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ORIGINAL ARTICLE

Clinical haemophilia

Does difference between label and actual potency of factor VIII concentrate affect pharmacokinetic-guided dosing of replacement therapy in haemophilia A?

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Abstract

Background: To account for interindividual variability in the pharmacokinetics (PK) of factor concentrates, PK-guided dosing is increasingly implemented in haemophilia patients. Calculations are based on provided label potency, but legislation allows a potency difference of ±20% between label and actual potency. It is unknown if these differences affect PK guidance.

Aim: Explore the effects of potency differences on individual factor VIII (FVIII) PK parameters and the prediction of FVIII trough levels of dosing regimens.

Methods: We analyzed individual preoperative PK profiling data from severe and moderate haemophilia A patients included in the OPTI-CLOT randomized controlled trial. Label and actual potency were compared, with data on potency provided by pharmaceutical companies. For both potencies, individual PK parameters were estimated and concentration-time curves were constructed by nonlinear mixed-effects modelling. Finally, we explored the effect of both the identified and the maximum legislated potency difference on predicted FVIII trough levels infused in a low and high dose regimen.

Results: In 45/50 included patients, actual potency was higher than its label potency. The median potency difference was 6.0% (range -9.2% to 18.4%) and resulted in varying individual PK parameter estimates but practically identical FVIII concentration-time curves. As expected, predicted FVIII trough levels were linearly correlated to the actual dose.

Conclusion: It is not necessary to take potency differences into account when applying PK guidance of FVIII concentrates in haemophilia A patients. However, when the patient is switched to another FVIII batch after PK-guided dosing, trough levels may deviate ±20% from calculations based on label dose.

KEYWORDS
Bayes Theorem, factor VIII, haemophilia A, pharmacokinetics, product labelling

1 | INTRODUCTION

Haemophilia A is a rare, X-linked recessive bleeding disorder characterized by a deficiency of coagulation factor VIII (FVIII). The severity is categorized according to residual FVIII levels, as severe (FVIII < .01 IU/ml), moderate (FVIII .01–.05 IU/ml) or mild (FVIII > .05 IU/ml). All patients are treated on demand with FVIII concentrate replacement therapy or desmopressin in the event of bleeding, or to prevent perioperative bleeding and long-term severe joint damage.[1,2] Most severe and some moderate patients additionally use FVIII prophylaxis to prevent spontaneous bleeding, while targeting for FVIII trough levels of >.01 IU/ml. Nevertheless, the achieved FVIII levels vary between patients due to interindividual differences in the pharmacokinetics (PK) of FVIII concentrate. To account for these differences, PK-guided dosing is increasingly implemented. Using the Bayesian approach, individuals' PK parameters are estimated using individual blood samples after a dose of FVIII concentrate, patient characteristics (covariates) and a population PK model.[3–5]

Individual FVIII PK parameters are influenced by covariates, most importantly age, blood group O and von Willebrand Factor (VWF) levels. Children and adolescents have a higher FVIII clearance (CL) per kilogram body weight than adults. In addition, older age remains significantly associated with a longer rFVIII half-life (T1/2), even after adjustment for CL and VWF.[6] VWF affects PK parameters due to its role as a chaperone for FVIII, protecting it from clearance from the blood circulation. Strikingly, a six-fold reduction of FVIII half-life is reported in the absence of VWF.[7,8] Blood group O is also associated with higher CL, most probably as these patients have 25% lower VWF levels.[7]

PK-guided dosing is performed using the potency provided in the label, that is, the amount of factor concentrate as stated on the label of a vial. However, legislation by the European Pharmacopoeia (EP) states that actual potency of a batch of factor concentrate is allowed to vary within 80%–120% of the declared label potency.[9] Clearance for an IV administration is calculated by dividing the dose by the area under the plasma concentration curve and volume of distribution (V) is calculated by diving the dose by the maximum concentration.[10] Therefore, we expect clearance and volume of distribution to change proportionally to the dose, and thus proportional to the difference between the label and the actual potency. No previous study yet has investigated whether this discrepancy in potency-impacts individual PK parameters clinically and thus hampers the prediction of FVIII levels by PK guidance. Therefore, this study explores the effects of difference between label and actual potency on individual FVIII PK parameters, and consequently, the dosing regimens as reflected by the prediction of FVIII activity levels.

2 | MATERIALS AND METHODS

We analyzed patient data from the individual preoperative PK profiles from the OPTI-CLOT randomized controlled trial. Detailed information on this trial can be found in the trial design paper[11] and recent publication.[12] In brief, this perioperative trial included patients with severe or moderate haemophilia A from Haemophilia Treatment Centres in the Netherlands to compare PK-guided iterative perioperative FVIII concentrate dosing with standard treatment. Following a bolus of 50 IU/kg FVIII concentrate, the preoperative PK profiles were constructed using three blood samples. A wash-out period was not applied but prior doses were recorded, enabling correction for residual FVIII levels from previous doses. More specifically, three prior doses were documented before PK profiling for both patients on prophylaxis and patients receiving on demand treatment. Ethical approval and informed consent by patient and/or caretakers was obtained.

