Received: 1 March 2019 | Revised: 29 May 2019 | Accepted: 28 June 2019

DOI: 10.1111/bcp.14070

SHORT REPORT

Future of the drug label: Perspectives from a multistakeholder dialogue†

Christine C. Gispen-de Wied[1] | Just Weemers[2] | Wouter Boon[3] | Peter G.M. Mol[1,4] | Pieter Stolk[5]

[1] Medicines Evaluation Board, Utrecht, Netherlands

[2] Pfizer Netherlands, Capelle aan den Ijssel, Netherlands

[3] Department of Geosciences, Copernicus Institute of Sustainable Development, Utrecht University, Utrecht, Netherlands

[4] Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, Netherlands

[5] Lygature, Utrecht, Netherlands

Correspondence
Christine C. Gispen-de Wied Medicines Evaluation Board. Netherlands Graadt van Roggenweg 500 3531 AH Utrecht.
Email: ccgispen@gmail.com

Regulating drugs does not end when market access has been granted. Monitoring drugs over the life cycle has become state of the art, inherent to evolving legislation and societal need. Here, we explore how the drug label could move along in a changing playing-field and become a sustainable label for the future. A dialogue between academia, government, the pharmaceutical industry and patient/societal organizations was organized by the Regulatory Science Network Netherlands. This is their view.

KEYWORDS

label, regulatory authorities, SmPC

1 | THE LABEL IN CURRENT PRACTICE

Drug labels reflect the outcome of the assessment of drug dossiers, as submitted by the applicant at the time of marketing authorization. They are the result of elaborate dialogue between applicant and regulator. One could view the regulatory process as a funnel: from a rich and vast amount of data emerges a clear and relatively succinct mandate to produce, sell and use a pharmaceutical product, within the framework of continuous monitoring and benefit–risk assessment. The conditions for use are laid down in the drug label, in Europe called the summary of product characteristics (SmPC). This convergence of information that leads to the label also has a downside: the process of establishing the label is rather exclusive in terms of the type and number of stakeholders involved. Moreover, scope and clinical relevance remain limited, as well as the level of adaptiveness, or responsiveness to emerging knowledge, over time. To investigate these challenges and come up with suggestions to make the drug label *future-proof*, we organized an open dialogue within the framework of the Regulatory Science Network Netherlands (RSNN; Box 1), with experts covering a wide array of stakeholders, i.e. companies (n = 52%), regulatory agencies (29%), universities (12.5%) and patient/societal organizations (6%). The total number of participants was 56. Three issues were raised.

First, we started exploring the stakeholder(s) responsible for constructing the SmPC: the applicant (usually a [bio]pharmaceutical company) and the regulator. From the perspective of the pharmaceutical industry, the responsibility for transposing reliable, high quality data into the label is with the applicant, i.e. the owner of the drug dossier, and liability issues are strongly related to the assessment, and ultimately granting of a marketing authorization. Marketing authorization has an economic value to the company and leaves little space for others to be involved. It is important to note that the label reflects the outcome of the assessment procedure at the time of marketing authorization, as performed by another stakeholder—the

† Outcome of the 3d Workshop 'What's in, What's out, What's relevant? – Towards a sensible label' of the Regulatory Science Network Netherlands, RSNN, held on June 20th 2018 (https://www.rsnn.nl)

regulator. It provides information about the safety, efficacy *and* uncertainties of a medicinal product in the treatment of a specific condition. Therefore, one could say that companies and regulators share a mutual responsibility for the label, because it is the result of a shared and interactive process. In reality, this means that the label signifies the conditions for the competent authority, or even the European Commission, to allow the company (or marketing authorization holder, MAH) to place the product on the market. This is essentially very restrictive in nature, and, as far as the law is concerned, other stakeholders have a rather limited, or no, involvement. Even though the wording of the label, and in particular the indication, is an extensive back and forth between the regulator and the applicant, and a compromise at the time of market authorization, regulatory authorities cannot add, for instance, an indication to a label. Therefore, we consider the MAH in practice the principal responsible stakeholder.

