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Manufacturing Date of Drug Substances - Regulatory Requirements

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ABSTRACT

The pharmaceutical industry is a very competitive field where human safety plays a superior role. For this reason, high standards for the quality of drugs are secured through the federal agencies. Moreover, in the last decades great progress was made in the consolidation of pharmaceutical guidelines due to the activity of the International Council for Harmonisation (ICH) which defines global standards for the pharmaceutical industry. Nevertheless, there are still some gaps in the regulatory guidelines which lead to some misconceptions among stakeholders or even direct misuse. One of such cases is the manufacturing date for drug substance, which is lacking the univocal definition in all current regulatory guidelines. Different options for decision making on assignment of manufacturing date for drug substance are discussed and evaluated in the current manuscript.

INTRODUCTION

The work of pharmaceutical companies relies on effective implementation of regulatory requirements for the drug manufacturing. The corresponding guidelines of EMA (The European Medicines Agency), FDA (United States' Food and Drug Administration), PMDA (Japanese Pharmaceuticals and Medical Devices Agency) and ICH enable the production of high-quality pharmaceuticals, which fulfil the safety needs of patients. It has to be noted that pharmaceutical companies operate in one of the most dynamic environments, whereby the number and complexity of global regulations are steadily increasing. However, the assignment of the manufacturing date for drug substances is a frequently encountered problem in the pharmaceutical industry which lacks sufficient regulation.

The ICH guideline Q1E “Evaluation for Stability Data” [1] provides recommendations on how to use stability data generated in accordance with the principles described in the ICH guideline Q1A(R2) “Stability Testing of New Drug Substances and Products” [2]. Consequently, the approach of how to generate and evaluate stability data in order to determine retest periods is sufficiently regulated. Moreover, the EMA’s questions and answers paper addresses the extension of retest periods of drug substances with respect to ICH Q7, 11.6. The EMA concluded that a) the purpose of a retest date is to ensure that the API is still suitable for use and b) that the retest date of a specific batch can be extended based on good science and long-term stability data [3]. Hence, the retest date is assigned based on the manufacturing date and the retest period. Surprisingly, there is no regulation provided regarding the assignment of the manufacturing date of drug substance.

Some stakeholders intentionally claim that the formation of the chemical core structure of a drug substance defines the manufacturing date. Others state that the date of the final packaging or the issuance of the certificate of analysis (CoA) should be considered as manufacturing date of the drug substance. Due to the lack of regulations and generally accepted principles in this field, it is important to justify the manufacturing date taking into consideration the underlying chemical nature of drug substances.

DISCUSSION

The crystalline drug substances were always privileged in the pharmaceutical industry because of they handleability and greater stability. The better solubility and higher dissolution rate are further important attributes of solid state drug substances

[4]. Therefore, it is not surprising that up to 70% of the drug substances are used in solid form at the present time [5]. Although cocrystal formation is a rapidly developing and highly promising field of crystal engineering [6], the salts of drug substances are still prevailing in industry. Hence, we would like to discuss the manufacturing date in the light of conventional production of fentanyl hydrochloride as an illustrative example.

The common way of synthesis of highly potent opioid fentanyl hydrochloride is depicted in Figure 1 [7]. Starting from 4-piperidone (1) the core structure of fentanyl (7) is achieved in three steps (a,b,c). Since fentanyl can also be used as a salt for drug product manufacturing, (7) is converted into the corresponding hydrochloride (8, d). Further physical treatment is normally needed in order to achieve the desired particle size which is achieved via micronization (9, e). Fentanyl can be used both as free base and as hydrochloric salt. The manufacturing date will be highlighted in regards to application of fentanyl hydrochloride in drug product dosage form manufacturing.