2.1 | Patient characteristics and potency difference

We collected the following patient characteristics: age, anthropometrics including lean body mass (LBM), VWF activity (VWF:Act), blood group, endogenous baseline FVIII level, detailed data on timing of blood sampling, FVIII concentrate dose, timing of dosing, brand and batch number of FVIII concentrate given during PK profiling. Pharmaceutical companies were asked to provide actual FVIII potency of all batches utilized for PK profiling. We excluded patients of whom we were not able to obtain a batch number or the actual vial potency. The actual potency was determined by chromogenic-substrate assay (CSA) except for Octocog alfa (Kogenate) that was measured by the one-stage assay (OSA) as required by the European Medicines Agency (EMA) guidelines. For each individual, we calculated the potency difference by subtracting the label potency from the actual potency. Subsequently, this difference was divided by the label potency to calculate the potency difference in percentages.

2.2 | Laboratory measurements

Preoperative PK profiles were constructed using FVIII levels from three set time points: at T = 4, T = 24, and T = 48 h after administration of standard half-life FVIII concentrate. Each study site measured these FVIII levels using OSA according to local protocol. However,

TABLE 1 Patient characteristics

No. (*n*; %) or median [IQR]	
Patient characteristics	
Number of patients	50
Age, years	47.5 [31.6–58.7]
Severe haemophilia patients (FVIII < .01 IU/ml)	31 (62.0%)
Blood group O	30 (60.0%)
Height, cm	178 [173–186]
Body weight, kg	83.0 [73.0–95.1]
Body mass index, kg/m^2	25.3 [23.3–28.2]
Ideal body weight, kg	71.0 [67.0–77.0]
VWF activity, IU/ml	.97 [.65–1.20]
Brand clotting factor VIII concentrate	
Octocog alfa[a]	14 (28.0%)
Octocog alfa[b]	17 (34.0%)
Moroctocog alfa[c]	3 (6.0%)
Plasma derived FVIII concentrate[d]	2 (4.0%)
Turoctocog alfa[e]	14 (28.0%)
Number of samples FVIII per individual	
2	1 (2.0%)
3	40 (80.0%)
4	9 (18%)

[a]Kogenate®.
[b]Advate®.
[c]Refacto AF®.
[d]Aafact®.
[e]NovoEight®.

we also measured all FVIII levels from PK profiles by CSA (Hyphen Bio) centrally at the Erasmus University Medical Centre Rotterdam using frozen plasma samples after study closure. This was performed as actual potency is routinely determined by CSA according to EMA guidelines, with exception of one FVIII concentrate in this study; Octocog alfa (Kogenate®). Similarly, VWF:Act levels were centrally measured with the latex immune assay on Sysmex CS 5100 coagulation analyzer (Sysmex, Ettenleur, The Netherlands) using the INNOVANCE® VWF Ac assay (Siemens Healthcare Diagnostics, The Hague, The Netherlands) which uses an antibody against GP1b binding site on VWF.

2.3 | Population pharmacokinetic modelling

PK analysis was performed using Bayesian estimation with the nonlinear mixed-effects modelling software NONMEM v7.4.1 Icon Development Solutions, Gaithersburg, MD, USA. The population PK models of Bjorkman et al.[13,14] were used to determine the individual PK parameters CL, volume of distribution in steady state (V_{ss})—as a function of the central (V1) and the peripheral (V2) volume of distribution—interdepartmental clearance (Q) and T½ using both label potency and actual potency. To illustrate the effect of using another assay, we calculated the two estimations of the PK parameters using both the CSA and OSA results. Further PK analysis were performed using the FVIII measurements by the same method of the actual potency measurement. Thus, since the potency of Octococ alfa (Kogenate®) is measured using OSA, we performed PK analysis of FVIII results using OSA. And since the potency of remaining factor concentrates is measured by CSA, we performed analysis using CSA results. The two estimations of the PK parameters were used to construct two concentration-time curves of the PK profiles. We used the individual PK parameters that were estimated from the actual potency for further analysis, as these are a patients' "true" PK parameters. To demonstrate the effect of potency difference when switching batches on the predicted FVIII trough levels by PK-guidance, we created six versions of both a low and a high prophylactic dosing schedule for a patient of 97 kg included in our dataset, for example, 1000IE and 3000IE Kogenate every 72 h, respectively. Using these doses, that reflect the label potency, we adapted the FVIII doses. Firstly, the doses were decreased by -20%

