECs). This change could be used to promote international alignment of regulatory requirements for post-authorisation lifecycle management. Such an alignment of requirements could fit together with the work the EMA is already undertaking globally in terms of promoting convergence, harmonisation and reliance. In so doing, the EU could play a key role in triggering further global harmonisation across variation systems, which would ultimately yield benefits in terms of sustainability of ATMP supply in Europe and worldwide, further underpinning Europe's competitiveness as described in the Draghi report.

Background

Revision of the Variation Regulation (1234/2008) and the Classification Guideline (C(2013) 2804) is being conducted to provide for simplification, efficient life-cycle management (including addressing challenges relating to the interplay of medicines and devices and for novel and more complex therapies) and to adapt to digitalisation. There is an opportunity here for the EU to play a leading role in driving international alignment across variation systems thereby improving lifecycle management at a global level.

The European Commission is in the process of revising the variation framework for medicines for human use to establish more efficiency during life cycle management and to reduce the administrative burden for both marketing authorisation holders and the regulatory authorities. The European Commission is also re-classifying specific variations into lower categories, adding flexibility regarding the level of technical information that must be provided, and clarifying the changes and data that must be communicated to the regulators.

Introduction: Drivers for Change

The field of ATMPs is still nascent, and the analytical and manufacturing technologies are rapidly evolving providing opportunity for production process and/or product optimisations during development or post approval. In addition, ATMPs often involve accelerated clinical development programs and a limited number of batches manufactured during clinical development resulting in limited manufacturing experience and the need for further process development after initial MAA approval, leading to an increase in post-approval variations. These process changes are intended to improve the process performance and product availability; however, such changes in the context of ATMPs can raise issues related to the boundaries of the product sameness, and their regulatory impact (i.e., variation vs line extension vs new MAA).

Due to the unique properties of ATMPs, and the rapid evolution of technologies, the variation guideline designed for chemical and “traditional” biological medicinal products creates a rigid framework that may block innovation, continuous improvements and potentially patient access. For instance, depending on the modality, the cells or plasmids could be considered to be starting materials, intermediates, or the product. Contingent on the classification, there could be different expectations for comparability, control, and lifecycle submissions.

In the case of personalised ATMPs (e.g., autologous cell therapies) which are produced for a specific patient, there are unique changes non-existent for other modalities, for example, changes to the plasmid starting materials within or outside the gene of interest. Those changes are not categorised in the current variation guideline which is causing classification constraints and very often increases administrative burden, including EMA queries and validation issues. Therefore, classification of ATMP unique changes in the variation framework would be very beneficial for the MAH and the regulators.

The European Commission intends to revise the variation regulation to address some issues, including database entry of Type IA variations and full implementation of ICH Q12, which can only be made after the revision of the general pharmaceutical legislation (GPL) is completed. There is an opportunity to ensure that the upcoming second revision of the variation regulation is appropriate for the lifecycle of ATMPs and enables the use of ICH Q12 concepts for ATMPs and promotes international alignment of regulatory requirements for post-authorisation lifecycle management. In

doing so, the EU could play a key role in triggering more global harmonisation across variation systems, which would ultimately yield benefits in terms of sustainability of ATMP supply in Europe and worldwide and further underpin Europe's competitiveness. Furthermore, Product Life Cycle Management ("PLCM") is being introduced into the Variations framework. This will have a positive impact on the current practice by focusing requirements for submission and assessment of changes on those changes with the greatest potential to impact patients.

Application of a Flexible Regulatory Framework under the Provisions of ICH Q12

The ICH Q12 Product Lifecycle Management guideline has reached step 5 in several jurisdictions, and this guideline works with ICH Q8 to ICH Q11 to provide opportunities for a more science and risk-based approach for assessing changes across the lifecycle. The use of ICH Q12 tools, such as the product lifecycle management (PLCM), could reduce the number of regulatory submissions for post-approval CMC changes by clearly distinguishing between changes that need to be reported to Regulatory Authorities from changes that can be managed solely within the pharmaceutical quality system (PQS). Other ICH Q12 tool, such post-approval change management protocols (PACMPs), can facilitate the implementation of CMC changes through prior agreement mechanisms, thereby improving the predictability for change implementation, and potentially accelerating implementation of changes (e.g., downgrading step 2 reporting to Notification Low).

Application of ICH Q12 and development of guidance on how to implement Q12 tools for ATMPs, including PLCM documents and PACMPs, should also be considered by EMA and guidance should be provided to support use of these tools for ATMPs. This could enable rapid implementation of changes with reduced reporting for these products.

The following case studies illustrate how ICH Q12 can be applied for ATMPs. Each case study has a specific scope and focusses on a specific product type; however, the aim is to stimulate thinking about how the ICH Q12 concepts could be applied more broadly in the ATMP space. As such, the suggestions provided in the case studies could be adapted and applied to other situations.

Case Studies

1. Plasmid Starting Material Changes

1.1. Scope and Background

For the manufacture of many viral-based gene therapy product, a series of different plasmids are used, and these are defined as starting materials for the manufacturing process. Within the dossier, all starting materials used for manufacture of the gene therapy active substance based on viral vectors should be listed and information on the source, quality and control of these materials must be provided.

