Reprocessing and Reworking of Active Pharmaceutical Ingredients

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Approval	Date:	Signature:
Author:	10.09.2026	Barbara Herzog
Technical verification:	30.09.2026	Federico Cimini
Formal verification (Release VS-QMI):	02.10.2026	Michelle Scheidegger

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1 Purpose and scope

ICH Q7, Part II of the EU GMP Guidelines and PIC/S PE 009 define reprocessing and reworking of active pharmaceutical ingredients and relevant GMP requirements. This Technical Interpretation describes the interpretation of certain aspects of these requirements, as expected by the Swiss inspectorates.

This document applies to the Swiss inspectorates which conduct inspections under the jurisdiction of Swissmedic (i.e. the Swissmedic Inspectorate and the inspectorates of the cantons according to art. 60 TPA), subsequently referred to as inspectorates. It applies to Active Pharmaceutical Ingredients (API). Drug products are excluded. The focus is on commercial APIs. Application to Investigational Medicinal Products (IMPs) by analogy.

2 Basics

- ICH Q7 including ICH Q7 Questions and Answers
- EU GMP Guideline Part II
- PIC/S PE 009 Part II
- ICH M4Q
- ICH Q11
- Guideline on the chemistry of active substances, EMA/454576/2016

3 Definitions and abbreviations

API	Active Pharmaceutical Ingredient
MA	Marketing Authorisation
Reprocessing	Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a chemical or physical manipulation step (e.g. crystallization, distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing
Reworking	Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g. recrystallizing with a different solvent). From a GMP point of view, reworking is generally not acceptable for biologic active substances.

4 Interpretation

	Question	Reprocessing	Reworking
1.	Is reprocessing/reworking an established process?	Yes, reprocessing refers to the repetition of an established and validated manufacturing process. However, it should be carried out only in exceptional, well justified cases, and not be used as a frequent measure to compensate for a non-robust process.	No. Reworking is an exceptional activity which cannot be considered as standard in a manufacturing process/MA. Reworking is generally not acceptable for biological active substances.
2.	Should the reprocessing/reworking process be described in the marketing authorisation file?	Yes, steps to be used occasionally for reprocessing should be clearly identified as such, and the conditions and prerequisites for their execution should be described in the marketing authorisation (see ICH M4Q, Quality, 2.3.S.2 and Guideline on the chemistry of active substances, EMA/CHMP/QWP/49484/2026). For biological medicinal products also refer to Questions and answers for biological medicinal products | European Medicines Agency (EMA) and EMA/CHMP/BWP/187338/2014 Section 6.2.3.).	This depends on the respective country. For EMA regions and Switzerland, reworking should not be included in the MA (see for example Guideline on the chemistry of active substances, EMA/CHMP/QWP/49484/2026), and should be carried out according to EU and PIC/S PE 009 Part II and ICH Q7. Reworking is generally not acceptable for biological active substances.
3.	Can conforming material be reprocessed/reworked? If yes: What are examples for conforming material that can be reprocessed/reworked?	In principle, yes, provided that it is soundly justified and covered by appropriate validation, as well as any additional measures to demonstrate that product quality, safety, and efficacy are not compromised. Examples: Reintroducing tailings, heels from centrifuges (bulk holding time requirements apply), mills, failed filter integrity test, etc.	No, conforming material cannot be reworked, as there is no justification. Reworking is generally not acceptable for biological active substances.
4.	Can non-conforming material be reprocessed/reworked?	Yes, non-conforming material can, in principle, be reprocessed. However, the possibilities are in general technically limited - for example, to re-concentra-	In principle yes. See Chapter 14.3 in PIC/S PE 009 Part II, Reworking. Reworking is generally not acceptable for biological active substances.

	Question	Reprocessing	Reworking
		tion steps in biological processes (usually performed during the ongoing batch manufacturing process, immediately after identification the deviation) or to re-crystallisations in synthetic molecules. The marketing authorisation dossier should clearly describe the circumstances in which reprocessing is possible, incl. which specification deviations may trigger such measures. Reprocessing in cases of out-of-specification (OOS) results requires a thorough investigation of the root cause of the non-conformity. Reprocessing to address microbial OOS results at microbiological control points is generally considered unacceptable.	
5.	Can an expiry date extension be achieved with reprocessing/reworking with batches which are close or beyond to expiry date?	No, this is not acceptable, as the definition of expiry date says, „after which it should not be used".	No, this is not acceptable, as the definition of expiry date says, "after which it should not be used". Reworking is generally not acceptable for biological active substances.
6.	Is carry over of residual materials into successive batch of the same intermediate of API considered as reprocessing?	Not considered as reprocessing. Holding time of API must be established in order to define the campaign length (number of batches per campaign). The length of campaign must be validated.	n.a.
7.	Can different batches, also with different defects, be mixed for reprocessing/reworking?	No, this is in general not acceptable.	No, this is in general not acceptable. Reworking is generally not acceptable for biological active substances.
8.	Can an OOS batch be mixed with an inspec batch prior to reprocessing/reworking?	No, this is not acceptable.	No, this is not acceptable. Reworking is generally not acceptable for biological active substances.

