# NEWSLETTER

No. 5 - 2018

RSNN
Regulatory Science Netwerk Nederland

**Dear Reader,**
**This is the fifth Regulatory Science Network Netherlands (RSNN) Newsletter. In this edition we report on the RSNN Workshop 'What's in, What's out, What's relevant? – Towards a sensible label' held on June 20th 2018, and announce upcoming meetings.**

## WHAT IS THE RSNN?

The RSNN, a network for experts from academia, government, the pharmaceutical industry, patient organisations, and others involved in regulatory activities related to drug development, aims to facilitate activities in the field of Regulatory Science in the Netherlands by stimulating dialogue and collaboration, and sharing information and methods. The RSNN is aligned with other European platforms active in the field. The RSNN Newsletter informs participants and stakeholders of activities and developments in the discipline.

## WORKSHOP "WHAT'S IN, WHAT'S OUT, WHAT'S RELEVANT? – TOWARDS A SENSIBLE LABEL"

In RSNN's third annual workshop, the topic of discussion was the role of the SmPC (Summary of Product Characteristics). Key questions of the workshop were: "Who should be the owner of this 'label'? What should be its role in the future? Who can be responsible for the development and updating-process? What kind of information should be included (or added) and which not?" In other words: "What should be done to maintain a meaningful SmPC?"

The focus of the key questions was on the incorporation of new knowledge and real-world evidence into the SmPC after product approval and its entry to the market. During the break-out sessions and after plenary discussion, a more fundamental question was added: "What is the place and role of the SmPC? What may we expect from it and what not?"

At the traditional network dinner, the role of the patient as a stakeholder in drug development and decision making was highlighted. Hans Büller introduced his innovative drug development model as the basis for Fair Medicine and Marie Elske Gispen addressed the importance of a human rights approach to defining the role of the patient in the (regulatory) process of drug development.

The workshop provided enough food for thought and formed the basis for several research questions. Participants also appreciated the opportunity to interact with others in a multidisciplinary setting and hearing/sharing several refreshing points of view.


**SAVE THE DATE:**
**1 October, 2018**

**RSNN SESSIONS AT THE 2017 FIGON DUTCH MEDICINES DAY**

Congres centrum
De ReeHorst

Bennekomseweg 24
EDE, the Netherlands

**www.figondmd.nl**

*[more on page 6]*



**CALL FOR AGENDA TOPICS: YOUR INPUT IS NEEDED!**

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info@rsnn.nl

**JOIN THE RSNN – The RSNN is an open network**

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**Anke Kip**
**e-mail: info@rsnn.nl**

**We also like to invite you to our LinkedIn group at:**
**https://www.linkedin.com/groups/8559430**

## OPENING AND KEYNOTE LECTURES

**Prof. Bert Leufkens**, chair of RSNN, opened the workshop with a warm welcome to all attendees. He reminded the audience of the recent formalization of the RSNN structure, in which there is also an important place for the patient perspective. This is the first meeting in the new context and Bert complimented the program committee on the topic of today, because all the envisioned stakeholders of the RSNN network are involved: patients, industry, regulatory, and healthcare professionals. In his view, the SmPC is an important regulatory instrument, also with respect to safety aspects, and therefore has to be suitable for all applications in daily practice.

**Dr Christine Gispen-de Wied** (vice chair RSNN), the chair of the workshop, outlined the program. The workshop started with five presentations that addressed the topic of today from five different perspectives: the need for reliable and up-to-date patient information, the legal status of the SmPC, its place in (academic) research, its interest for industry, and its relationship with 'real-world-evidence', including the experience of professionals in clinical practice.

### THE SMPC AND THE NEED FOR RELIABLE AND UP-TO-DATE PATIENT INFORMATION

The first speaker was **Dr Annemiek van Rensen** (PGOsupport, MEB). She took the audience on a patient journey with the focus on patient information as reflected in the SmPC. Annemiek stated that there is a gap between the information in the SmPC and the patient's needs: many of the questions a patient may have will not be answered by the information in the SmPC. The SmPC does not provide, for instance, information on treatment choice or on combining different medicines, information that may be included in professional guidelines. Practical information on how to use the drug with food, alcohol, or other medication often is lacking. Information on the best way to stop taking the drug is also not included. Altogether, this suggests that the SmPC is not (primarily) designed for direct use by patients and health care professionals. The SmPC reflects the outcome of discussions between a pharmaceutical company and regulatory authorities; it is established at the time of authorisation and hardly changes during the life cycle of a medicine, except for new indications and important safety information.