BOX 1 | The Regulatory Science Network Netherlands (RSNN) explained

WHAT IS THE RSNN

The RSNN, a network for experts from academia, government, the pharmaceutical industry, patient organizations 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 (https://www.lygature.org/regulatory-science-network-netherlands-rsnn).

Second, we discussed the value of labels during the clinical application of medicines. Apparently, this value is not always immediately recognised by patients and consumers. They indicated a gap between the information in the label and the patient's needs. Questions that any patient may have are not always answered adequately by the information in the label (or its derivative, the patient information leaflet). It does not provide, for instance, information about treatment choice, or the use of a product in treatment regimens, as can be found in professional guidelines. This raises the question of whether the label is suited to act as a clinical guidance document. One could also see the benefits of broadening the applicability of the label beyond detailing the conditions for obtaining a marketing authorization. As explained, the label is, legally, not intended as medical guideline, but may be used by health professionals as a source of information, e.g. to update clinical treatment guidelines. However, this does not mean that the label cannot be the vessel to provide tailored information toward patients' and health care professionals' needs. In current practice, there are venues in different (regulatory) decision-making bodies[1] for patients and consumers, together with the scientific community and society at large, to express their views. Their rights and obligations as stakeholder are, however, not well defined, and therefore the impact of these stakeholders is not self-evident.[2]

What is already known about this subject

- The drug label is part of the market authorization.
- The label is perceived as a *contract* between the marketing authorization holder and regulatory authorities.
- Other parties are usually not involved in the process of drafting the label

What this study adds

- A multistakeholder view on how the label could improve over the drug life-cycle.
- An innovative approach to enable effectiveness data become part of the label.
- Defined conditions for shared responsibility that need legal and regulatory consideration.

Third, labels are subject to continuous monitoring and adjustment but are not sufficiently adaptive. In the current legal framework, safety signals, originating from any source, may find their way, through the Pharmacovigilance Risk Assessment Committee (in EU) into the label because of specific pharmacovigilance legislation. During the workshop, this was perceived as a one-sided and skewed adaptiveness towards safety and limited because stakeholders other than the MAH, e.g. regulatory authorities or the scientific community, cannot add any information related to clinical effectiveness of a product. Evidence generation is not only done by pharmaceutical companies, but also, and increasingly so after marketing authorisation, by other organizations. Typical investigator driven research topics are the (appropriate) use, the dose, or new indications (drug rediscovery) of medicines. For this type of research, both interventional trials and observational studies in patient (outcome) registries or electronic health records are used. The results of these studies hardly lead to adjustments of the label, apart from the mentioned safety issues, as illustrated by the **5-fluorouracil** (5FU) case and dose adjustment in the treatment of colorectal and breast cancer[3,4] (see Box 2). The label change was based on safety considerations and a warning was added to the label in section 4.4. Likewise, a dose adjustment in section 4.2 of the label could have been decided on, provided both efficacy and safety issues of a product are considered of equal importance. Either way, the 5FU case demonstrates the need for a system that allows new information to be incorporated in the label based on both risk *and* benefit data of a drug. Most evidence generated from other sources than the MAH, as in the 5FU case, does find its way extensively into professional guidelines and patient information, based on published papers and conference presentations. It is considered a *lost opportunity*, if these findings are not used constructively for refining the label. If we accept

the label as the core data source for efficacy and safety of a drug throughout its life-cycle, it is difficult to understand that it can only cover part of the information available. From the perspective of a pharmaceutical company, to take responsibility for the accuracy, quality and reliability of data generated by another stakeholder, outside of their span of control, requires a data environment of full transparency with regard to data quality, source, etc.[5] Such an environment is currently not in place.

