NEWSLETTER

RSNN
Regulatory Science Netwerk Nederland

Dear Reader, this is the first Newsletter of the Regulatory Science Network Netherlands (RSNN). The RSNN was founded October last year during the Dutch Medicines Days organized by FIGON, the integrative platform for innovative drug research in the Netherlands. The RSNN brings together a variety of experts who are involved in regulatory activities related to drug development, and who work in academia, the government, pharmaceutical industry, patient organisations, and other disciplines. The founding of RSNN is a logical follow-up to several well-attended and successful regulatory science meetings organized by the CBG- Medicines Evaluation Board, Dutch Association of Pharmaceutical Medicine (NVFG), and the TI Pharma Escher-project. During these meetings, attendees recognized that a network would be an excellent instrument to facilitate activities in the field of regulatory science in the Netherlands, something RSNN aims to achieve by stimulating dialogue, and sharing information and methods via collaborations. The network aligns with other European platforms that are active in the field of regulatory science, under the umbrella of the 'One Public Health' motto.

The aim of the RSNN Newsletter is to give an update on the RSNN activities to those who are active in the regulatory science area, and also to provide its readers with the latest developments in the field.
In this Newsletter we summarize the presentations and discussions of a RSNN symposium on the role of biomarkers in the regulatory process. This symposium was held on July 7 2016.

Symposium biomarkers voor het voetlicht: Een andere kijk op registratie

The first RSNN symposium was opened by Prof. dr. Bert Leufkens who stressed in his introduction that within the current regulatory environment all stakeholders need to interact at an early stage of drug development. This can be done as part of regulatory science [1], which is a discipline that aims to improve the efficiency of the regulatory system and facilitate a more objective benefit/risk assessment [Box 1]. A first step to sharing outcomes of regulatory science is to bring all stakeholders to the table, stimulate open conversations, and support steps towards the changes needed in the regulatory process. The establishment of the RSSN in this sense is an excellent initiative.
More than 60 invited participants listened to the lectures of five speakers and at the end of the day continued the discussion during a light dinner where Prof. dr. Adam Cohen (Centre for Human Drug Research, Leiden) added more food for thought in his dinner speech, when he reviewed the recent tragic events at a French CRO. He made it clear that improvements are needed in the regulatory process by recognizing the importance of pharmacology and the use of biomarkers. In his comment on the dinner speech Sander van den Bogert (University Utrecht) made a plea for more transparency (e.g., via publications) before and during the execution of clinical studies.

BOX 1: Regulatory Science, a CBG-MEB definition

Regulatory Science is the science of developing and validating new standards and tools to evaluate and assess the benefit/risk of medicinal products, facilitating sound and transparent regulatory decision making. Through analysis of regulatory frameworks itself and its effectiveness, however, regulatory science can also advance knowledge of these systems in general

ADAPT SMART

Fortunately ,during the symposium it became clear that the regulatory environment and its processes are changing. Dr. Andre Broekmans (Escher/Lygature) presented ADAPT SMART (Accelerated Development of Appropriate Patient Therapies), an Innovative Medicines Initiative's (IMI) multi stakeholder project with 32 participants that is focused on the implementation of Medicines Adaptive Pathways to Patients (MAPPs). MAPPS seeks to foster access to beneficial treatments for the right patient groups at the earliest appropriate time in the product life-span in a sustainable and affordable fashion. This is done without compromising current standards for approval. Adaptive licensing or adaptive pathways projects like MAPPs achieves this goal by collecting early evidence generated in smaller numbers of patients for the initial licence and then collecting

confirmatory evidence (real world data) generated on an ongoing basis via active surveillance in larger group of patients for the full licence. MAPPS is a model that is in development. An essential element of the model is the collaboration and open communication between all stakeholders at the beginning and throughput the process. In the early phase of drug development these parties select those medications that could be developed via MAPPS in an efficient manner and during their development monitor the process. ADAPT SMART operates within the current legal framework and will not provide policy recommendations, rather it will generate recommendations and proposals for further research. Several ADAPT SMART workshops have been held recently, including on the development of eligibility criteria and the assessment of the consequences of this model through scenarios for products to enter an adaptive pathway. Reports will be available soon and publications will follow. For more information see the ADAPT SMART website [2].

