Regulatory Science Network Netherlands (RSNN) Expert Meeting

The RSNN expert meeting on 'Label modification based on evidence deriving from investigator-initiated trials' was held on the 23rd of June 2020. This meeting continued upon the discussion of a previous RSNN expert meeting concerning the medicine's label/summary of product characteristics[1].

Evidence obtained by means of investigator-initiated trials has the potential to demonstrate a medicines effectiveness and safety outside of its registered indication. However, such research does not always result in an extension of the indication. Moreover, it raises the following questions: can investigator-initiated trials be used to modify the label, what kind of data is required for this purpose, and who is permitted/able to initiate this process?

For the purposes of the meeting, the *Drug Rediscovery Protocol* (DRUP) trial served as an example. One of the cohorts in the DRUP trial includes patients with microsatellite instability-high (MSI-H) tumours who are being treated with nivolumab[2]. Based on the results obtained within this cohort, the pilot *personalised reimbursement* model was launched in collaboration with the *marketing authorisation holder* (MAH), the National Health Care Institute (Zorginstituut Nederland) and the health insurers[3]. This model has been included in the DRUP trial.

Twenty-three experts and stakeholders were invited to discuss this theme. The selected participants possess great understanding and have experience in this specific topic from their work experience in government, industry, patient organisations, hospitals and/or universities. The meeting was held under the *Chatham House Rule*. This report contains a brief summary of that discussion.

1. Extension of an indication based on evidence deriving from investigator-initiated trials

Investigator-initiated trials have the potential to provide novel evidence for the efficacy and safety of an existing medicine. One such example (as mentioned above), is the use of nivolumab to treat MSI-H tumours. In Europe, no anti-programmed death-1 (PD-1) therapy (such as nivolumab) has been approved for the treatment of patients with MSI-H tumours, even though evidence that this medicine may be effective in this particular patient population is mounting[2,4]. In the Netherlands, nivolumab has been made available to patients with MSI-H tumours through the DRUP pilot project. It now remains to be seen whether this data could be included in the label, as an extension of the indication. While discussing this topic, those present indicated whether or not they were interested in modifying the label. The following considerations to modify the label were discussed during the meeting.

The considerations <u>in favour of</u> modifying the label include:

- Registration authorities will review the data independently, which serves to confirm the medicine's efficacy and safety;
- In the case of medicines registered through the EU centralised procedure, extension of the therapeutic indication will apply to all Member States. Since reimbursement for off-label use differs from one European Member State to another, central extension of the indication mitigates any national differences in availability;
- Including data from investigator-initiated trials, provided that these comply with the registration requirements, prevents the development of any disparities between clinical practice and the label;

- At present, the evidence for the efficacy of *off-label* medicine use is not included in specific EMA procedures, such as granting an *orphan designation* and determining *significant benefit*. This can be avoided by registering the indication.

The considerations opposing modifying the label include:

- The current role of the label (describing a medicine's properties and its officially sanctioned use) does not necessarily require the inclusion of data deriving from investigator-initiated trials;
- In many cases, it is the MAH who is responsible for modification of the label. However, once the medicine is off patent and is being produced by generic manufacturers, such updates may lose their benefit;
- Modifying the label could potentially have adverse repercussions for the MAH (e.g. a restriction of indication or a new price negotiation);
- Pharmaceutical companies will have to allocate valuable time and resources for the collection of data from investigator-initiated trials, and to compose a licensing application. This involves a degree of risk, if there are no guarantees concerning an extension of the indication.

Research questions

- What is the label's current role, and what role should it have in the future? Should the label function as a source document that can accommodate any new data (including *real-world data*) – a dynamic label?
- Would a central approach, such as a label modification, be in the patients' best interests?
- What is the best procedure to launch an EU-wide process designed to include compelling data from the literature in the label?
- Is it important for *real-world evidence*, concerning *off-label* use for example, to be included in the label?
- Is it possible to modify the label without impacting Section 4.1 of the label (therapeutic indications)? For instance, could modifications be restricted to Section 5.1 of the label (pharmacodynamic properties)?
- What steps can be taken to ensure that evidence obtained from investigator-initiated trials will not be lost when these are not being used for extension of a label.