BOX 2 | The example of the 5-fluorouracil (5FU) case and label adjustment

Dose adjustment based on an investigator driven study: the 5FU case

Fluoropyrimidines such as 5FU and capecitabine are widely used anticancer drugs for the treatment of colorectal cancer and breast cancer. The enzyme dihydropyrimidine dehydrogenase (DPD) plays a key role in fluoropyrimidine metabolism. DPD deficiency, which occurs in 3–5% of the population, is associated with increased risk of severe/fatal toxicity. Upfront screening and dose individualization can improve patient safety. The Dutch Cancer Institute (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 2-fold 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 did not result in a change in the SmPC. As a follow-up, the NKI-AVL wrote a letter to European Medicines Agency in January 2017. Subsequently, DPD-dependent dosing was discussed in the Pharmacovigilance Risk Assessment Committee, with input from NKI-AVL and the marketing authorisation holder, and in the PharmacogenomicsG Working Party, which resulted in a positive advice to the Committee for Medicinal Products for Human Use (CHMP). In the end, after discussion with the marketing authorisation holder, the proposed rewording of section 4.4 of the SmPC was adopted.

Altogether, one could argue that in current practice, the label serves as target product profile for a marketing authorization and is not fully suitable as information source for patients and prescribers in daily practice. This position is rather monolithic and static, raising the question of whether, and how the label could be made suitable and sustainable as a future source of key drug information in a rapidly changing environment where the emphasis is on timely marketing authorization *vs* understanding the drug in clinical practice.

2 | A SUSTAINABLE LABEL FOR THE FUTURE

To make the label a state-of-the-art document throughout the drug's life cycle, we propose that the process to come to a sustainable label for the future requires a model of shared stakeholders' responsibility. The MAH, regulatory authorities, patients/consumers, health care professionals and the scientific community all need to contribute.

As a first step, we recognise the label as an essential document for granting the marketing authorization. The label is not only a crucial document for the applicant; it is also the basis for liability questions, and an important source for documents such as the patient information leaflet. 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. This does not mean that the information at the time of marketing authorization cannot be optimized and more tailored towards user and prescriber needs. We expect that this optimization will find its way as a natural consequence of the patient/societal and scientific community engagement in the drug development process before and at the time of marketing authorization provided rights and obligations of the *new* stakeholders are well defined; the label as core product information document at the time of authorization. Once authorized, other aspects regarding clinical use should be specified in professional guidelines by medical professionals, e.g. by defining the product's place in clinical treatment regimens. We conclude that reliable and actual patient information should be based on professional guidelines with respect to treatment (options) at one end, and on the label with respect to product safety and efficacy information at the other end. This means that the different stakeholders involved in the development and maintenance of the label, and those involved in the development and maintenance of professional guidelines, should interact with each other and influence each other in an optimal way, inherent to the model of shared stakeholder's responsibility that we propose. Preferably, early interaction between different stakeholders, as foreseen in concepts, such as the priority medicines scheme PRIME, could be explored. In doing so we must realise that daily clinical practice differs significantly between countries and therefore, this process is not without challenge, and asks for a willing attitude towards harmonization.

As part of our second step, we recognise that the label should follow the drug life cycle and should thus be apt to provide information acquired over time on efficacy and safety, based on a medicine's use in daily practice. Building a system where new information from different sources can fuel the label to become an up-to-date data source for the actual use of drugs in daily practice is paramount. However, criteria for the reviewing of these kind of data are needed. Any scientific progress, new regulatory requirements and new (clinical effectiveness) data that may come from additional phase 3 randomized controlled trials, phase 4 randomized controlled trials (e.g. outcome trials) and *real-world evidence* (observational studies) can provide a new

perspective on the efficacy and safety. The use of new types of data, including nonpropriety data from e.g. investigator-initiated pharmacodynamics or drug–drug interaction studies, is useful to include in the label because it evaluates the use, and the 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. There is a need for legislation or mandate for European Medicines Agency committees, to allow data from other stakeholders than the applicant, i.e. the MAH, to be reviewed—according to usual standards—and find its way into the drug label.