Maybe we should accept that the SmPC is only one of the information sources, next to several other more educational/practical ones such as patient leaflets, informative websites (Apotheek.nl, kijksluiter.nl) and professional guidelines. By accepting its limitations, we can bridge the gap between the information in the SmPC and the patient's needs and requirements.

### THE LEGAL STATUS OF THE SMPC

Then **Dr Joris Langedijk** (Brabers) focused on the legal aspects of the SmPC. From this perspective, the SmPC is a document required within the EU before a medicine is authorised for marketing. Since the introduction of the European legislation on medicinal products the purpose of the legislation has been to safeguard public health – both from dangerous and ineffective medicines – while at the same time the legislation should not hinder the development of the pharmaceutical industry or the trade in medicinal products within the EU. Since the introduction of the European laws on medicinal products many

more requirements have been added, for example regarding the package leaflet, advertisements, and pharmacovigilance. What hasn't changed is the key position of the marketing authorisation holder (the company) in the process of market approval. Other stakeholders have a rather limited involvement in this process as far as the law is concerned. The application for market approval is submitted by a company and the marketing authorisation is granted to the company. Basically the competent authority gives permission to the marketing authorisation holder to place the product on the market under certain conditions. The SmPC – which is part of the marketing authorisation – reflects the outcome of the assessment procedure. It provides information about the safety and efficacy of the medicinal product in the treatment of a specific condition. The SmPC may be used by healthcare professionals as a source of information but is not intended as a medical guideline. After market approval, the company has to comply with a number of obligations, for example to keep the product information up to date with scientific knowledge and to report adverse drug reactions. Also, liability issues are strongly related to the current practice of market approval (including drafting the SmPC). Next, the marketing authorisation (of which the SmPC is a part) has an economic value to the company. In the current legal framework, the regulatory authorities cannot, for example, add a therapeutic indication to the label. However, the aforementioned does not necessarily mean that the legal framework cannot be amended in order to reposition the label.

## THE SMPC IN RELATION TO (ACADEMIC) RESEARCH

The next speaker was **Dr Saco de Visser** (ZonMw). He addressed the impact of new data or new information on the SmPC, generated by others than the marketing authorisation holder.

Research is not only done by pharma companies but also by other organisations. Typical research topics are the (appropriate) use, the dose, or new indications (drug rediscovery) of medicines. For this research, both intervention studies and patient (outcome) registries are used. ZonMw stimulates this type of research since the outcomes can support the implementation of new treatment policies and can optimise daily practice. However, Saco indicated that – as far as he knows – the results of these studies never lead to adjustments of the SmPC. Yet all this evidence does find its way into professional guidelines and patient information via scientific papers and conferences. Another remarkable fact: over 50% of pharmacotherapy is off-label. Saco provided the example of the well-known story of Avastin, now a first line treatment for exudative macular degeneration. However, its use for this indication is still off-label. How come? According to Saco this is because there is a gap between the purpose of the SmPC in the pharmaceutical industry (e.g. obtain market approval), and its use in daily practice. The latter is much more complex and driven by the healthcare providers, patients, reimbursement issues, incentives by health insurance companies with respect to reimbursement, and so on (Figure 1). These two different worlds do not meet, so in his view, the SmPC should stick to its role as the final step of the process toward the "target product profile". It is not suitable as information for patients and prescribers in usual care. As a possible solution for the valid need to optimise patient information, he pleaded to further develop and implement other central information carriers next to the SmPC.

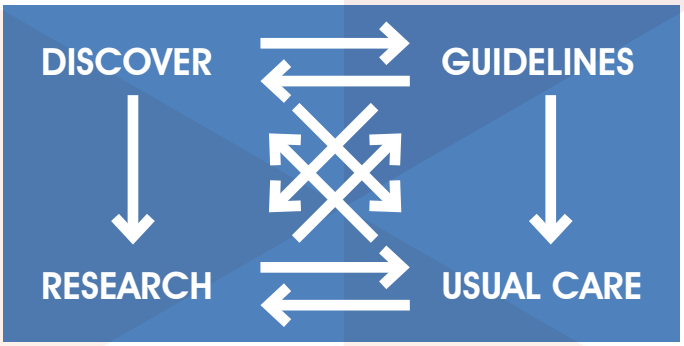


**Figure 1: The real world is complex and dynamic**

## THE INTEREST OF THE SMPC FOR INDUSTRY

Then **Dr Filip Mussen** (Janssen) gave his view on the needs and challenges with respect to the addition of new efficacy data in the SmPC from the perspective of a regulatory professional working for a pharmaceutical company. He reminded the participants of the obligation of the marketing authorisation holder to provide complete and accurate efficacy and safety information about the product and that scientific progress and new regulatory requirements are respected. What does this mean in daily practice?