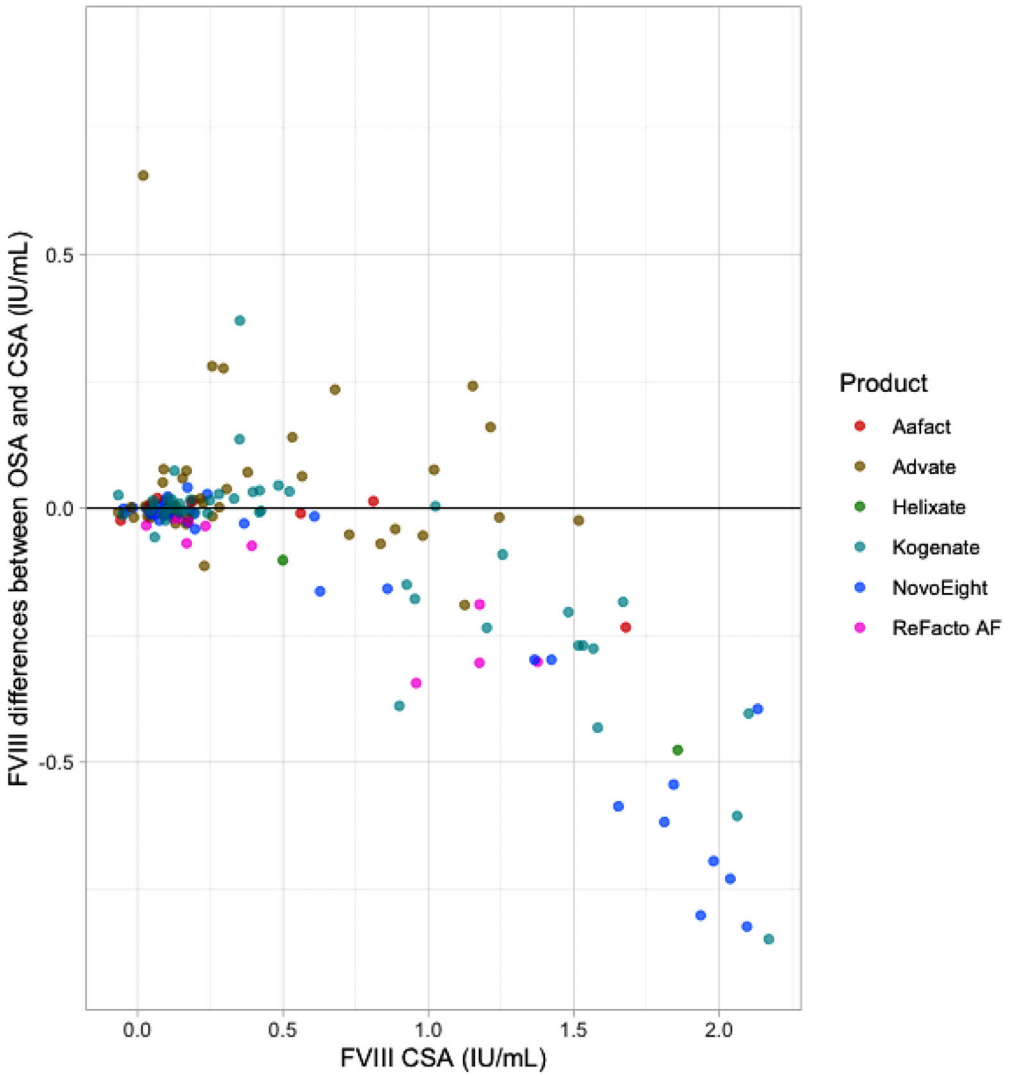

FIGURE 1 Differences in FVIII measurements between OSA and CSA. Differences were calculated as follows: FVIII OSA – FVIII CSA. As clearly can be seen, the difference between OSA and CSA depends on the FVIII level. Median difference between OSA and CSA is -.01 (IQR -.06-.013)

(version 2) and then increased by +20% (version 3) to represent the range of potency difference according to the range allowed by legislation. Secondly, we multiplied the FVIII doses by the range of potency difference as found in our study (version 4 and 5). In the same way, the median potency (percentage) that was found in our study was used to create the final sixth version of the FVIII dosing schedule. These six versions of these two specific dosing regimens, enable us to analyze the effects of potency difference on predicted FVIII trough levels.

2.4 | Statistical analyses

All statistics were conducted in R (R Core team, 2020). Descriptive statistics were expressed as medians and inter quartile range (IQR), or as counts with percentages.