It is desirable to have minimal changes to the plasmid starting materials after approval; however, this might not always be feasible or practical for the MAH. Changes that may occur post approval include:

a) Change in plasmid manufacturer (addition or replacement)
b) Change in plasmid manufacturing process (e.g. change of *E. coli* strain, change of medium, change of process parameters)
c) Change in plasmid specifications and analytical methods

Many changes to these starting materials would currently be categorised as Type II variations within the EU. However, a risk-based approach should be considered to determine the reporting category for the variation. Where there is no potential for an impact on the safety and efficacy profile for the product, the proposal is to reduce the reporting category from Type II to Type IB.

1.2. Submission in Accordance with EU Variation Classification

The changes to these starting materials are currently categorised in accordance with European Commission Regulation No 1234/2008 (final version published 22 September 2025) as described in the table below.

Variation Category	Conditions to be fulfilled	Documentation to be supplied	Procedure Type
Q.I.a.1: Change in the manufacturing site of a starting material/ intermediate used in the manufacturing process of the active substance or change in the manufacturing site (including where relevant quality control testing sites) of the active substance: d) Addition or replacement of a manufacturing site of: • a biological active substance or • a biological starting material /reagent/raw material/intermediate used in the manufacture of a biological active substance which may have a significant impact on the quality, safety or efficacy of the finished product or • a material for which an assessment is required of viral safety and/or TSE risk	–	–	II

Variation Category	Conditions to be fulfilled	Documentation to be supplied	Procedure Type
Q.I.a.2: Change in the manufacturing process of the active substances or starting materials for biological active substance: b) Major change to the manufacturing process which may have a significant impact on the quality, safety or efficacy of the finished product	–	–	Type II
Q.I.b.1: Change in the specification attribute and/or acceptance criteria of an active substance, starting material/reagent/intermediate used in the manufacturing process of the active substance: g) Change outside of the specification acceptance criteria for starting material/ reagent/ intermediate which may have a significant effect on the overall quality of the active substance and/or the finished product	–	–	Type II
Q.I.b.1: Change in the specification attribute and/or acceptance criteria of an active substance, starting material/reagent/intermediate used in the manufacturing process of the active substance: l) Replacement of a specification attribute with its corresponding analytical procedure	–	Not a consequence of a commitment to review specification; not a result of unexpected events arising during manufacture and is not as a result of a safety or quality issue. The analytical procedure remains the same. The change is fully described.	Type IB
Q.I.b.2: Change in test procedure for active substance or starting material/ reagent/ intermediate used in the manufacturing process of the active substance: g) Introduction, replacement or change to a biological/ immunological/ immunochemical analytical procedure for starting material/ reagent/ intermediate, used in the manufacturing process of an active substance	–	Comparative validation results, or if justified comparative analysis results showing that the current analytical procedure and the proposed one are equivalent.	Type IB

It is essential to demonstrate the suitability of plasmid starting materials following changes and the suitability of the plasmids is ensured by their respective preparation processes and their control strategy (e.g., release tests, stability monitoring, controls inherent to the process). It is also essential to demonstrate that there is no impact on the drug substance, so that submission of these changes would therefore be accepted as a variation rather than a line extension. A line extension could be required if the drug substance could be defined as a New Active Substance and this would result in a significant review time and could delay implementation of this change.

The preparation and control of plasmid starting materials are developed in accordance with product specific studies and prior knowledge, and take into account international guidelines and monographs (EMA Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal

products (CPMP/BWP/3088/99), Ph. Eur., Monograph 5.34, FDA Guidance for Industry: Chemistry, Manufacturing, and Control Information for Human Gene Therapy Investigational New Drug Applications, USP 1047).

The typical information, presented in *Section 3.2.S.2.3 Control of Materials*, on the plasmid starting materials is summarised below:

- Manufacture of the plasmids
  - Manufacturer
  - Manufacturing process description
  - Control of the manufacturing process
- Control of materials for plasmid manufacture
  - Generation of the plasmids
  - Preparation of the plasmid cell banks
  - Specifications and testing of the plasmid cell banks
  - Stability and storage of the plasmid cell banks
- Release specifications and testing of the plasmids
- Stability and storage of the plasmids

1.3. Use of ICH Q12 Tools for Post-approval Changes

1.3.1. Use of a PACMP

The lifecycle of these starting materials could be facilitated by the introduction of a PACMP, which is possible under the current revision of the variation regulation. A PACMP outlining a sponsor's approach to the introduction of changes to the starting materials could be submitted at time of initial submission of the Marketing Authorisation Application or post-approval. This PACMP would outline the quality risk management approach applied for the introduction of these new starting materials and the subsequent criteria and data package to be used to ensure the suitability of the new starting materials in the manufacture of the gene therapy active substance. The approval of the PACMP would then allow for decreased reporting and could be used repeatedly as starting materials for the manufacture of drug substance are changed.