New (clinical) data that provide a new perspective on efficacy, may come from additional phase 3 randomised controlled trials (RCT), phase 4 RCTs (e.g.

outcomes trials), and 'real world evidence' (RWE, e.g. patient-reported data). RWE is very useful to include in the SmPC because it evaluates the use, and benefits and risks of medicines in more clinically diverse settings and patients, and under conditions that reflect the use of treatments in actual clinical practice.[1]

Examples of new clinical data that trigger the need to update the indication in the SmPC are for instance a shift from second to first line treatment or the use of a new hard endpoint. However, in Filip's view, the SmPC should not be revised when just the place of the product changes within the total therapeutic arsenal: "the SmPC is not a therapeutic guideline".

Then there is the scenario of a totally new indication, usually based on data from RCTs generated by the pharmaceutical company herself. The off-label use of the product is something else. But how should off-label use of the product - often based on small academic RCTs, RWE or other sources - be addressed in the SmPC? What are the minimum requirements in terms of level of evidence, quality, or supporting documentation? Is this part of the obligation of the marketing authorisation holder to provide complete and accurate efficacy and safety information?

To provide some examples, Filip mentioned that all these questions are part of the actual debates related to new oncology medicines, the place of RWE, and patient-reported data.

## THE SMPC IN RELATION TO 'REAL-WORLD-EVIDENCE': A CASE FROM CLINICAL PRACTICE

The last speaker was **Dr Frans Opdam**, internist-clinical pharmacologist (NKI-AVL, MEB), who shared his experience with changing the SmPC based on academic research data showing that there is clinical value of DPYD-guided dosing of fluoropyrimidines.

Fluoropyrimidines such as 5-FU and capecitabine are widely used anti-cancer drugs for the treatment of colorectal cancer and breast cancer. The enzyme DPD plays a key role in fluoropyrimidine metabolism (Figure 2). DPD deficiency, which occurs in 3-5% of the population, is associated with increased risk of severe/fatal toxicity. Therefore, upfront screening and dose individualization can improve patient safety. However, in the ESMO guideline DPD testing is not routinely recommended, and therefore the NKI-AVL took the initiative to conduct a prospective study to individualise the dose of fluoropyrimidines based on genotyping.[2]

The results showed that DPYD*2A carriers had twofold increased exposure to 5-FU, meaning that a dose reduction of 50% would be sufficient to achieve the desired clinical effect. It was also shown that the genotype screening strategy did not increase the total costs. Based on these results and on the basis of a subsequent conducted meta-analysis, a practical dosing table for dose-adaptation for four different DPYD variants was developed.

The data were published in 2016, but this did not result in a change in the guidelines, or the SmPC. As a follow-up, the NKI-AVL wrote a letter to the EMA in January 2017. Subsequently, DPD-dependent dosing was discussed in the PRAC, with input from NKI-AVL and the marketing authorisation holder, and in the PG Working Party which resulted in a positive advice to the CHMP. In the end, after discussion with the marketing authorisation holder, the proposed rewording of section 4.4 of the SmPC was adopted.