3 | RESULTS

3.1 | Patients characteristics and PK profiling

At time of analysis, 62 patients were included in the OPTI-CLOT trial. Twelve of these patients were excluded from our study due to unknown batch number ($n = 9$) or a batch number untraceable to a pharmaceutical company ($n = 3$) (Supplementary Figure S1). Patient characteristics are depicted in Table 1. A total of 50 patients were included with a median age of 47.5 years old (range 4.0–76.9), of which four children who were 4, 12, 16, and 17 years at study inclusion. Median body weight was 83.0 kg (range 18.0–133.5) and lowest VWF:Act was .33 IU/ml. For the majority of patients (80%), three PK profile FVIII blood samples were available at the following time points: (1) within the first 4 h (range: 13 min – 4 h and 37 min), (2) at T = 24 h and (3) at T = 48 h after FVIII administration. Additionally, a FVIII trough level was taken

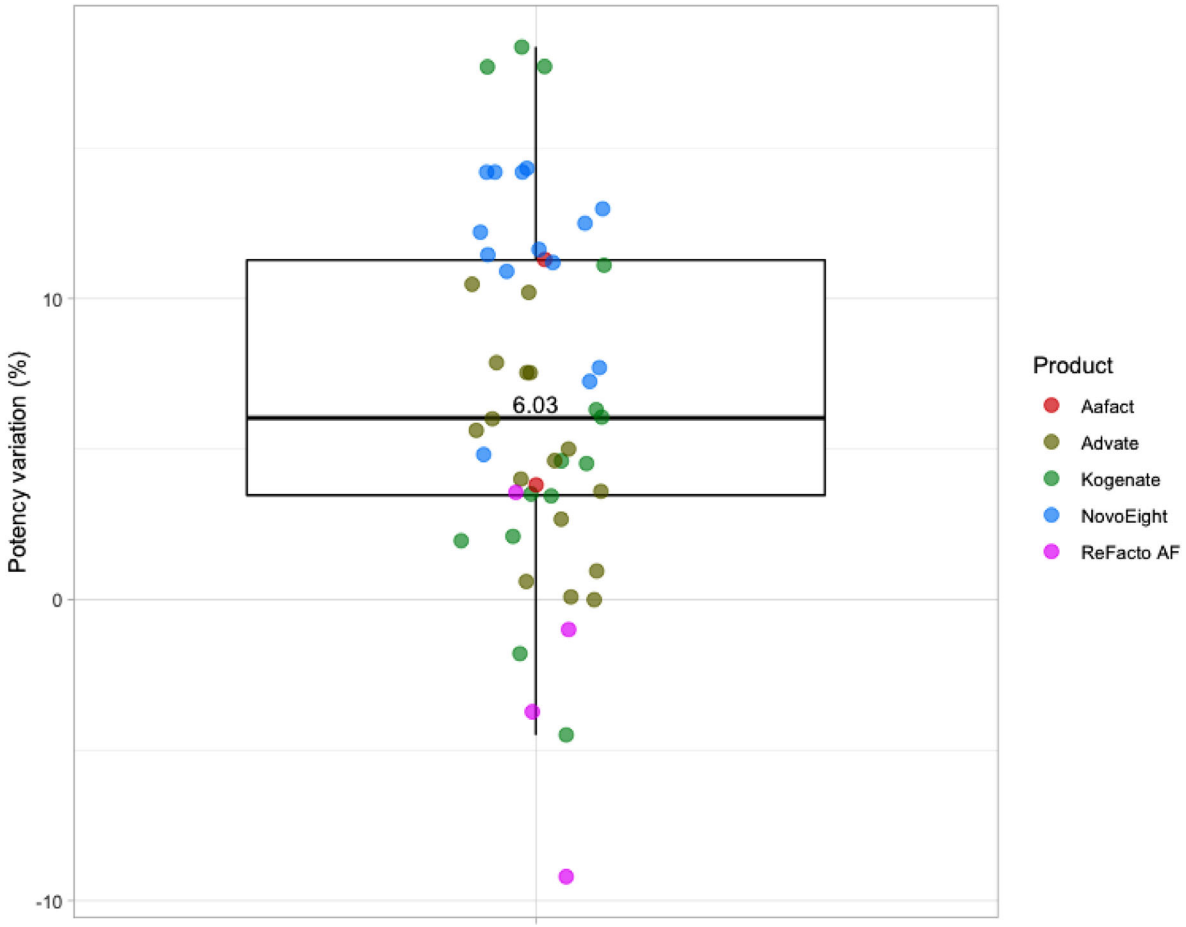

FIGURE 2 Potency difference as identicated in our study population for each product. Potency difference in percentage was calculated as follows: (actual potency – label potency)/label potency) × 100. Only five patients had a lower difference reflecting a lower actual potency than the label potency. The whiskers depict the 2.5th and 97.5th percentile of the data, whereas the box depicts the interquartile range. The median difference is represented by the black horizontal line and the exact number inside the boxplot

for clinical reasons in nine patients. Missing data included VWF:Act at PK time point T = 48 h and measured height in respectively eight (16.0%) and five (10%) patients. Differences of FVIII measurements between CSA and OSA are shown in Figure 1.