Thus, we propose a scenario where the end goal is one that the label of the future should become a *balanced rolling document*, i.e. suitable to contain sensible information about the product's efficacy and safety throughout its entire life-cycle, from the time of marketing authorization. By *sensible*, we mean that we accept that the information in the label at the time of marketing authorization can also be replaced by new information, if appropriate. We consider this a courageous step forward in efficient regulation; it is easier to add information to the label than to decide on redundancy.[6]

3 | CHALLENGES FOR A SHARED STAKEHOLDER APPROACH

It is evident that the scenario described is not an easy way forward, but following the proposed developments, it offers the opportunity to focus discussions on the label in a stepwise approach: at the time of market authorization and when the drug is on the market and used in practice. For this approach to be successful, several challenges have to be addressed:

- We need to (re)define each stakeholder in practical and legal context within the current regulatory and legislative framework.
- There is a need for clarification of legal aspects within the current framework, e.g. liability issues.
- We need to decide on the use of *other* data, i.e. not directly obtained by the MAH, and define terms of data quality, transparency, data sources and access.
- We need a regulatory framework conducive to uptake of investigator initiated nontraditional data in the label.

Finally, to further this process of regulatory innovation, we advocate two resolutions steps: (i) fuel discussions through the RSNN at European Medicines Agency level; and (ii) promote multi-stakeholder regulatory research proposals in academia and beyond, e.g. participate in Innovative Medicines Initiative, IMI projects.

4 | CONCLUDING REMARKS

We asked ourselves questions such as: what should be the purpose of the *label of the future*? What kind of information should be included (or added) and what kind of information is redundant? Who should be the *owner* of the label and who can be responsible for the development and updating processes? We concluded on the need for a shared stakeholder's responsibility and drafted a scenario that covers a 2-step approach, i.e. defining the label at the time of marketing authorization and thereafter. We identified potential (legal) barriers that need to be investigated, but, when further explored in the scientific regulatory community, may pave the way for next steps, making the label future-proof.

ACKNOWLEDGEMENTS

The authors would like to acknowledge all participants of the workshop for their views expressed in open dialogue.

COMPETING INTERESTS

The authors have no conflict of interest to declare other than the authors' affiliation. The views expressed in this article are the personal views of the author(s) and may not be understood nor quoted as being made on behalf of, or reflecting the position of, their organizations.

CONTRIBUTORS

All authors contributed to the paper as experts in their specific fields. C.G.-d.W. initiated the paper and took the lead in writing. J.W. provided content from the industry perspective and regulatory science in general. P.S. took part in conceptualizing the content of the paper. P.M. provided content from a regulatory perspective and regulatory science in general. W.B. provided content from an academic perspective and regulatory science I general.

ORCID

Christine C. Gispen-de Wied https://orcid.org/0000-0002-5323-2716

REFERENCES

1. https://www.ema.europa.eu/en/partners-networks/patients-consumers/eligible-patients-consumers-organisations
2. Hearry D, Landgraf C, Warner K, et al. EUPATI and patients in medicines Research and Development: guidance for patient involvement in regulatory processes. *Front Med (Lausanne)*. 2018;5:230.
3. Deenen MJ, Meulendijks D, Cats A, et al. Upfront genotyping of DPYD*2A to individualize fluoropyrimidine therapy: a safety and cost analysis. *J Clin Oncol*. 2016;34(3):227-234.
4. Dreyer N. Advancing a framework for regulatory use of real-world evidence: when real is reliable. *Ther Innov Regul Sci*. 2018;52(3):362-368.
5. Henricks LM, Lunenburg CATC, Cats A, Matthijssen RHJ, Guchelaar HJ, Schellens JHM. DPYD genotype-guided dose individualisation of fluropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol*. 2018;19(11):1459-1467.
6. Vermeer NS, Duijnhoven RG, Straus SM, et al. Risk management plans as a tool for proactive pharmacovigilance: a cohort study of newly approved drugs in Europe. *Clin Pharmacol Ther*. 2014;96(6):723-731.

How to cite this article: Gispen-de Wied CC, Weemers J, Boon W, Mol PGM, Stolk P. Future of the drug label: Perspectives from a multistakeholder dialogue. *Br J Clin Pharmacol*. 2019;85:2442–2445. https://doi.org/10.1111/bcp.14070