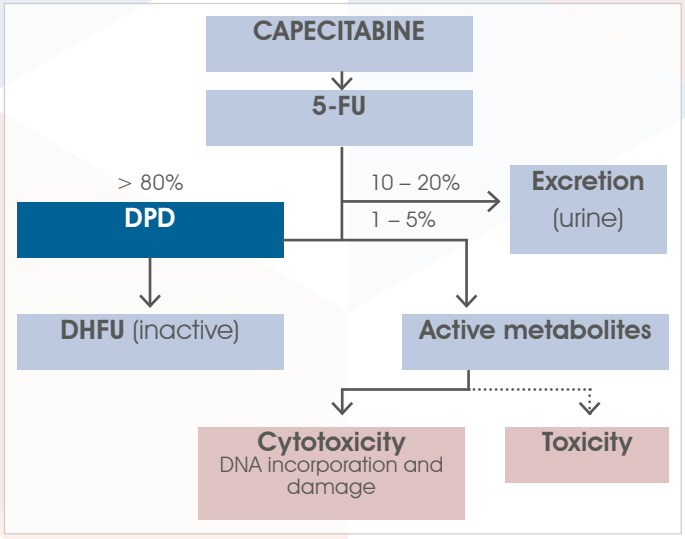


**Figure 2: Role of DPD in fluoropyrimidine metabolism**

This example shows that SmPC updates initiated by a non-pharma stakeholder can be successful. However it is a long, step by step process, which is also illustrated by the fact that the starting dose table is still not adopted in the SmPC. At the same time it has to be said that updating professional guidelines is also a slow-moving process and after discussion, Christine concluded that this is also an important aspect: "who follows who?"

## BREAK-OUT SESSIONS AND PLENARY DISCUSSION

After the five keynote lectures, all participants joined one of the four break-out panels. Each of these panels had a specific topic: efficacy/indication (2 break-out sessions), posology/mode of action, and safety. The participants were asked to identify cases, to cluster these and identify the underlying problems, and to formulate possible solutions. Moreover, they were asked to formulate research questions when appropriate. The feedback from the break-out sessions was summarised by the break-out co-chairs and during plenary discussion the points of view were sharpened.

In general, the SmPC was recognised as an essential document that is important in getting a medical product registered and on the market. In this respect, the SmPC is a crucial document for the pharmaceutical industry. It is also the basis for liability questions and an important source for documents such as patient information leaflets. It should therefore be reliable and up-to-date with respect to the safety and efficacy of the product itself, and not per se its application and use in daily practice as part of the therapeutic arsenal as a whole. Several workshop participants made it clear that the latter aspects, in relation to and interplay with other medical interventions, should be specified in professional guidelines by medical professionals. One of the key outcomes of the workshop was therefore that reliable and actual patient information should be based on professional guidelines with respect to treatment (options) at one end, and on the SmPC with respect to product safety and efficacy information at the other end. This means that both the stakeholders involved in the development and maintenance of the SmPC, and those involved in the development and maintenance of professional guidelines should interact with each other and influence each other in an optimal way. How and where this relationship can be improved, in order to bridge the gap, are useful questions for further research in the field of regulatory science. In doing so we must realise that daily practice is different between countries within Europe and therefore this will be a challenging process.

Christine Gispen-de Wied, who moderated the discussion, concluded that the break-out sessions have yielded many suggestions for improvement of the SmPC and for further research. Recognising the SmPC as a document that serves two separate purposes: authorising a drug for marketing, besides provision of reliable information on the product, offers us new understanding and opportunities for change. Then she gave the floor to Bert Leufkens for his closing remarks. Getting back to his introduction, he stated that we have to find ways to keep the SmPC sustainable for the future. Not as an (isolated) document on itself, but as a means to an end, and with the flexibility to focus on the different potential roles of the SmPC in the lifecycle of a drug. This context is more complex today than it was 20 years ago. It currently also imposes higher demands on the presentation of the information, which is a great challenge in order to bridge the gap between the various needs and expectations of the different stakeholders. This is where the RSNN as a network can contribute: it has succeeded today by organising this workshop and the commitment of all participant in lively discussions.

## DINNER SPEECHES

### FAIR MEDICINE: AN INNOVATIVE DRUG DEVELOPMENT MODEL

At the traditional network dinner, the role of the patient as a stakeholder in drug development and decision making was highlighted. Prof. Hans Büller, introduced his innovative drug development model as the basis for Fair Medicine, of which he is one of the directors and founders. By taking a multi-stakeholder approach where investment is shared, Fair Medicine includes, beyond academics and industry partners, the patient as a stakeholder from beginning to end. This new business model is based on five principles: the participating parties strive to a common objective: a safe, effective and affordable product, they invest together and are transparent about the project's efforts, investments and progress, and last but not least, products must be priced at socially acceptable levels. This 'shared' drug development is the key aspect of Fair Medicine and offers new opportunities to keep medicines affordable, especially also for rare diseases. [www.fairmedicine.eu]

### THE IMPORTANCE OF A HUMAN RIGHTS PERSPECTIVE IN DEFINING THE ROLE OF THE PATIENT

The second speaker was Dr Marie Elske Gispen, post-doc researcher at the University of Groningen,

who specialises in the intersection of international human rights law, bioethics, and pharmaceutical sciences. In her speech, she addressed the importance of a human rights approach to defining the role of the patient in benefit/risk assessment and decision-making. In her view, the MEB and EMA in different ways give the patient a formalised role in medicine regulatory decision-making, but these governmental bodies should further strengthen the position of the patient in line with a common set of principles such as the human rights norms. They should move beyond passive stock taking and instead empower patients as rights-holders and thus stakeholders along the pharma lifeline. She mentioned Fair Medicine as a positive example in this context. Finally, she expressed the hope that these types of initiatives will increase the relevance of mainstreaming human rights in discussions on patient participation in drug development and show the importance of further exploring rights-based models of patient participation.