	Question	Reprocessing	Reworking
9.	Is an investigation required prior to reprocessing/reworking?	In general reprocessing should be treated and documented as a deviation. Depending on the situation, an investigation may not be necessary. It should however be defined if additional testing for verification or validation is needed.	Any reworking should be treated and documented as a deviation with a full investigation and the need to define additional actions. Although in principle it is not strictly prohibited to evaluate the quality of the batch after reworking based on a single batch, this practice is strongly discouraged as it is very difficult to collect enough data to guarantee the quality of the batch. An approach that involves the production of at least three batches and complete validation is preferable. If there is no irrefutable evidence of quality, the batch must be rejected. If the product is out of stock and meets an irreplaceable need for patients, it is necessary to contact the relevant authority before making a final decision on the fate of the batch. Reworking is generally not acceptable for biological active substances.
10.	In case of contract manufacturing, what should be covered in the quality agreement with regards to reprocessing/reworking?	The terms of reprocessing should be covered in the quality agreement and the contract giver informed about reprocessing.	The terms of reworking should be covered in the quality agreement and the contract giver in general informed upfront about reworking. Reworking is generally not acceptable for biological active substances.
11.	Is it allowed to reprocess/rework a batch more than one time?	This depends on the product and process. It should be demonstrated that any reprocessing has no impact on the quality of the API.	Not applicable, since reworking is an exceptional activity. Reworking is generally not acceptable for biological active substances.

	Question	Reprocessing	Reworking
12.	Is a validation of the reprocessing/reworking process required?	Reprocessing should be validated and is normally taking place within the validated manufacturing process. However, if the established impurity profile is altered additional verification is needed.	Yes, any reworking should be validated (see also answer # 9). Reworking is generally not acceptable for biological active substances.
13.	Do the reprocessed/reworked batches have to be placed on stability?	This should be decided on a case-by-case basis. The batch is preferably included in ongoing stability studies	Yes, stability studies are required. Reworking is generally not acceptable for biological active substances.
14.	What is the manufacturing date of a reprocessed/reworked batch?	The manufacturing date of a reprocessed batch refers in general to the manufacturing date of the original batch (before reprocessing). Any exception (e.g. chemical reaction), should be justified.	The manufacturing date of a reworked batch refers in general to the original batch (before reworking), Reworking is generally not acceptable for biological active substances.
15.	What is the re-test period or shelf life of a reprocessed/reworked batch?	A reprocessed batch may retain the original re-test period or shelf life only if supported by appropriate data. Where reprocessing could negatively impact stability, a shorter re-test period or shelf life shall be assigned unless stability data demonstrate equivalence to the original material. Any assigned period must be scientifically justified, documented, and approved within the quality system.	A reworked batch may retain the original re-test period or shelf life only if supported by appropriate data. Where reworking could negatively impact stability, a shorter re-test period or shelf life shall be assigned unless stability data demonstrate equivalence to the original material. Any assigned period must be scientifically justified, documented, and approved within the quality system
16.	Is it required that a batch, which underwent a reprocessing/reworking step, is identified as such on relevant Certificates?	Traceability in the batch documentation should be ensured. The batch record, but not necessarily the Batch Certification Document, should identify it as a reprocessed batch. The batch should receive a new batch number. In case of contract manufacturing, the quality agreement should define how the customer is informed.	Traceability in the batch documentation should be ensured. The batch record, and preferably the Batch Certification Document, should identify it as a reworked batch. The batch should receive a new batch number The quality agreement should define how the customer will be involved in the decision making.

	Question	Reprocessing	Reworking
			Reworking is generally not acceptable for biological active substances.
17.	Is it required, that any reprocessed/reworked batch is listed as such in the PQR?	Yes, any reprocessing of batches should be listed as such in the PQR.	Yes, any reworking of batches should be listed as such in the PQR.

5 Changes to the previous version

- None, first version

6 Annexes

- None