1.3.2. Use of a PLCM Document

Identification of Established Conditions and their Reporting Categories

As the scope of the changes being discussed can be controlled through ECs, variations could also be managed using a PLCM document, thus resulting in a downgrade to the variation classification. Use of ECs is not currently possible under the current revision of the variation regulation but could be introduced in the future revision.

The registration of a PLCM document may be more beneficial in situations where recurrent changes in the starting material are anticipated. A summary of the risk-based approach used to identify the elements that would be necessary to ensure product quality is presented below:

- Impact on product quality: the drug substance is not produced at the plasmid manufacturing step; however, safety related attributes could be impacted at this stage and carried over into subsequent steps. Some process parameters and input materials can have an impact on the characteristics of the plasmids which could then impact the consistency of downstream steps.

- Probability: Prior knowledge and product specific data indicates that the probability of occurrence of negative impact on product quality is highly dependent on the plasmid preparation process.
- Detectability: Potential impact may be tested at different levels, including plasmids, process intermediates and at the level of the drug substance, at release or through storage. There should be no need to monitor the drug product as drug product manufacture may be limited to filing and that changes to the plasmid would have no impact on the drug product.

Based on the risk assessment, the following elements (summarised in the table below) are identified as sections that contains ECs, as they are considered necessary to assure product quality:

Changes	Justification Plasmid Starting Materials	Category
Plasmid manufacturer	With no change in plasmid sequence or to the plasmid cell banks, comparable methods of manufacture, a satisfactory GMP qualification audit and no change in the release specification, there would be no impact on product quality, confirmed by in-process control and release testing.	EC
Method of production	Manufacturing process used to prepare new plasmid batches can impact subsequent expansion steps, and ultimately product quality.	EC
Control of plasmid batches	Starting materials should be appropriately controlled at appropriate stages to demonstrate their suitability for drug substance intermediate and drug substance production. This includes parameters or attributes that can impact subsequent expansion steps, and ultimately product quality.	EC
Characterisation data	Characterisation tests are performed at appropriate stages. They inform on the product and process and are generally not intended to be repeated on a routine basis.	Supportive information
Intermediate and drug substance control	The suitability of the plasmid is verified, including tests at the level of drug substance or relevant intermediate, and through in-process testing, as appropriate.	EC *

* *Elements related to drug substance/drug substance intermediate controls are also considered EC but will be managed in accordance with the EC identified for the drug substance control strategy which are not further discussed in this example.*

Proposed Reporting Categories

EC and reporting categories for changes to plasmid manufacture, control and storage are provided in the following table which serves as the basis to define the PLCM document. This is not an exhaustive list of examples but contains suggested ECs to be considered on a case-by-case basis. Acceptance criteria may be expected but are not proposed in this table.

As outlined in the table on the classification of the variations in accordance with the published guideline, these changes would be classified as Type II or Type IB variations, and the use of ECs gives the potential to reduce the variation classification further, as outlined below.

Stage		Plasmid Starting Material Proposed EC and reporting categories (White boxes indicate EC and their reporting categories; **grey boxes are not-EC**.)		Reporting	Comments / Justifications
	Section	***3.2.S.2.3 Control of Materials***			
Plasmid Preparation	Preparation process and storage	Description of preparation process and storage are applicable to current and future plasmid batches		NM	EC will include description of the preparation process and storage for current and future plasmid batches. Upon approval of the ECs, new plasmid batches will not be reported as long as they are prepared and stored in the same location as the previous batches, and controlled in accordance with the approved EC. Changes of manufacturer or to the preparation process will be reported as NM.
Plasmid Control	Safety and impurities testing	A260/280 Ratio Purity	##	NL	
		DNA Homogeneity	##	NL	
		Endotoxin	##	NL	
		Residual Host Genomic DNA	##	NM	
		Residual Host Protein	##	NL	
		Residual Host RNA	##	NL	
		Sterility	No Growth	NM	
		Mycoplasma Contamination	Negative for the presence of Mycoplasma	NM	
		Osmolality	Report [mOsm/kg]	NR	
		pH	Report	NR	
	Strength and identity testing	Appearance	Clear and colourless	NR	
		Concentration	Report [mg/mL]	NR	
		Identity	Size Confirmation	NL	
		Plasmid Identity (Sequence Confirmation)	Identical to reference sequence	NM	

Stage		Plasmid Starting Material Proposed EC and reporting categories (White boxes indicate EC and their reporting categories; **grey boxes are not-EC**.)		Reporting	Comments / Justifications
		Restriction Digest (PA)	Matches expected restriction pattern or client supplied reference material	NM	The control strategy applied to plasmid batches includes proposal of tests and limits that are considered EC, as they will ensure proper quality of the plasmid in subsequent steps. Taking into account that the active ingredient is not produced at this stage, and that product CQA are not directly impacted by this step (except for safety aspects), changes to the preparation or control are considered as low to moderate risk. Elements that could ultimately impact product quality are considered moderate to high depending on their severity and the control strategy. For instance, changes to identity test and restriction digest are considered as low to moderate considering that these elements would be confirmed by the sequence confirmation of the plasmid that is considered as high risk (PA).
Plasmid Storage	Storage conditions	Change in storage conditions in accordance with stability protocol		NL	
	Stability	Change in stability protocol		NL	
		Change in shelf life in accordance with stability protocol		NL	

***PA**: Prior Approval (PAS, Type II, PCA, etc.); **NM**: Notification Moderate (CBE 30, Type IB, MCN, etc.); **NL**: Notification Low (CBE 0, AR, Type IA, MCN, etc.); **NR**: Not Reported.*

indicates that acceptance may be required but are not proposed in this table.