## LITERATURE


1. Dreyer N. Advancing a framework for regulatory use of real-world evidence: when real is reliable. Therapeutic Innovation & Regulatory Science. 2018; 52: 362-368.

2. Deenen MJ, Meulendijks D, Cats A, Sechterberger MK, Severens JL, Boot H, Smits PH, Rosing H, Mandigers CM, Soesan M, Beijnen JH, Schellens JH. Upfront genotyping of DPYD*2A to individualize fluoropyrimidine therapy: a safety and cost analysis. J Clin Oncol. 2016 Jan 20; 34(3): 227-34.


## RSNN SESSIONS AT THE 2018 FIGON DUTCH MEDICINES DAY

On Monday, 1 October, the Regulatory Science Network Netherlands (RSNN) will be holding two parallel sessions during the FIGON Dutch Medicines Days (DMD). There will be many opportunities to explore and discuss Regulatory Science, and we are pleased to share with you the updated and final program.

The speakers will reflect on and discuss the topic from different perspectives: regulatory, industry, academic, HTA, and patient-focused.

## PROGRAMME

### 9:00-11:00 MORNING SESSION

**Regulatory challenges for the next wave of cancer therapies**

Chair: Sjaak Bot (Janssen)

**Invited speakers:**

Marcel Hoefnagel (CBG-MEB)
Harm Hermsen (Xendo)
Pauline Evers (nfk)

**Selected abstract:**

Renske Ten Ham (UU)

### 14:30-16:30 AFTERNOON SESSION

**Evidence generation for innovative products in oncology**

Chair: Marjon Pasmooij (CBG-MEB)

**Invited speakers:**

Paula van Hennik (CBG-MEB)
Alwin Otten (Janssen)
Jürgen Kuball (UMC Utrecht)

**Selected abstract:**

Brenda Leeneman (EUR)

OCT 1

## CORS CONFERENCE 2018, COPENHAGEN

### 19 NOVEMBER 2018: UNIVERSITY OF COPENHAGEN, MÆRSK TOWER, NIELSINE NIELSEN AUDITORIUM

This year, the Annual Copenhagen Centre for Regulatory Science (CORS) Conference is dedicated to the 'Impact of drug regulation on health and society', which is a hot topic, given the recent debates about the role of drug regulations on the approval of medicines and medical devices. On the one hand, if the drug regulations are overly strict, then there is a risk that it can impede innovations and state-of-the-art medical treatments. On the other hand, if the drug regulation shifts towards a more loose approach, then it might endanger the health and well-being of the patients.

The CORS conferences provide a unique platform for discussion and debate for a wide range of experts (academia, regulators, industry, and patient representatives). Every year, the conference attendees highly rated the variety of perspectives and points of view from different stakeholders, the international input of the conference, and the unique combination of high-level speakers and attendees.

For more information and the programme visit:
https://pharmacy.ku.dk/research/cors/events-2018/cors-annual-conference-2018/


## LYGATURE PARTNERSHIPS MEETUP

lygature

On November 1 2018, Lygature will organise its yearly partnerships meetup event with again an interesting programme and the opportunity to network.

## PROGRAMME

**09.30** Walk-in and coffee

**09.45** Opening (plenary)

**10:00** Opportunities for Bringing Better Medical Solutions to Patients (5 parallel sessions, including the Regulatory Science session: 'Extrapolation in Regulatory Science')

**12:00** Lunch and networking

**13.30** Keynote lecture by Tomas Salmonson, current chair of the Committee for Medicinal Products for Human Use, CHMP, European Medicines Agency, EMA

**14.30** Coffee break

**15.00** Essentials for Successful Collaborative Innovation (5 parallel sessions)

**16.30** Feedback from Parallel Sessions (plenary)

**17.00** Networking drinks reception

For more information visit:
http://events.lygature.org/program-2018

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