Pharmacokinetics definitions in regulatory documents: transfer from small molecules into biologics

“...the present level of clarifications concerning the calculations of biologics washout is insufficient.”

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A pharmaceutical industry devotes great attention to the studies focused on the biologics (BL). This trend has not diminished for several decades. In recent years, its dynamics have increased significantly due to an expiration of patent protection terms of many crucial BL. One of the significant sources of principles that pharmaceutical industry is following are agency guidelines. The guidelines proposed by the agencies not only determine the requirements for the sponsors, but also create the standards in the field of defining terms which are specific to various areas. One of the areas that gains a large number of register agency guidelines is pharmacometry and more precisely, pharmacokinetics. Once BL was available on the market, guidelines on pharmacokinetics of BL were developed. The mechanisms of absorption, distribution, elimination and metabolism of BL differ significantly from small molecules (SM). That is why, some definitions of phenomena and processes used for a long time for SM require clarifications in the case of BL. Several definitions used for SM cannot be applied to the field of BL. One of the areas that requires harmonization and clarification are the terms ‘long half-life drug’, ‘elimination half-life’ and the rules of determination of ‘washout’ period in the crossover studies.

The aim of the presented commentary is to point out the inaccuracies present in agency guidelines especially the problems linked to the therapeutic monoclonal antibodies (mAb). Inappropriate interpretation

of definitions and regulations might lead to incorrect design of pharmacokinetic studies.

‘Long half-life drug’ or ‘longer’

The current definition of ‘long half-life drug’ regarding SM is a drug with a half-life in the elimination phase ($t_{1/2\text{kel}}$) >24 h. However, there is no separate regulation concerning this term in the guidelines for BL. The only exception with reference to BL is the term ‘products with a longer half-life (e.g., more than 5 days)’ [1]. Inaccuracy is especially significant with reference to bioequivalence studies (BE). There is a principle according to which such studies in the case of ‘long half-life drug’ could be finished within 72 h after drug administration (‘truncated area under the curve’) [2]. This principle could not be used with reference to mAb as it clashes with the basic feature of mAb, where $t_{1/2\text{kel}}$ is usually counted in days and weeks. Consequently, the BE with mAb very often last many weeks [3]. The basis of determining a threshold of 24 h defining ‘long half-life drug’ is the total transit and absorption of drug substance after oral administration (max 72 h). In case of mAb, it can be accepted that the absorption might last even 7–8 days (subcutaneous administration). However, $t_{1/2\text{kel}}$ of mAb is extremely long due to the binding with the neonatal Fc receptor (FcRn). This is a result of drug redistribution on the level of interaction with FcRn rather than real protein catabolism. Therefore, the following question arises: since it is ethical to shorten

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the sampling period in the case of BE with reference to SM, could a similar regulation for BL be proposed? In the case of mAb, defining the term 'long half-life drug' and the time in which the sampling should be made in BE, would shorten the clinical part of the studies. This approach seems to be justified as the 'elimination phase' for mAb is often totally or partly a derivative of the flip-flop effect and does not describe a real elimination process. Currently, there exists only one US FDA guideline, the term of 'products with a longer half-life (e.g., more than 5 days)' [1] with reference to BL. On the grounds of this wording, 5 days could be accepted as a threshold, from which long $t_{1/2\text{kel}}$ with reference to BL is considered. This, in turn, would mean that the sampling time of BL with a long $t_{1/2\text{kel}}$ could be completed in the time equal to $(3 \times 5_{\text{days}}) + t_{\text{max}}$ where t_{max} is the time of maximal concentration (C_{max}) after a single drug administration. In practice, such an interpretation of the guideline would mean that for BL with $t_{1/2\text{kel}} > 5$ days and $t_{\text{max}} = 8$ days, BE after single drug administration could be completed in the time equal to $(3 \times 5_{\text{days}}) + 8$, that is in the 23rd day after drug administration.