2. Change of Cell Bank Starting Material

2.1. Scope and Background

A common feature of ATMP products is an accelerated clinical development with manufacturing process development lagging behind resulting in the commercialisation of a process needing updates for improvement of the manufacturing efficiency and capabilities or implementation of novel technologies. Manufacturing of in vivo adeno-associated virus (AAV)-based Gene Therapy products is one example where early manufacturing platforms are often based on adherent cell culture and transient triple transfection resulting in modest productivity and high production cost. Continuous improvement and shift to more innovative approaches are essential to meet patient demand and access to these innovative therapies. The transition from adherent cell culture to a suspension process using a stable cell line is one potential optimisation during the product life cycle. This change aims to secure the product supply chain, enhance productivity, and reduce the Cost of Goods (COGs) making the product more affordable. In addition, modifications are often implemented in the purification process to increase yield and enhance overall product quality. Ensuring the robust analytical comparability of the product manufactured with the updated process is critical for maintaining efficacy and ensuring patient safety throughout the product life cycle.

2.2. Submission Strategy in Accordance with EU Variation Classification

Under the current regulations (Notice to Applicants, July 2019)[1] the introduction of a new cell bank starting material for an active substance could be categorised as an extension application due to changes to the active substance. However, in some instances the submission of a Major Variation of Type II (B.I.a.2.c) in accordance with the European Commission Regulation No 1234/2008 (final version published 22 September 2025) was considered acceptable (please refer to table below).

Variation requested	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure Type**
Q.I.a.2: Change in the manufacturing process of the active substance, intermediate of an active substance or starting materials for biological active substance b) Major change to the manufacturing process which may have a significant impact on the quality, safety or efficacy of the finished product	–	–	Type II

The use of a PACMP can support the introduction of a change of cell banks and associated process updates via a Type II variation instead of a Line Extension. In addition, it can help increase the certainty and transparency for the submission category by reducing the ambiguity in the current regulation related to changes of cell banks starting materials.

In reference to EMA/CHMP/CMDh/CAT/BWP/828612/2022, no new active substance claim is being made as a result of the change to the cell banks:

- No first intent claim asserting substantial differences in basic structural elements, biological characteristics, and/or biological activity

[1] Guideline on the Categorisation of Extension Applications (EA) versus Variations Applications (V), July 2019

- No third intent claim: no significant differences in properties related to safety and/or efficacy, stemming from variations in molecular structure, nature of the source material, or the manufacturing process

2.3. Use of ICH Q12 Tools for Post-approval Changes

2.3.1. Submission of a PACMP

The introduction of a new cell bank starting material could be facilitated by the establishment of a PACMP. Submission of a PACMP is possible under the current revision of the variation regulation. However, clarification is needed in the second revision that this could be applied to the introduction of a new cell bank starting material.

A PACMP outlining a sponsor's approach to the introduction of changes to the cell bank including consequential process adaptation could be submitted at time of initial submission of the Marketing Authorisation Application or post-approval. This PACMP would outline the quality risk management approach applied and the subsequent criteria and data package to be used to ensure the suitability for the manufacture of the gene therapy active substance. The approval of the PACMP would then allow for decreased reporting and pre-align the supporting data set and hence ease the introduction of process improvements into the life cycle of a gene therapy product.

PACMP Case Study: Methodology

Ensuring the comparability of the product manufactured with the updated process is critical for maintaining efficacy and ensuring patient safety.

A PACMP can outline the comparability assessment including a comparison of release parameters against pre-specified acceptance comparability criteria as well as a comprehensive assessment of critical quality attributes through extended characterisation of the product examining expressions, post-translational modifications (PTMs), and the integrity of structural elements. Emphasis is put on evaluation of potency related critical quality attributes, which are tested with orthogonal assays, including one bioassay which relates to the therapeutic effect. Furthermore, as prespecified in the PACMP, a comparison of impurity profiles is conducted as well as a comparative stress stability study.

PACMP Case Study: Results and Conclusion

The comparability assessment demonstrates that the majority of the product quality attributes are within the pre-specified comparability ranges with a few exceptions. Differences are observed in the impurity profile i.e. different HCP pattern as well as a modified ratio of viral capsid proteins VP1/2/3. The risk assessment concludes that there is no impact expected on the safety profile based on the differences observed. The updated manufacturing process leads also to an increased percentage of full capsids i.e. a change from 45% to 60% full capsids which is an intentional improvement target by the updated manufacturing process. The product potency and efficacy are not impacted by this intentional CQA modification since dosing of the product is based on viral genome copies. The improved impurity profile may enhance safety assurance through the reduced amount of empty capsid not contributing to the therapeutic effect. In general, the impact of empty capsids is still speculative in terms of decoy versus activation of the immune system and, therefore, the potential impact on immunogenicity will be investigated within the long-term follow-up plan.

