“No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in Section 10.20 or the use of raw materials or intermediates pending completion of evaluation).”

(ICH Q7, 2.17)

“The applicant should set appropriate controls and should justify the proposed specification for the actual and potential impurities that are reasonably expected in a proposed starting material, based on the scientific knowledge and available information.”

(ICH Q&A on Q11, 5.13)

“The API manufacturer should demonstrate a thorough knowledge of the quality of the SM and its impact on the quality and safety of the final API.”

(APIC Position paper on API SM, 2014)

**QUESTION 1**

What would you as inspector expect to see in order to demonstrate a thorough knowledge of the quality of both SMs and their impact on the quality of the final API?

You may list and describe the elements of a system likely to ensure this thorough knowledge.

Q: Can the Lifecycle Management section of ICH Q11 (Section 9) apply to starting materials?

A: Yes. Changes in earlier synthesis steps (upstream) must be made in accordance with the quality assurance system of the applicant. Residual risks in regards to the drug substance quality are to be assessed. The corresponding regulations of ICH Q7 and ICH Q7 Q&A document (Chap. 7 and 13, respectively), Q9 and Q10 (Chap. 2.7) must thereby be applied to starting materials as well.

(ICH Q&A on Q11)

**QUESTION 2**

Change control of SMs suppliers: what should be considered by the API manufacturer/ how to do it appropriately?
“An on-site audit (of suppliers of materials) is not required; however, an on-site audit could be a useful tool in the evaluation of a supplier.”
(ICH Q&A on Q7, 7.4)

5. Regular audits of the starting or raw material supplier should be undertaken which verify compliance with controls for materials at the different stages of manufacture.
(GMP, annex 2)

“Audits are not mandatory as per current GMP and should be considered on a case by case basis.”
(APIC “How to do” Document, 2018)

QUESTION 3
Assuming that the API manufacturer audits suppliers of one API starting material, what would you ask for and check in terms of evaluation of suppliers?

“Companies should consider redefining the API Starting Material for well-established products. This offers the opportunity to reduce the overall GMP requirements for early manufacturing steps and to shift the focus to be on the control of the critical synthetic steps starting from the redefined API Starting Materials. […]”
(APIC: “How to do” document, 2018)

QUESTION 4
During your inspection you observe/discover/take notice that the company is in process of “redefining” one of its intermediates (Px) to an API starting material. I.e. some batches have already been produced with this “redefined” product.

How would you handle this situation?