Biosignatures

It is not only adaptive licensing or adaptive pathways that can play a distinct role in improving regulatory processes, but also the use of biomarkers to diagnose, monitor and select patients for clinical trials. Prof. dr. Dick de Zeeuw (Department of Clinical Pharmacy and Pharmacology University Medical Center Groningen) presented research data produced by his group at the University of Groningen showing that a single biomarker, such as blood pressure (a surrogate marker), is not sufficient to assess whether patients with Diabetic Kidney Disease (DKD) are responding to treatment nor if they will develop complications. To achieve both a effectiveness and risk evaluation, the response of multiple biomarkers is needed. A composite of the responses of all these indicators will potentially give a better indication of whether a diabetic patient with DKD will be effectively protected [3]. This response score is not only valuable in trial evaluation but also for the effectiveness of medication for the individual. Dick de Zeeuw stressed that it is important in this context to realize that the response to the drug of each indicators varies between individuals. The response scoring thus opens the door towards precision or personalized medicine. Trials that align better with clinical practice and are targeted to include those who respond to well to the treatment (the right treatment for the right patient) and exclude those that show side effects are needed to look into this, such as in the Study Of Diabetic Nephropathy With Atrasentan (SONAR) trial [4]. Further research by de Dick de Zeeuw and his colleagues in Groningen is planned, for instance as part of the IMI Diabetic kidney disease biomarkers (DKD-BM) call, with a project called Beat DKD, a project focused on the application of systems-biology techniques into risk and response prediction.

'Orphanisation'

The development of more targeted therapies for selected patient groups prompts the question of how these therapies will be registered and for what indication? Is the composite biomarker part of the indication? And will these treatments not then become pseudo-orphan drugs that are not available for other patients who might benefit from this treatment? This a potential disadvantage that was brought up in the lecture by dr. Steff Schutte (Vice President and Head of Regulatory Affairs EMEA, Astellas), who at the start elegantly refreshed the memory of the audience on what the standard definition of a biomarker is [Box 2], and that in fact they can be defined in several ways: as an objective measure of a biological process, a surrogate endpoint, as a clinical endpoint, or as a disease-related biomarker [5]. Steff Schutte also noted that biomarkers are particularly useful in three major areas: 1) drug development, 2) diagnosis and/or prognosis, and 3) patient management. All three domains are directly involved in the personalised treatment of patients.

But not only the 'orphanising' effect of the use of biomarkers can be a hurdle to their use in clinical development. Steff Schutte also mentioned other disadvantages of the implementation of the use of biomarkers and personalized medicine [Box 3]. These hurdles need to be taken into account since the use of biomarkers is an essential part of making the registration process more efficient and bringing better therapies to patients by allowing selection of patients.

BOX 2: NIH definition of a biomarker [6]
The NIH Biomarkers Definitions Working Group defines a "biomarker" as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention."

BOX 3: Advantages and disadvantages of biomarkers and personalized medicine	
Advantages	*Disadvantages*
Supports patient selection	Investment is needed to better understand the disease and its linked biomarker
Improves drug development by enriching trial populations	Complex patient screening makes clinical trials more complex and of longer duration
Supports the optimization of benefit/risk	Smaller target patient populations
Increases adherence to therapy	Biomarker tests can reduce access to treatments
Improves treatment costs	Smaller clinical studies and thus smaller safety database
Allows better differentiation vs other treatments	Excludes patients that might benefit treatment
	Could lead to 'orphanising' of treatments
	Could lead to pseudo-specificity

As an example of a new, recently approved biomarker, Steff Schutte presented data from a recent meta-analysis (20 trials, 1475 patients) on programmed death-ligand-1 (PD-L1) expression in tumours and its role in predicting disease progression after treatment with checkpoint inhibitors targeting the PD-1 pathway. The overall response rate after treatment with 2 checkpoint inhibitors was significantly higher in PD-L1 positive (39% and 30%) patients in comparison to PD-L1 negative patients (23% and 11 %), which was much higher than the response rate for chemotherapy (~10%). The difference was significant for melanoma and non-small cell lung cancer (NSCLC), respectively, but not for genitourinary cancer. In the USA this led to registration of one of the checkpoint inhibitors for those patients that are PD-L1 positive. However, this step still excludes a substantial proportion of patients that are PD-L1 negative (25%), which is a potential negative effect of the use of biomarkers not only in cancer treatment but also in other diseases. Nonetheless, biomarkers are needed to improve the efficiency of the registration process and bring the right treatment to the right patient. Further innovations and closer collaboration between all stakeholders [7] will support the appropriate use of biomarkers in a broad range of disciplines in the near future.

Impact on Reimbursement and HTA

The changing regulatory environment will also have an impact on the reimbursement process and health technology assessments (HTA). Do individually targeted treatments also mean individually targeted reimbursement? Marja Kuijpers (Dutch National Health Care Institute, DNHCI/ZiN), in the last lecture of the symposium, explained how the National Health Care Institute currently approaches this problem. Four criteria are used when assessing whether a treatment will be reimbursed: 'scientific proof' and daily practice (relative efficacy new treatment vs. standard of care according to guidelines), the need, absolute costs (budget impact), cost-effectiveness and applicability. When assessing companion diagnostics or biomarkers a number of questions are asked: What scientific clinically relevant evidence is provided for the use of companion diagnostics or biomarkers in combination with targeted therapies? Does clinical benefit lead to long-term health improvements vs standard treatment? What is the analytical (specificity and selectivity) and clinical validity (for diagnosis and prognosis, predictive value of response and side effects) and finally what is the impact on the cost of a treatment and cost-effectiveness (including the effect of false positives and negatives). Until now only a few biomarkers have been successfully part of benefit/risk evaluations in EMA registration files. Companion diagnostics are more usually used (BOX 4), and not composite biomarkers, like the one that was presented in the lecture of Dick de Zeeuw. It is clear that it will take several years before these more complex biomarkers or 'biosignatures' become part of submissions. Not only does their appropriate use in clinical studies and the link with clinical outcomes need to be defined, but also their place and impact on the HTA process should get more attention, which is something that in most cases also applies to 'the more straightforward' companion diagnostics. The road is lengthy.