In conclusion, the differences in manufacturing process and the resulting products quality are considered to not impact biological and functional characteristics and hence will not have a

significant impact on quality, safety and efficacy. Therefore, no additional clinical and/or non-clinical studies are deemed necessary in the context of the comparability assessment.

In addition, no substantial differences are claimed based on:

- **Basic structural elements, i.e.**
  - Identical AAV serotype (vector capsid ID/ LCMS)
  - Same capsid proteins: VP1/VP2/VP3; variation only in range of abundance (LCMS & CE-SDS for quantitation/ratio)
  - Same regulatory elements driving the target gene expression (Sanger Sequencing)
  - Identical therapeutic sequence (Sanger Sequencing)
- **Biological characteristics, i.e.**
  - Same tissue tropism
  - Comparable infectivity
  - Comparable expression level of the transgene and transgene itself
- **Biological activity**
  - Potency matrix assay results within comparability AC (potency)
  - Infectivity, expression assay, in vitro functional assay
  - In vitro mouse model - demonstrating that in vitro functional assay is mirroring the biological activity - not leveraged
- **No differences in nature of the source material**
  - Biotechnological manufacturing based on same HEK293 host cell origin

The data package including the outcome of the comparability assessment supports the submission of Major Variation in notification of the change.

In reference to EMA/CHMP/CMDh/CAT/BWP/828612/2022, no new active substance claim is made:

- No first intent claim: no substantial differences in basic structural elements, biological characteristics, and/or biological activity
- No third intent claim: no significant differences in properties related to safety and/or efficacy, stemming from variations in molecular structure, nature of the source material, or the manufacturing process

The absence of first and third intent claims, not warranting the classification of a new product, justifies the submission of a major variation submission under the existing Marketing Authorisation.

2.3.2. Submission of a PLCM document

Due to the complexity of the described change in cell banks starting material and consequential process manufacturing changes, the application of a PLCM is not suitable.

3. Addition of Alternative Manufacturing Suites for Cell-based Medicinal Products

3.1. Scope and Background

For cell-based medicinal products, increased demand in many cases results in frequent additions of a manufacturing suite(s).

As long as the manufacturing process is not impacted and/or changes are minimal based on a risk assessment, e.g. alternative equipment of equivalent performance or minor suite adaptations, a risk-based approach could be implemented and a lower variation category could be applied.

In most of the cases, the addition of an alternative manufacturing suite for cell-based medicinal products manufacture (including additional suites for vector) generally results in the submission of a variation and a risk-based approach is not currently implemented for the assessment of these changes. In fact, based on the risk assessment, a lower variation category could be applied, and this would be beneficial for both the authorities and the Applicants.

Using a risk-based approach, an assessment of the ICH Q12 principles and the impact of the changes on the quality established for the pre-change product should be considered to determine the reporting category for the variation.

Where there is no potential for an impact on quality for the product, the proposal is to reduce the reporting category. In some cases, the addition of identical suites, based on risk assessment outcome, could be even downgraded and covered under GMP activities as indicated on the EMA Website Quality Questions and Answers: Quality *What changes in manufacturing sites, buildings and rooms are covered by the company Quality Assurance System (GMP)* and *Changes in equipment used in the manufacturing process. What changes are covered by the company Quality Assurance System (GMP)?*

In some cases, such changes result only in updates to the process validation section (Section 3.2.S.2.5) with new verification data for the alternative suite, and the facilities and equipment section (Section 3.2.A.1) to update sites layouts etc. Other Module 3 Sections are not impacted. In particular, there is no impact to the manufacturing process description and the overview of the critical process controls (Section 3.2.S.2.2 or 3.2.S.2.4, respectively). Therefore, such activities could be covered under GMP and the Company Quality systems, and could be implemented upon successful completion (if concluded from the risk assessment).

Suite definition: A suite is defined as a space formed by a room or a group of rooms within the manufacturing site where the manufacturing operations take place for a given product.

Line definition: set of equipment of activities used repeatedly and in order to manufacture given product.

3.2. Submission Strategy in Accordance with EU Variation Classification

3.2.1. Example for Editorial Change:

A registered manufacturing site created a new suite for a product within the same building with the same equipment as currently registered. The site was inspected for GMP compliance and a new GMP certificate was issued including this new suite.

3.2.2. *Examples for Type IA Variation:*

A registered manufacturing site created a new suite for a product within the same building with equivalent equipment as currently registered with no changes or non-significant changes to process parameters (based on Risk Assessment outcome). The site was inspected for GMP compliance and a new GMP certificate was issued including this new suite.

3.2.3. *Example for Type II Variation:*

A registered manufacturing site created a new suite for a product within the same building with new equipment with potentially significant changes (based on Risk Assessment outcome) to process parameters. The site was inspected for GMP compliance and a new GMP certificate was issued including this new suite.