3.2 | Potency difference and PK parameters

The dose of administered vials ranged from 250IE to 3000, that is, in some patients, vials were administered multiple times (e.g., 3 × 1000IE) and/or doses were combined (e.g., 1000IE and 2000IE). Actual potency was identical to label potency in one patient, higher in 45 patients and lower in four patients. The median absolute difference in potency was 244 IU (IQR: 124.5-442.0, range: -368.0 to 918.0). This corresponded to a median potency difference of 6.03% (IQR: 3.46–11.275, range: -9.20% to 18.36%). Figure 2 shows all potency differences and discriminates between the different factor concentrates. As expected, these potency differences resulted in differences between the estimations of the PK parameters CL, Vss and T1/2, as the same measured FVIII levels but different FVIII doses (actual vs. label) were used to estimate PK parameters. The difference in estimation of the PK parameter is proportional to the potency difference, as is illustrated in Figure 3, that shows a linear trend. The PK parameter estimations can be found in Supplementary Table S1. As expected, higher actual FVIII dose resulted in higher estimations of CL and V_{ss}, and lower T1/2, as T1/2 is inversely related to CL. In contrast, potency difference did not change the estimations of Q and V2, which can be explained by the absence of interindividual variability in these model parameters. This also causes the linear trend instead of an exact linear line in Figure 3.

3.3 | Influence of potency difference on FVIII PK profiles

The difference between the two PK parameters—based on label potency or actual potency—did not affect the constructed FVIII concentration-time curves of the PK profiles. These two curves show individual overlap, as is clearly seen in Supplementary Figure S2. This means that the PK profiles are identical, while different individual PK parameters are estimated as described above.

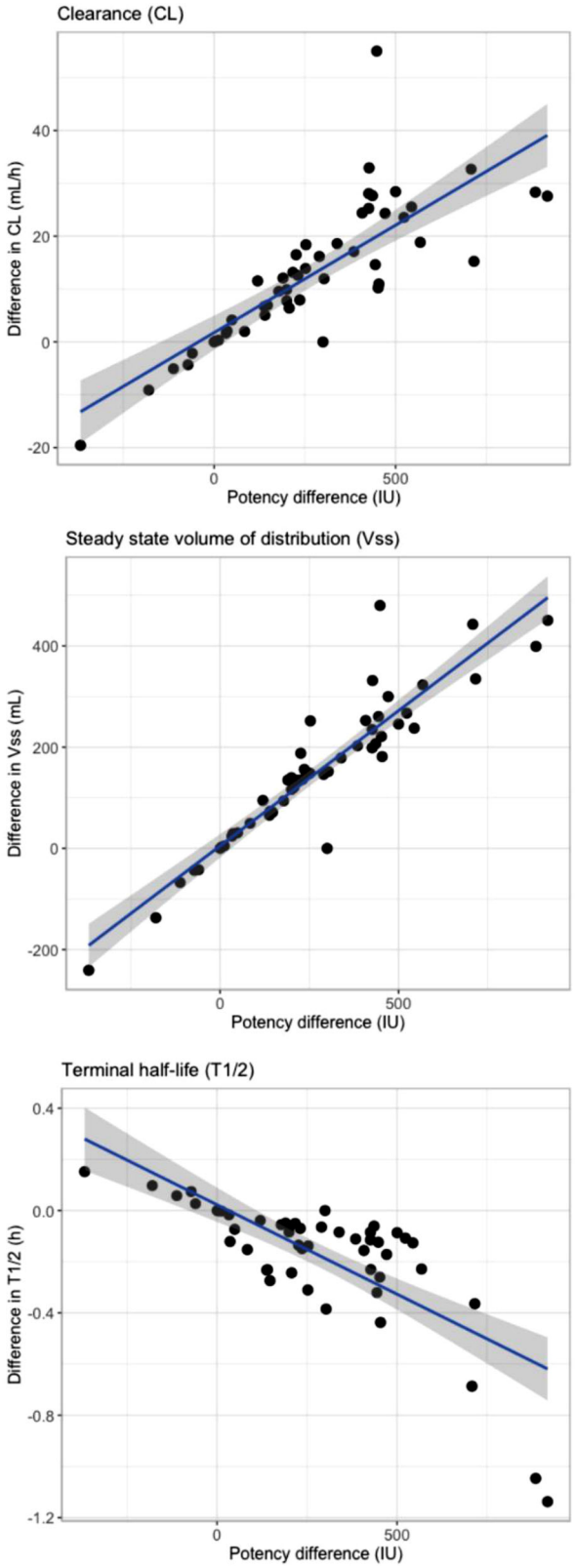

FIGURE 3 Influence of potency difference on difference in estimations of PK parameters clearance (CL), steady-state volume of distribution (V_{ss}) and terminal half-life (T1/2) as estimated using both label and actual potency. Difference is calculated by subtracting the estimation of label potency from actual potency

