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 [Rebiﬁ®]) 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.


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

J.S. Peñatardo1; N. Riba1; V. Dominguez1; J. Camarero2; X. Carne1,2; and G. Calvo1,2

1Clinical Pharmacology Department, Hospital Clinic, Barcelona, Spain; 2Spanish Agency of Medicines and Medical Devices, Madrid, Spain; and 3University of Barcelona, Barcelona, Spain

**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.

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

**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.

**Disclosure of Interest:** None declared.

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

M.-L. Ovesjö1; and Y. Böttiger

Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden

**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
Clinical Therapeutics

clinical and preclinical) and skills needed to perform adequately during the following 18 month internship that is required to obtain the medical license. CP contents, results, and student perceptions from the first 3 occasions are presented.

Patients (or Materials) and Methods: The examination takes place in the last semester of the 5.5-year training program. The 6 stations are equally weighted in the total result. The students can pass the exam if they fail at 1 station, as long as their average score is sufficient. The CP station has consisted of a computer-presented patient case with questions, aimed at assessing prescribing skills and has also included preclinical aspects. Students have been allowed to use the Internet to search for information but not to interact with other persons. The cases so far have included the evaluation of possible side effects in an elderly patient with polypharmacy admitted after falling, drug prescribing to a pregnant woman with a urinary tract infection and migraine, and the reasoning about terminating or continuing treatment with several medicines initiated by another prescriber. Students' perceptions of the exam were collected through group interviews or questionnaires in direct connection to examination.

Results: Five percent of students failed the exam as a whole, whereas the failure rate at the CP station was somewhat higher; 7% to 14%. The failure rate was higher at the stations with more theoretical content such as CP, compared with stations assessing skills in communication and physical examination or procedures. Within the CP station, preclinical questions had a higher failure rate than the more clinically oriented. Also, only 16% of prescription forms were filled out correctly. Students' comments have included that it is essential that the scenarios are perceived as authentic and that it is difficult to go from practical stations, like a cardiac resuscitation scenario, to "computer patients." A few technical problems with the computers were perceived as very disturbing.

Conclusion: A clinical pharmacology station can be a valuable part of an integrated final exam and is well suited for the assessment of practical prescribing performances, as well as students' abilities to integrate preclinical knowledge and clinical reasoning. Scenarios must be perceived as authentic, and access to the Internet can thus be a natural part of the setting.

Disclosure of Interest: None declared.

OC008—THE EFFECT OF A STRUCTURED MEDICAL RECORD ON THE RECORDING OF THERAPEUTIC INFORMATION AND COMMUNICATION BETWEEN DOCTORS

R. Van Unen1,2; J. Tichelaar1,2; M. Richir1,3, and T. de Vries1,2
1RECIPE(Research and Expertise Center In Pharmacotherapy Education); and 2Department of Internal Medicine, Section Clinical Pharmacology and Pharmacotherapy, VU University Medical Center, Amsterdam, the Netherlands

Introduction: In contrast to the diagnostic part of the medical record (MR), the therapeutic section of the MR is currently unstructured and does not provide guidelines on which items of the (pharmacotherapy) therapy are essential to note in the MR. The omission of this information could result in prescribing errors and miscommunication between doctors. A previous study showed that both junior doctors and clinical consultants believe it is important to note extensive information in the MR about the selected (pharmacotherapy) therapy. This study investigated the effect of a structured MR on the completeness of therapeutic information in the MR and the extent to which doctors felt informed about the treatment (as an indicator of communication between doctors).

Patients (or Materials) and Methods: Fifteen junior doctors working in the outpatient department of internal medicine in 7 Dutch teaching hospitals recorded therapeutic information for 2 weeks in regular, unstructured MRs. Subsequently after receiving a short training, they had to record their therapeutic information for 4 weeks in a structured MR. The structure contained 21 therapeutic items that should be recorded. The recording of these therapeutic items was then evaluated in 223 unstructured MRs and 197 structured MRs. After this evaluation, independent clinical consultants in internal medicine were asked to score, on a 5-point scale, the extent to which they felt informed about the treatment.

Results: Seven of the 21 (33%) therapeutic items were recorded in significantly (P < 0.05) greater detail in the structured MRs. Clinical consultants did not feel significantly more informed about treatment (score 3.9 with unstructured MRs and 4.0 with structured MRs; P = 0.25).

Conclusion: Structuring the therapeutic part of the MR improves the documentation of therapeutic information, but doctors did not feel more informed about the treatment.

Disclosure of Interest: None declared.

OC009—AN ASSESSMENT OF THE ACCURACY OF HORIZON SCANNING PREDICTIONS OF MEDICINE USE IN THE SCOTTISH NATIONAL HEALTH SERVICE

M. Bennic1; J. Dear2; E. Dunlop Corcoran3; S. Hems3; S. McTaggart3; R. Newham1; and C. Waugh3
1Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow; 2Edinburgh University/BHF Centre for Cardiovascular Science, Queen's Medical Research Institute; and 3Information Services Division, NHS National Services Scotland, Edinburgh, United Kingdom

Introduction: The Scottish Medicines Consortium (SMC) provides advice about the clinical and cost-effectiveness of newly licensed medicines to the National Health Service (NHS) in Scotland, and since 2005, SMC has also provided early intelligence on medicines still in development through publication of “Forward Look” reports. Forward Look predictions are helpful in supporting resource planning by NHS Boards, but there are challenges in accurately estimating the uptake of a medicine that is still in development. This study examined how actual medicine use compared with predictions provided in Forward Look Reports and SMC advice.

Patients (or Materials) and Methods: Twenty-eight medicines were selected in line with specified criteria. Data on the predicted uptake of these medicines at year 1 were extracted from Forward Look reports and SMC advice and compared with actual medicine use data from national primary and secondary care datasets. The data were summarized in medicine profiles and reviewed by clinicians to identify factors that may have impacted on the accuracy of predictions provided in Forward Look reports and SMC advice.

Results: Of 28 medicines selected for evaluation, the actual acquisition cost per patient per annum was consistent with Forward Look predictions for 11 medicines, higher for 14 medicines, and lower for 3 medicines. Of 22 medicines in the sample that were accepted for use or restricted use by SMC, the actual uptake at year 1 was consistent with Forward Look predictions for 4 medicines and with predictions in SMC advice for 3 medicines. Forward Look was more likely to overestimate the uptake than the SMC advice. Review of the medicine profiles identified 7 factors that may explain the variation between predicted and actual medicines uptake:
- SMC “not recommended” advice
- Accuracy of the predicted acquisition cost and number of patients (uptake being the product of these)
- Availability of alternative treatment
- Comparative costs and service implications