3.2.4. *Variation Classifications:*

The variation classification based on different conditions in accordance with European Commission Regulation No 1234/2008 (final version published 22 September 2025) is outlined in the table below:

Variation requested	**Conditions to be fulfilled**	**Documentation to be supplied**	**Type**
Q.I.a.1. Change in the manufacturing site of a starting material/ intermediate used in the manufacturing process of the active substance or change in the manufacturing site (including where relevant quality control testing sites) of the active substance d) Addition or replacement of a manufacturing site of: • biological active substance or • a biological starting material / reagent/ raw material/ intermediate used in the manufacture of a biological active substance which may have a significant impact on the quality, safety or efficacy of the finished product or c) a material for which an assessment is required of viral safety and/or TSE risk	New suite is within the same site where the activity occurs already. Exact same equipment will be used. Suite is covered by a GMP certificate. No update on Module 3 except Section A.1.	Updated Modules GMP certificate	Editorial update
	New suite is within the same site where the activity occurs already. Minor site adaptations covered by risk assessment. Suite is covered by a GMP certificate.	Updated Modules (S.2.5, S.2.6, A.1) Risk assessment Results from minimum of one technical run could suffice (or case by case basis). GMP certificate	IA
	New suite is within a different site. Major changes based on the risk assessment. Suite is covered by a GMP certificate or GMP inspection may be required.	Updated Modules (S.2.2, S.2.5, S.2.6, A.1) GMP certificate Risk assessment Comparability demonstrated	II

3.3. Use of ICH Q12 Tools for Post-approval Changes

3.3.1. *Use of a PACMP*

The lifecycle for addition of manufacturing suites could be facilitated by the introduction of a PACMP, which is possible under the current revision of the variation regulation. A PACMP outlining a sponsor's approach to the introduction of changes to the new suites, especially when changes are required, could be submitted at the time of the initial submission of the Marketing Authorisation

Application or post-approval. This PACMP would outline the quality risk management approach applied for the introduction of additional suites and the subsequent criteria and data package to be used to ensure the suitability of the new suite is the manufacture of the gene therapy active substance. The approval of the PACMP would then allow for decreased reporting and could be used repeatedly.

3.3.2. Use of a PLCM Document

Agreement of ECs for the process using a PLCM document may facilitate future additions of alternative manufacturing suites within the same facility. Use of ECs is not currently possible under the current revision of the variation regulation but could be introduced in the future revision. However, the use of a PACMP would be more appropriate for adding alternative facilities at a different facility, as outlined above.

4. Replacement of a Test Method with Improved Analytical Technology for Control of AAV-based Finished Products

4.1. Scope and Background

Analytical measurement capabilities for the analysis of pharmaceutical active ingredients and finished products will continually evolve as innovative technologies are developed and commercialised. These advancements may result in overall improvements, for example, increased detectability or reduced variability. At the time of marketing authorisation, sponsors should apply available state-of-the-art methodology for control methods. However, advances in analytical technology often occur post-licensure. This situation is particularly relevant for ATMPs since the complex nature of these modalities is continually driving innovations in methodologies used for analysis.

The ability to implement changes to the quality control strategy post-licensure is challenging due in part to the variations guideline that systematically excludes biologics, including ATMPs, from Type I variation categories. The increased regulatory burden may delay or inhibit adoption of improved analytical methodologies into existing control strategies. By applying a science and quality risk-based approach, it should be possible to implement certain changes to analytical test methods for ATMPs with a Type I variation as discussed in this case study. This concept is illustrated for a change from qPCR to ddPCR methodology for titre determination of an AAV product.

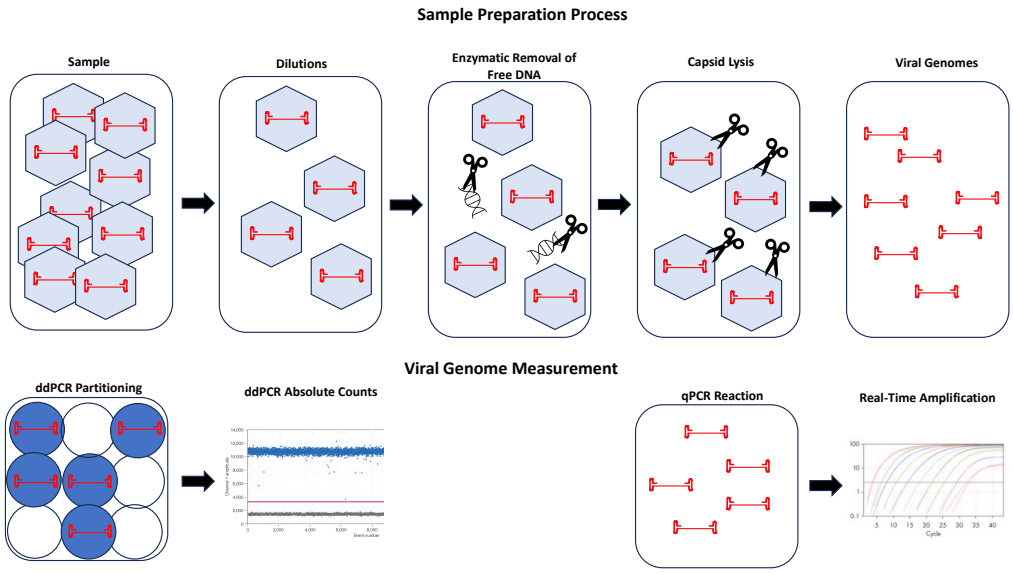
4.2. Quantitative PCR and Droplet-Digital PCR

Clinical dose measurement of AAV gene therapies is more complex than many other therapeutic modalities. AAV Titre assays used for clinical dosing should be well-controlled to ensure consistent clinical dosing with intermediate precision ≤15% CV and accuracy of ±20% (Quantitation of AAV-Based Gene Therapy Products, FDA 2018). Conventional qPCR has traditionally been used to quantitate viral genomes but several variables including the need for a standard curve and real-time measurement, can lead to inconsistent results and fall short of expected method performance.