A methodological reflection paper is currently in development by the European network on HTA (EUnetHTA) [8], and discussions are ongoing on how to control costs by introducing 'pay for performance', for instance, or 'graded cost-effectiveness' when biomarkers are used to select groups of patients with different levels of response to treatment.

Discussion

This first RSNN symposium ended with a short discussion and the conclusion by the moderator of the meeting, dr. Christine Gispen-de Wied (CBG), that we are still left with many questions and challenges. It is clear that biomarkers are needed if we want to improve the development of treatments and bring them, in a sustainable and affordable fashion, to the right patient groups at the earliest appropriate time in the product life-span, for instance via adaptive pathways supported by projects like Adapt-SMART. Currently, however, most known/approved biomarkers function as diagnostic tools, and not for the monitoring of patients in trials or as an outcome measure. These types of biomarkers are more complex and resemble "biosignatures" or biological patterns of clinical response. How to validate these more complex biomarkers is still a puzzle. Will their use, particularly in drug development programmes that are based on adaptive designs, not lead to orphanisation of treatments? And as Marja Kuijpers pointed out, biomarkers can save money but can increase costs as well; so how can this be controlled and keep things affordable? Are 'pay for performance' and 'graded cost-effectiveness' potential solutions?

BOX 4: Companion Diagnostics used in EMA submissions

1. Overexpression of HER2 combined with the use of trastuzumab in patients with breast cancer
2. EGFR-expression and wild-type RAS-gene (exon 2, 3, 4 from KRAS and NRAS) combined with the use of cetuximab in patients with colorectal carcinoma
3. BRCA-1/2 mutated gene combined with the use of olaparib (PARP-inhibitor) in patients with ovarian cancer
4. Class III mutation in CFTR-gen (1B text mentions 10 mutations) combined with the use of ivacaftor in cystic fibrosis patients
5. Homozygous F508del-mutation in CFTR-gene combined with the use of ivacaftor/lumacaftor in cystic fibrosis patients

What will happen with those patients that were not 'biomarker selected' for treatment? And if during the implementation of an adaptive pathway the therapy does not work for the target group, do we start all over again from the beginning?
Key to all these discussions is the input from and collaboration between all parties, not only during drug development, but at all levels in the regulatory process, and not only by professionals but also by patients [9].
The RSNN is now here to support this collaboration at all levels and share solutions.

Further recommended reading
Cohen AF et al. The use of biomarkers in human pharmacology (Phase I) studies. Annu Rev Pharmacol Toxicol. 2015;55:55-74.

Next meeting
At the FIGON Dutch Medicines Days (3-4 October 2016), the RSNN will organize two regulatory science sessions. This is an opportunity to hear more on the role of biomarkers, meet colleagues, and join the ongoing discussions! The general programme can be found on http://www.figondmd.nl/day-to-day-program. Click here to register: http://www.figondmd.nl/content/figon-dmd-registration-1.
The full RSNN programme of the RSNN sessions will be announced soon.

Join RSNN
For those who would like to join the RSNN, refer to the contact details at the end of this Newsletter
More information on the RSNN will be available soon on: http://figon.nl/en/Rsnn
And on our linked in page: https://www.linkedin.com/groups/8559430

Literature
[1] http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm228206.htm | [2] http://adaptsmart.eu/ | [3] Heerspink HJ et al. A novel approach for establishing cardiovascular drug efficacy. Nat Rev Drug Discov. 2014 Dec;13(12):942 | [4] https://clinicaltrials.gov/ct2/show/NCT01858532 | [5] Niciu MJ et al. Biomarkers in mood disorders research: developing new and improved therapeutics. Rev Psiquiatr Clin. 2014; 41(5): 131–134 | [6] Wagner JA et al. Strategic approach to fit-for-purpose biomarkers in drug development. Annu Rev Pharmacol Toxicol. 2008;48: 631-51. | [7] http://www.biomarkersconsortium.org/ | [8] http://www.eunethta.eu/news/closed-public-consultation-draft-methodological-reflection-paper-personalised-medicine-and-co-d | [9] http://p4mi.org/

Contact
Information: Peter van Meer | Email: p.v.meer@cbg-meb.nl
Join the RSNN: Barbara van Veluw – Greebe | Email: b.v.veluw@cbg-meb.nl