2. Ownership and submission of the data

In the post-market phase, new findings are often assessed in the context of pharmacovigilance. Any potential safety issues are continuously monitored. When there is sufficient evidence, this safety data can be incorporated into the label. On the contrary to safety data, evidence deriving from investigator-initiated trials concerning the efficacy of a medicine is less likely to be included in the label. When the MAH produces novel evidence for an existing medicine (such as efficacy in an indication for which it has not yet been registered), the MAH is in the position to submit these data to a registration authority. However, if a researcher produces such findings, they cannot be submitted to the registration authority. The reason for this is that the investigator is not the 'owner' of the Active Substance Master File. Moreover, clear agreements must be reached concerning the ownership and use of the data, to enable the MAH to apply for label modification. Furthermore, additional factors are involved that could impede the submission of these data. For instance, the interests may differ between researchers and MAHs.

One important perspective that emerged during the discussion was that high-quality scientific findings should always be incorporated into the label, regardless of who conducted the research. However, during the discussion it became clear that the both the possibilities within the current regulatory system as well as the party responsible to initiate the procedure are not entirely clear. Should only one party take the lead in this, or should several parties (including regulators, industry, health care, and academic institutes) cooperate to achieve this goal? Based on the perspectives of the various parties present, the necessity for an explorative pilot was emphasized.

Research questions

- What are the regulatory constraints with regards to utilizing investigator-initiated data as a source to modify the label?
- How should the regulatory system be shaped to permit/enable parties other than the MAH to initiate modification of a label?
- Could the issue of label modification based on the results of investigator-initiated trials be resolved by specific regulatory procedures?

3. Level of evidence

Before a medicine can be registered, it needs to meet specific requirements (which are defined by law). One of these requirements is that the trials must be performed in accordance with GCP guidelines. Furthermore, sufficient evidence needs to be provided to reliably assess the balance between efficacy and safety of the medicine in question. Registration authorities (e.g. the FDA and the EMA) can adopt different views on what constitutes for them as 'sufficient evidence' while composing a benefit-risk-balance. These differences in interpretation can cause specific medicines to be approved by some regulatory agencies but not others. Investigator-initiated trials are often based on in-house protocols that do not meet specific registration requirements. The level of evidence is another key factor. Randomised controlled trials (RCTs) are considered to be the gold standard while assessing the benefit-risk ratio. However, in some cases performing an RCT is not an option. This might be because the disease in question is rare, or because only a small subgroup of patients can be identified based on a rare genetic profile. If an RCT is not an option, it remains to be seen how much evidence would be considered sufficient to demonstrate the efficacy and safety for a specific medicine. This raises questions about the *level of evidence* required to authorise a medicine, especially with regards to small-scale trials that show promising results. Would their data suffice to apply for registration, or would it have to serve merely as a basis for an RCT? Moreover, stakeholders may have different opinions/views regarding the evidence needed to ensure efficacy and guarantee safety.

Research questions

- What kind of evidence is considered sufficient for registration purposes, especially in the case of *single-arm trials*? What are the key endpoints in this regard?
- Is data obtained from *single-arm* trials assessed in comparable approaches between different registration authority? When it comes to clinical benefit, how high should the bar be set?
- Would it be possible for registration authorities to follow an alternative procedure to express a positive review of results obtained from investigator-initiated trials, without leading to a modification of the label? For instance, by means of a quality mark that could be used when considering potential reimbursement for off-label use.

4. Call for action

At the end of the meeting, various stakeholders expressed a clear desire to take action. To this end, a follow-up meeting will be scheduled. This will enable us to explore the available options in greater detail and, perhaps, to launch a pilot project.

References

[1] Gispen-de Wied, Weemers J, Boon W, et al. Future of the drug label: Perspectives from a multistakeholder dialogue. Br J Clin Pharmacol. 2019;85:2442-2445.

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