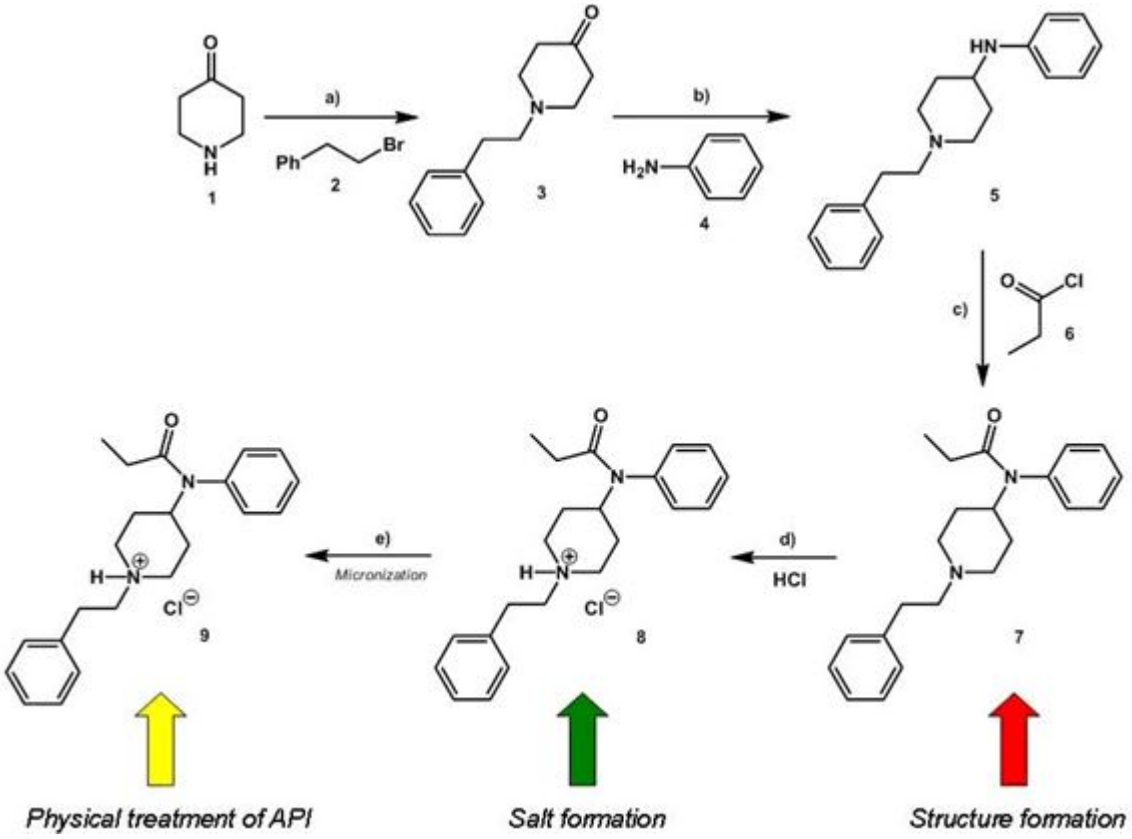

Figure 1. Synthesis of Fentanyl Hydrochloride

The case mentioned above already results in several possibilities for setting the manufacturing date. The drug substance core structure (7) is directly responsible for the pharmacological activity and this is a main justification for declaring the manufacturing date at this stage. However, compound (7) possesses absolutely different physiochemical properties than the corresponding hydrochloride salt (8). Additionally, (7) is not necessarily used in drug product manufacturing, what clearly contradicts the definition of the drug substance in ICH Q7 (“any substance…intended to be used in the manufacture of a drug product”) [8]. Therefore defining the manufacturing date on this stage is only applicable if fentanyl base (7) is directly subjected to the drug product manufacture.

In step d) fentanyl base (7) is treated with hydrochloric acid and the corresponding salt (8) is crystallized. Crystallization is one of the most crucial and very often underestimated steps in pharmacological industry [9]. This process unequivocally impacts crystal size and its habit, which have a significant effect on the drug substance stability and drug release properties [10]. Almost 50 years ago such problems were recognized and extensively investigated [11,12]. Thus, assigning the manufacturing date to this stage complies with 1) the requirements of the ICH Q7 [8]; and 2) the concerns about drug stability and bioavailability [10].

The optional micronization providing fentanyl hydrochloride (9) could affect its properties because of higher surface area [13]. Although chemical nature of drug substance is not changed and desired particle size is obtained, one should always bear in mind the stability risk which is added. Even the solid-state chemical reactivity could be impacted since some drug substances can potentially react with excipients in the formulation [14]. Moreover, one has to consider that in many cases, the physical

treatment of the drug substances is performed at a later time than the synthesis. Following the worst case and setting the manufacturing date on the stage of fentanyl hydrochloride (8) will definitely eliminate such risks.

CONCLUSIONS

This discussion has addressed considerations for assigning the manufacturing date for chemical synthesis of the drug substance. Different options for decision making on assignment of manufacturing date for drug substance are discussed and evaluated in the current manuscript.

If the compound wiih the chemical structure responsible for the pharmacological activity is not immediately used in drug product manufacture and additional preparatory steps are performed, it should not considered as corresponding drug substance and manufacturing date is not applicable in this case. Physically treated drug substance can be potentially considered as a starting point of manufacturing date, taking into consideration its stability and only after evaluation of retest period.

The retest date can be assigned as follows:

a) Based on the retest period of the physically treated drug substance and the date of the physical treatment, or

b) Following the worst case, based on the retest period of the physically treated drug substance and the date of the crystallization of the drug substance.

It is generally advisable to assign the manufacturing date to the last crystallization step performed and before any physical treatment. At this stage all physiochemical properties are settled and additionally to other parameters the stability of the pure drug substance is well controlled.

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