AAV viral genome quantification requires pre-analysis sample preparation to remove contaminating DNA, lyse viral capsids, and dilute samples into the dynamic range of the assay prior to PCR measurement (Figure 1). qPCR measures amplification of the target DNA in real-time and a threshold value (Ct) is interpolated into a known reference standard curve for calculating a viral genome concentration via linear regression. The qPCR standard curves used in a titre method require careful orthogonal quantification and characterisation. Due to the real-time measurement, qPCR reactions also require near 100% efficiency for precise and accurate measurements. qPCR methods are sensitive to factors that can impede efficient amplification such as inhibitors present in samples and DNA secondary structures.

Droplet digital PCR (ddPCR™) eliminates the need for a standard curve and real-time measurement, thereby minimising the impact of standard curves and PCR reaction efficiency. After preparing a PCR reaction, ddPCR partitions the DNA and PCR reagents via oil-emulsion into ~20,000 droplets per reaction. After thermal cycling amplification, each droplet is counted for positive or negative fluorescence. Poisson statistics are used to calculate an absolute concentration of viral genomes in the sample. The lack of a standard curve, reduced impact of PCR efficiency, absolute concentration determination and recent improvements in instrumentation have resulted in ddPCR becoming the superior methodology for AAV titre assays.

Figure 1: Viral Genome Titration Workflow for qPCR and ddPCR.



Each sample is diluted into the dynamic range of the assay. Then, DNase treatment removes contaminating particles followed by capsid lysis via Proteinase K treatment, detergent, or heating. Viral genomes are then measured with ddPCR or qPCR. ddPCR partitions DNA molecules into ~20,000 individual droplet PCR reactions. Each droplet is measured for fluorescence. Poisson statistics are used to calculate an absolute concentration of viral genomes in the sample. qPCR measures amplification of the target DNA in real-time and a threshold value (Ct) is used to interpolate into a known reference standard curve for calculating a viral genome concentration.

4.3. Submission in Accordance with EU Variation Classification

As PCR reagents used reagents from biological origin, changes to these analytical test methods would currently be categorised as Type II variations, with a classification of B.I.b.2 for drug substance testing and B.II.d.2 for drug product testing in accordance with European Commission Regulation No 1234/2008 (final version published 22 September 2025), as described in the table below.

Although reagents from biological origin are used, the technology has reached a high level of maturity where such change would lead to improvement of the control strategy, and such a change should be able to follow a Type IB category. In this case, the data package would include the proposed analytical method description (3.2.S.4.2. and / or 3.2.P.5.2), the analytical method validation (3.2.S.4.3 and / or 3.2.P.5.3) and the data demonstrating comparability between the two methodologies (3.2.S.2.6 or 3.2.P.2.3 as appropriate). An example of the data that could be used to support the qPCR to ddPCR method change is provided in the following sections for illustrative purposes.

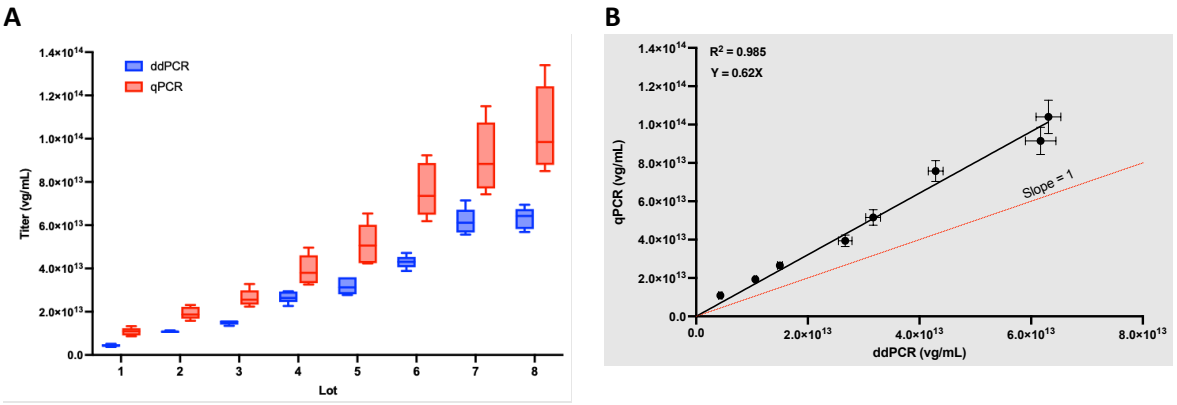
Variation Category		Conditions to be fulfilled	Documentation to be supplied	Procedure Type
Q.I.b.2 Changes to analytical procedure for active substance or starting material/ reagent/ intermediate used in the manufacturing process of the active substance c) Introduction, replacement or substantial change to a biological/ immunological/ immunochemical analytical procedure for an active substance	Q.II.d.2 Change to analytical procedures for the finished product c) Introduction, replacement, or substantial change to a biological/ immunological/ immunochemical analytical procedure for a finished product.	–	–	II