3.4 | Influence of potency difference on predicted FVIII trough levels when patient switches between batches

The predicted FVIII trough levels for the patient described as an illustrative example, receiving FVIII doses of 1000 IU or 3000 IU every 72 h, are compared in Figure 4. The six scenarios of potency difference are depicted in this figure. It is apparent that FVIII trough levels are linearly correlated to the actual dose. Thus, the percentage potency difference results in an equal percentage difference of predicted FVIII trough levels. This also means that a when a maximum difference of 20% is present, the maximum effect on the predicted trough levels is +20%. In the illustrated examples, the differences in predicted FVIII trough level between the label dose and the median actual dose were .00081 and .0024 IU/ml for the low and high dosing schedule, respectively. The differences in predicted FVIII trough levels between the maximum legislated potency difference and the label dose were .0027 IU/ml and .0080 IU/ml for the low and high dosing schedule, respectively. We consider these differences not to be clinically relevant. Importantly, since a patient could hypothetically receive a FVIII dose with actual potency -20% lower than its label potency, followed by a dose +20% higher than its label potency, the maximum potency difference may amount to +40%. This would lead to differences in predicted FVIII trough levels of .0054 IU/ml and .016 IU/ml for the low and high dosing schedule in our patient, respectively.

4 | DISCUSSION

This study aims to investigate the difference between label and actual potency of standard half-life FVIII concentrates and the effect on the prediction of FVIII activity levels when treating according to PK guidance. The observed median potency difference of 6.03% resulted in differences in PK parameters with concomitant higher CL and V_{ss} and lower T1/2, but the FVIII concentration-time curves of the individual PK profiles were identical. Importantly, differences between label an actual dose causes a proportional difference in FVIII trough levels, in case a patient switches batches after PK-guided dosing advice. This may also be the case when treating with extended half-life factor concentrates, as these exhibit linear PK as well.

The potency difference that we identified (median 6.03%, range: -9.20% to 18.36%) is in accordance with the ±20% difference range as stated by the EP guidelines. Importantly, actual potency was higher than batch potency in 45 of 50 patients, which resulted in maximal FVIII levels and optimal protection against bleeds without additional costs. In our European study, pharmaceutical companies measured the potency difference mostly by CSA as described in EMA guidelines. The mean difference that (6.03%) we established, is in agreement with a difference of 10% as found in another multicentre study. In this study, Moroctococ alfa (Refacto AF®) was measured by seven laboratories by CSA relative to the Refacto Laboratory Standard (RLS) method. Contrastingly, when compared to WHO 6th International Standard FVIII