In conclusion, present guidelines apply a single definition of 'long half-life drug' to both SM and BL [2,4]. As a consequence of ambiguous records, it is not possible to shorten the sampling time of BE with reference to BL and calculate 'truncated area under the curve'.

'Elimination half-life' or 'terminal half-life'

$t_{1/2\text{kel}}$ is calculated on the grounds of elimination rate constant (k_{el}). k_{el} is determined based on a slope of the final portion of the concentration–time curve after a single drug administration. The same principle concerns SM and mAb. However, it is currently known that mechanisms, which allow the observation of k_{el} among SM and mAb, are completely different. In the case of SM, such typical elimination mechanisms such as renal clearance, liver metabolism, fecal, urinary and biliary elimination etc. are responsible for the k_{el} value. These mechanisms are crucial elements which affect the k_{el} value of SM. Nonetheless, the above-mentioned mechanisms have no impact on the k_{el} value for mAb. The main role in the maintenance of long $t_{1/2\text{kel}}$ of mAb is attributed to the interaction with FcRn. FcRn for mAb is a sort of depot form. Here, we are facing with the mechanism of drug redistribution that could take place in all body cells that express FcRn. This means that the reaction rate constant that describes the final portion of the concentration–time curve in the case of mAb illustrates simultaneous elimination and a meaningful part of the drug redistribution in the whole body. This not only illustrates a constant of elimination process but

also a major part of the redistribution process. It is thus difficult to compare $t_{1/2\text{kel}}$ of SM and mAb where $t_{1/2\text{kel}}$ value is calculated based on two groups of completely different processes. At present, crucial drug registering agencies use the terminology: 'elimination half-life' and 'terminal half-life' arbitrarily.

To sum up, the current use of 'terminal half-life' in the guidelines should be reserved for mAb, where k_{el} is not equal to the reaction rate constant mainly illustrating elimination processes. On the other hand, 'elimination half-life' should be used for SM with easy-to-define elimination processes.

Washout period in crossover trials

The calculation of the value of washout period is one of the most significant elements of crossover studies. The crossover trials are one of the most common used schemes in the case of BE for SM. With reference to BL, it is not always possible to use such a scheme due to prolonged washout. Depending on the agency, the proposed washout period lasts $5\text{--}10 \times t_{1/2\text{kel}}$ of a drug. This means that for BL with $t_{1/2\text{kel}}$ equal to 11 days the washout period with a stringent approach will last 111 days, and with a minimal approach, 55 days. On the other hand, there is a restriction that 'longer half-life drugs' (for BL $t_{1/2\text{kel}} > 5$ days) should be used for parallel instead of cross-over design. This way, the agency complies with the WHO principle that the washout period should not be longer than 4 weeks [5]. As a result, there is no coherence between FDA regulations concerning BL, SM, WHO regulations and what is practiced in the case of BL crossover trials. The guideline records are now dead and in the wake of the lack of specific clarifications, the guidelines will diminish in quality significantly. The guidelines, whose aim is the standardization of washout period are not usually used [6–9]. The current guidelines do not also bring any new ideas with reference to the way of determination of washout period for the pharmacodynamic parameters and analysis of immunogenicity. The only cues that are mentioned in the guidelines concern the indications for crossover design in case of the drugs for which the pharmacodynamic effect disappears with increasing drug concentration and in case of 'a low incidence of immunogenicity' [10].

In conclusion, it could be stated that the present level of clarifications concerning the calculations of BL washout is insufficient. A politics 'case by case' does not work and the guidelines do not meet expectations.

Conclusion

One of the aims of creating guidelines on the international level is to establish the standards and harmonize them. The guidelines do not always keep up

with the requirements of their addressees. However, it is not hard to resist the impression that the basic principles concerning a pharmacokinetic study design of SM are much more precise in the guidelines than concerning BL. In the agency guidelines with reference to SM, there are many details that allow the proper design of studies [11]. However, it is not always possible to apply the same definitions and terms from SM to BL without making more specific considerations.

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