Single-enantiomer Drug Substances

For the 11 single-enantiomers, the stereochemical characterization was not reported (Fig. 4). It does not necessarily mean that the Japanese authorities did not receive any information, but it means that no stereochemical characterization was described in the data summaries. In Japan, reviewers use data summaries as a primary assessment document and technical reports as an additional tool, because significant issues are described in data summaries in the Japanese review system. On the other hand, reviewers directly assess individual technical reports on chemistry, manufacturing and control (CMC) in U.S.A.

The stereochemical characterization was reported for all the substances which were produced by asymmetric synthesis or asymmetric resolution, and hence we supposed that the stereochemical characterizations of the 11 single-enantiomers were regarded as less significant for the following reason: Those 11 substances were synthesized from single-enantiomeric starting materials containing multi-chiral centers such as sugars and steroids; Synthetic procedures of those substances were regarded as ensuring their stereochemistry.

ICH-Q6A guideline says that the identity tests should be capable of distinguishing both enantiomers and the racemic mixture for a drug substance developed as a single enantiomer. However, the specification for assuring chirality was not adopted for the three single-enantiomer drugs. One of them had one-chiral center, and the others had multi-chiral centers. Although the reason for rejected specifications is not clear from the data summaries, it might result from the fact that the NDA of three drugs were submitted during the transitional period for implementing Q6A, or those three substances might be regarded as retaining their starting material chirality, or the specification for assuring chirality might be considered to be meaningless.

Also, no pharmacokinetic study on chirality was reported in the data summaries of the 25 (67%) single enantiomers (Fig. 6), 19 of which had multi-chiral centers. In contrast, the chiral inversion was reported for the four single enantiomers with multi-chiral centers, however, less or equal two chiral centers were investigated in those enantiomers. For the single enantiomer with multi-chiral centers, their chiral inversion and isomer-specific metabolism tended to be considered to be complicated and unimportant.

Racemic Drug Substances

Based on the guidelines, we reassessed the justifications for developing the 10 racemates rather than a single enantiomer.

The pharmacologic activity and the pharmacokinetic profile of the individual enantiomers should be characterized, because rapid interconversion *in vivo* was not observed for all of the 10 racemic drugs. Although the principal pharmacological activity was characterized for the individual isomers of the 10 racemic drugs, the pharmacokinetic profiles of the individual enantiomers were not reported for the one. It might be one of the reasons for not reporting that this racemic drug has been a common therapeutic agent for long time in worldwide.

According to the guidelines, it is ordinarily sufficient to carry out toxicity studies on the racemate. The toxicity study of each isomer was not reported for the three racemic drugs, because both enantiomers of these three racemates indicated similar pharmacological activities.

Relating to stereochemical characterization, it is recommended to perform chromatographic tests in addition to optical rotatory tests for mixtures of optical isomers. The chiral HPLC analysis was not performed for the one racemic drug. This racemic drug has been a common therapeutic agent for long time in worldwide, and the Japanese authorities did not require additional stereochemical characterization.

In conclusion, the trend in the Japanese pharmaceutical development is increasingly moving toward the development of single isomers rather than racemates. The chiral development approaches approved in Japan were essentially consistent with the approaches recommended by the guidelines. The racemic drugs, which shared only 13% in the new chemical drug substances, had some rationale to be developed as racemates. Decline of racemic drugs development may continue in Japan as well as worldwide, because some studies need to be carried out with not only a racemic mixture but its component enantiomers.

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