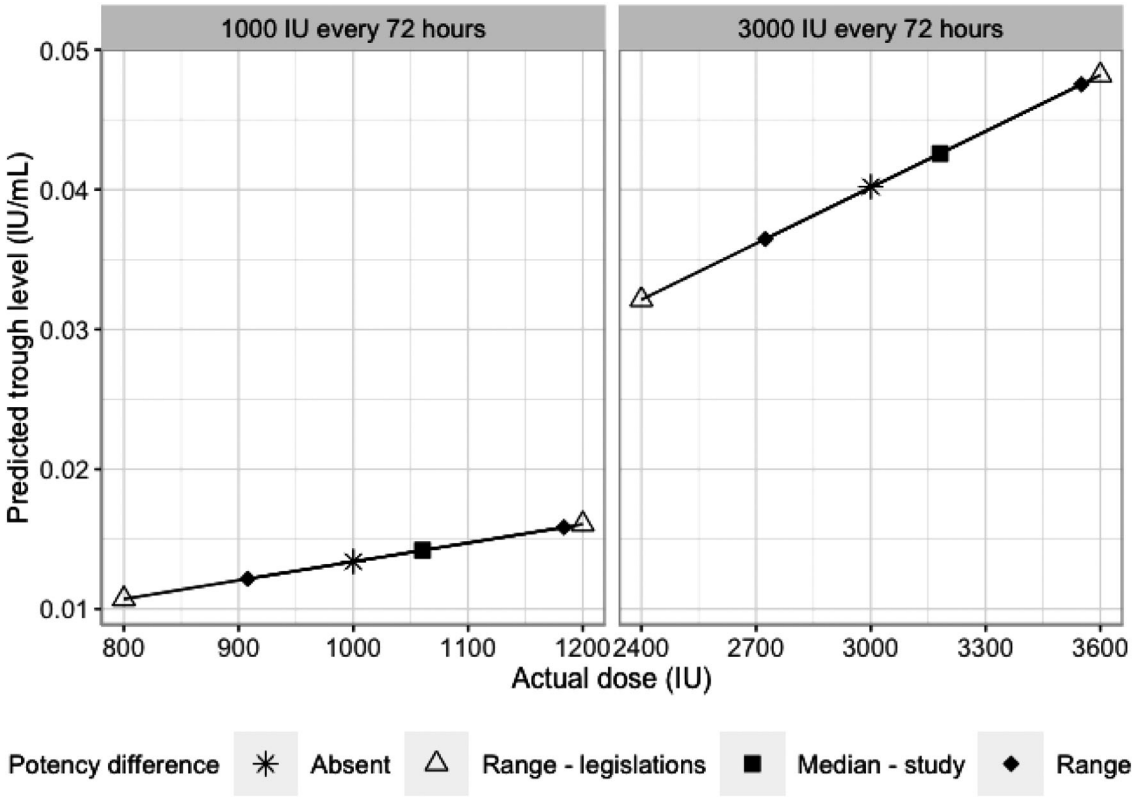

FIGURE 4 Effect of potency differences on predicted FVIII trough levels corresponding to both a low (left panel) and high dose regimen (right panel) for an example patient from the dataset of 97 kg. The exact actual FVIII concentrate doses on the left panel are as follows: 800 IU (minimum legislated difference of -20%), 908 IU (minimum identified difference of -9.2%), 1000IU (difference absent), 1060.3 IU (median identified difference of + 6.03%), 1183.6 IU (maximum identified difference of +18.36%), and 1200 IU (maximum legislated difference +20%). The exact actual FVIII concentrate doses on the right panel are as follows: 2400 IU (minimum legislated difference of -20%), 2724.0 IU (minimum identified difference of -9.2%), 3000 IU (difference absent), 3180.9 IU (median identified difference +6.3%), 3550.80 IU (maximum identified difference +18.36%), 3600 IU (maximum legislated difference of +20%). The linearity of the predicted data points demonstrates the correlation between label and actual FVIII concentrate dose on predicted FVIII trough levels. Figure 4 shows a patient with a bodyweight of 97 kg. Yet, because this patient had a relatively low CL (134 ml/h), effect of the potency difference on the predicted FVIII level was relatively large. Therefore, for clinical purposes, this patient will demonstrate the largest effects of potency differences. When calculating potency difference for a patient with an average CL and a bodyweight of 75 kg on a high dose FVIII regimen (3000IE every 3 days), a potency difference of -20% and subsequently +20% would result in a difference of predicted FVIII trough levels of only .0048 IU/ml)

Concentrate or EP #2 methods, mean estimates ranged from 21% to 31% lower than the label potency.[15]

We expected to find a linear relation between the potency difference and the PK parameter estimations. However, because the model does not include the interindividual variability of Q and V2, these parameters are fixed. Therefore, Q and V2 cannot change proportionally to dose, and this difference is additionally included in V1 and CL. This explains the linear trend in Figure 3 instead of a complete linear association.

The most important findings from our study were as follows: Firstly, the percentage potency difference resulted in an equal percentage difference in predicted FVIII trough levels. Because of this percentage effect on predicted FVIII trough, Figure 4 is—although it shows only one example of a patient with a body weight of 97 kg—still illustrative. Secondly, potency difference—both the difference as identified in this study and the maximum allowed difference—did not clinically affect predicted FVIII trough levels. However, in the exceptional case when a patient for instance firstly receives a dose with a potency difference of -20% (e.g., 2400IE in a 3000IE label dose) and secondly a dose with a potency difference of +20% (e.g., 3600IE in a 3000IE label dose), the difference in predicted FVIII trough level of .016 IU/ml could be clinically relevant (Figure 4). To our knowledge, this effect on FVIII trough levels has not been investigated previously. Nonetheless, our results reflect those by Lambert et al., who determined FVIII recovery of a recalibrated B-domain depleted FVIII concentrate which contained 20% more FVIII concentrate per batch. The FVIII recovery values have been found within the expected FVIII range.[16]

To our knowledge, this is the only study which investigates effects of potency differences on individual FVIII PK parameters, with regard to FVIII trough predictions and dosing regimens in haemophilia A patients. Another strength of this study is that we matched the method of FVIII measurement to the method of the actual potency measurement. Both OSA and CSA are used for potency labelling and clinical monitoring of patients. The United States Food and Drug

