of biological sample exploitation. During PK calculations, many researchers merely use for dose the nominal amount declared, overlooking the noticeable biases that may result in the assessment of PK parameters. The aim of this work was to evaluate the biases related to doses injected of a biosimilar drug in 2 Phase I clinical trials.

Patients (or Materials) and Methods: In trial A, 12 healthy volunteers received different doses of a biosimilar of interferon beta-1a by either subcutaneous (SC) or intravenous (IV) injection. The doses were prepared by partially emptying 0.5-mL syringes supplied by the manufacturer (drop count procedure). In trial B, 12 healthy volunteers received 3 different formulations of the drug by IV injection (biosimilar without albumin [HSA], biosimilar with HSA and original brand [Rebif®]) and 2 different formulations as multiple SC injections (biosimilar HSA-free and original brand). In both trials, the actual dose administered was calculated as: D = C·V – losses. The product titer C was assessed by ELISA. The volume administered IV was assessed by weighting. Losses were evaluated by in vitro experiments. Finally, the binding of 125I-interferon to HSA was evaluated by counting the free and HSA complexed molecule fractions separated by gel filtration.

Results: Interferon was not significantly adsorbed onto the lines used for its IV administration. In trial A, the titer was very close to the one declared (96 ± 7%). In trial B, it differed significantly (156 ± 10% for biosimilar with/without HSA and 123 ± 5% for original formulation). In trial A, the dose actually administered showed a large variability. The real injected volume could be biased up to 75% compared with the theoretical volume (for the lower dose administered [ie, 0.03 mL]). This was mainly attributed to a partial re-aspiration of the drug solution before withdrawing the syringe needle. A strict procedure was therefore applied in trial B to avoid these inaccuracies. Finally, in trial B, 125I-Interferon beta-1a binding to HSA appeared time dependent and slow, reaching 50% after 16-hour incubation, which is close to steady state reported for the comparator Rebif®.

Conclusion: These practical examples (especially biases on actual titer and volume injected) illustrate that actual dose assessment deserves attention to ensure accuracy for estimates of clearance and distribution volume in the scientific literature and for registration purposes, especially for bioequivalence studies.

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OC006—CRITICAL REVIEW OF THE VALIDATION PROCESS OF SIX PREDICTIVE BIOMARKERS: HOW GOOD IS THE QUALITY AND QUANTITY OF THE EVIDENCE?

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Introduction: Increasing efforts have been made on the research of new predictive biomarkers in drug development, particularly in oncology. In this context, the validation process represents a difficult task with some potential methodologic limitations. In the present study, we will perform a critical review of the validation process of 6 key biomarkers in oncology.

Patients (or Materials) and Methods: Six biomarkers were selected considering their relevance in drug development over the last decade in oncology: HER-2, EGFR, KRAS, C-KIT ALK, and C-Met. A review of literature was performed in PubMed, Cochrane, and EMBASE, and in regulatory agencies public websites. A critical review of available data in relation to regulatory requirements (EMA and FDA) has been conducted considering the following elements: at which stage of drug development the biomarker was considered in defining the target population; type of clinical data used for the biomarker validation process; impact of the biomarker in the final labeling; and availability of a standardized test applicable in clinical practice.

Results: Results are displayed according to recommendations of regulatory agencies on the necessary procedural steps for the validation process preapproval.

	Triggering Facts	Labeling Implications	Standarized Test
HER-2	Biomarker-based drug development	Restricted labeling to HER2 overexpression or HER2 gene amplification	+
EGFR	Failed studies in NSCLC	Unrestricted labeling in US	–
		Negative opinion in EU	–
		EGFR+ patients at a later stage once prospectively validated	
KRAS	Failed studies in mCRC	KRASwt in EU Negative opinion in US	
		KRASwt at a later stage in US and EU once prospectively confirmed	+
C-KIT	Exploratory analyses through the different indications	Not reflected in labeling	–
ALK	Biomarker-based drug development	Restricted labeling to anaplastic lymphoma kinase (ALK)-positive in NSCLC	+
C-Met	Biomarker-based drug development	Not reflected yet	–

Conclusion: Data analyzed allow to distinguish 2 different scenarios. Those situations in which the biomarker development was the consequence of a primarily failing drug development strategy (EGFR and KRAS) and those in which the biomarker was a key element prospectively considered in drug development (ALK, HER2, C-KIT and C-met). Regulatory decisions were adopted sometimes based on purely retrospective strategies. The authors will critically describe such circumstances and the potential clinical implications of such decisions.

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OC007—ASSESSMENT OF CLINICAL PHARMACOLOGY SKILLS AS PART OF THE NEW INTEGRATED FINAL EXAM FOR MEDICAL STUDENTS AT KAROLINSKA INSTITUTET

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Introduction: An integrated final exam for medical students was introduced at Karolinska Institutet, Stockholm, Sweden, in 2012. The exam is scenario based and consists of six 20-minute stations, 1 of which has been designed to assess clinical pharmacology (CP) skills. The overall aim of the exam is to assess the knowledge (both