4.3.1. Data Example

A bridging study would be conducted comparing the validated qPCR and ddPCR titre assays. This study will include eight samples with varying viral genome concentrations evaluated at least six times with each method. Two trained analysts will perform half the runs across each method. All data will meet pre-established method acceptance criteria. A linear regression will be performed to evaluate the relationship of the results generated by the two methodologies.

Figure 2 shows an example of the data analysis approach that would be applied to support the method change. Titre values obtained by both methods are plotted (panel A) and demonstrate a strong linear relationship between the two methods (R^2 of 0.985) and improved precision obtained with ddPCR. The slope of the model (panel B) is used to determine the analytical shift between assays and a correction factor for matching the clinical dose to the new analytical method. In this example, a linear model of Y=0.62*X provided the best least squares fit, where Y is the ddPCR result and X is the qPCR result for a given sample.

Figure 2: Side by Side Testing of qPCR and ddPCR Methods Including 8 Lots



A. qPCR values and ddPCR values of each lot. Box plot central line represents the median value with the box hinges extending from 25th to 75th percentiles and the whiskers showing the minimum and maximum values observed. qPCR values are in red and ddPCR values in blue.

B. The mean value of each lot is plotted with qPCR value on the y axis and the ddPCR value on the x-axis. The red line shown represents a 1:1 relationship or a slope of 1.0 for reference. The black line represents the linear fit between ddPCR and qPCR using the mean values for each sample with SEM bars.

4.4. Use of ICH Q12 Tools for Post-approval Changes

4.4.1. Use of PACMP

While changes to test methods using biological reagents would be categorised as Type II variations in accordance with EU Variation Classification B1.b2.d), it might be possible to justify a Type IB B1.b.2 e) using a science- and risk-based approach. For example, a PACMP, which is possible under the current revision of the variation regulation, could enable a reduced reporting of change for the step 2, but it would require the approval of the PACMP as a Type II which may limit the efficiency of the approach. The registration of a PACMP may have more value in situations, where for instance, it is registered for multiple products, or it is used to manage registration risk.

A PACMP outlining a sponsor's approach to the assessment of advancing analytical technologies could be submitted at time of initial submission of the Marketing Authorisation Application or post-approval. This PACMP would outline the quality risk management approach in assessing new analytical technologies and the subsequent criteria and data package to be used to validate the new method(s) for use in the control strategy for ATMPs. The approval of the PACMP would allow for decreased reporting (Type IB or Type IA depending on the type of method) and could be used repeatedly as analytical control strategies are modernised.

4.4.2. Use of PLCM Document

Alternatively, the Applicant could register a PLCM document where ECs and their reporting categories could be proposed for the analytical procedure. While use of ECs is not currently possible under the current revision of the variation regulation, it could be introduced in the future revision. The sponsor and agency can then agree to the conditions and documentation that would have to be met. Such conditions and documentation may include:

Conditions:

1. There is no change in limits/acceptance criteria outside the approved limit for the approved assay release/stability

2. The method of analysis is the same and is based on the same analytical technique or principle
3. The modified analytical procedure maintains or improves performance parameters of the method

Supporting Documentation:

1. Copies or summaries of the revised analytical procedure
2. Validation/qualification results if new analytical procedures are used
3. Comparative results demonstrating that the approved and proposed analytical procedures are equivalent or better
4. Documented evidence that consistency of quality is maintained

The approval of EC would allow for decreased reporting and could be used repeatedly as analytical control strategies are modernised.

Conclusions

Due to the unique properties and complexity of ATMPs and the rapid evolution of technologies, the variation guideline designed for “traditional” biological products creates a rigid framework that may block product innovation, improvement and patient access.

The proposed revisions to the variation regulation to address some issues, including database entry of Type IA variations and full implementation of ICH Q12, can only be made after the revision of the general pharmaceutical legislation (GPL) is completed. There is an opportunity to ensure that the upcoming second revision of the variation regulation is appropriate for the lifecycle of ATMPs and enables the use of ICH Q12 concepts for ATMPs. The case studies on plasmid changes, manufacturing site changes, analytical method changes and changes to cell bank starting materials provided in this paper show how application of ICH Q12 and development of guidance on how to implement Q12 tools for ATMPs could be considered. Such updates could enable rapid implementation of changes with reduced reporting for these ATMPs. The initial changes to the variations classification guideline are providing some simplification and helping towards efficient life-cycle management, but further simplification could be made for ATMPs and the case studies on replacement of test methods and starting material changes show how further simplification could be implemented for ATMPs.

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