Administration (FDA) favours OSA measurement of potency, while EMA dictates the use of a CSA to quantify both label and actual batch potency. Although both assays indirectly measure FVIII activity, these different tests result in varying outcomes and inaccuracy, depending on the characteristics of the different concentrates. Our results clearly demonstrate differences in FVIII measurements between the CSA and OSA during PK profiling. In literature, studies demonstrate +40% higher potencies of immuno-purified FVIII concentrates measured by OSA, and +20% higher potencies of B-domain deleted recombinant product measured by CSA.[17,18] No literature reports on potency differences as measured by OSA. However, potency assignments measured by OSA may lead to additional inter-laboratory variability, due to the high number of varying reagents and plasma standards.[17,19] Other factors that contribute to discrepancies are the choice of reference standard, the presence or absence of VWF in the reference standard, diluents in the assays and the source of phospholipids.[20]

Our study also has some limitations. Firstly, the interlaboratory variation between pharmaceutical companies of the measurements of the actual potency of batches may have influenced our calculations, although we assume these influences are negligible. Secondly, we provided predicted FVIII trough levels of versions of only two dosing regimens. However, since there is a linear effect of potency difference on the predicted trough, we do not believe it is necessary to show more dosing regimens. Furthermore, we calculated predicted FVIII trough levels using PK parameters based on the actual dose, whereas in clinical practice pharmacologists use label dose. Nevertheless, using the actual dose reflects the real-life PK parameters. It may be argued that our results are biased due to the exclusion of twelve patients from the OPTI-CLOT randomized trial study due to untraceable actual potencies. However, we do not expect that these exclusions lead to bias as patient characteristics of both groups were similar. Similarly, our results are not influenced by repetitive batch numbers as no patient received a dose with exactly the same batch or batch combinations identical to another patient.

5 | CONCLUSION

In conclusion, the observation that actual potency of FVIII concentrate is often higher than that of label potency has only minimal consequences for estimation of individual PK parameters. This is confirmed in FVIII concentration-time curves and PK-guided FVIII dosing predictions and advice, as the FVIII trough level is demonstrated to maximally deviate ±20% from the estimated FVIII trough level when patients receive another FVIII batch. Therefore, our study indicates that discrepancies between actual and label potency are negligible when applying PK guidance of FVIII concentrates in haemophilia A patients.

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The SYMPHONY NWO-NWA consortium which aims to orchestrate personalized treatment in patients with bleeding disorders, is a unique collaboration between patients, health care professionals and translational & fundamental researchers specialized in inherited bleeding disorders, as well as experts from multiple disciplines. It aims to identify best treatment choice for each individual based on bleeding phenotype. In order to achieve this goal, work packages (WPs) have been organized according to three themes, for example, Diagnostics (WPs 3&4), Treatment (WPs 5–9) and Fundamental Research (WPs 10–12). This research received funding from the Netherlands Organization for Scientific Research (NWO) in the framework of the NWA-ORC Call grant agreement NWA.1160.18.038. Principal investigator: Dr. M.H. Cnossen. Project manager: Dr. S.H. Reitsma.

Beneficiaries of the SYMPHONY consortium: Erasmus MC and Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, project leadership and coordination; Sanquin Diagnostics; Sanquin Research; Amsterdam University Medical Centers; University Medical Center Groningen; University Medical Center Utrecht; Leiden University Medical Center; Radboud University Medical Center; Netherlands Society of Hemophilia Patients (NVHP); Netherlands Society for Thrombosis and Hemostasis (NVTH); Bayer B.V., CSL Behring B.V., Swedish Orphan Biovitrum (Belgium) BVBA/SPRL.

CONFLICT OF INTEREST

MC has received grants from governmental and societal research institutes such as NWO, ZonMW, Innovation fund, from private funds, institutional grants and unrestricted investigator research grants/educational and travel funding from the following companies over the years: Pfizer, Baxter/ Baxalta/ Shire, Bayer Schering Pharma, CSL Behring, Sobi Biogen, Novo Nordisk, Novartis and Nordic Pharma, and has served as a member on steering boards of Roche and Bayer. All grants, awards and fees go to the institution.

RM has received governmental and societal research institutes such as NWO, ZonMW, and Innovation Fund and unrestricted investigator research grants from Baxter/Baxalta/Shire/Takeda, Bayer, CSL Behring, and Sobi. He has served as an advisor for Bayer, CSL Behring, Merck Sharp & Dohme, and Baxter/Baxalta/Shire/Takeda. All grants and fees were paid to the institution.

AUTHOR CONTRIBUTION

Iris van Moort enrolled patients, performed blood sampling for pharmacokinetic analysis and collected the data. Colin C. Spence aided in data collection. Tine M.H.J. Goedhart performed statistical analyses and is main author of the manuscript together with Colin C. Spence. Laura H. Bukkems performed population pharmacokinetic calculations. Moniek P.M. de Maat, Michel C. Zwaan, Marjon H. Cnossen, Ron A.A. Mathôt supervised the study. All authors substantially contributed to the writing and critically revised the manuscript, with approval of the final draft.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study will be made available by the corresponding author after a reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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