AESGP EFPIA and EGA
Response to NIVEL Study Reports PIL-S and PIL-BOX
January 2016

Introduction

A joint industry task force, which includes representation from AESGP, EFPIA and EGA has reviewed the NIVEL Study reports and recommendations published on 4 November 2015 (PIL-S[1]and PIL-BOX[2] studies) and consolidated the comments with the respective associations. The pharmaceutical industry has continuous interest in this topic and AESGP, EFPIA and EGA and some of their member companies contributed to the NIVEL research project. Pharmaceutical industry welcomes the reports and concurs with many of NIVEL's conclusions and recommendations. However, pharmaceutical industry considers that overall the recommendations could be more ambitious and innovative.

PHARMACEUTICAL INDUSTRY Overall Conclusions

1. **The reports do not fully explore the opportunities that existing and evolving technologies can and will bring:**
    a. **The benefits of the replacement of paper leaflets by electronic drug information for rapid ability to provide updated, "real-time" versions electronically rather than relying on potentially outdated information provided in paper copies;**
    b. **For addressing readability, content and layout issues and for addressing the lack of space for multi-languages-packaging.**
    c. **The reports do not cover specific issues like availability of medicines in smaller markets nor hospital-only used products where electronic information would be particularly useful.**

2. **NIVEL's reports miss the opportunity to suggest and emphasise the benefits of the development of an enhanced concept of product information, which is adapted to the medication process (including information during the consultation with healthcare professionals (HCPs), advice from HCPs, re-visiting the information at the point of administration, information for the user/patient at home). It could make use of a European electronic single access solution to the provision of both the package leaflet (PL) and the summary of the product characteristics (SmPC). The role that this approach can play in addressing the identified shortcomings should be better highlighted and even prioritised.**

3. **The role of PLs and SmPCs should be evaluated in the overall context of the health system and regarded as one part to improve (digital) health literacy. The user-friendliness and adapted language are important for this purpose. Any option within the current legislation should be used to address also the need of people with lower literacy levels. The increased use of the European Public Assessment Report (EPAR) summaries for the public may also be considered.**

[1]http://ec.europa.eu/health/files/committee/75meeting/pil_s.pdf
[2]http://ec.europa.eu/health/files/committee/75meeting/pilbx.pdf

Pharmaceutical industry fully supports providing comprehensive, accurate and up-to-date information on medicinal products both for patients and HCPs. Such information must be easily accessible, and allow the patient/HCP to obtain, identify and use the information necessary to meet their individual needs, for the most effective and safe use of the medicine.

Overall, the recommendations of the NIVEL reports are moving in the right direction. It is welcome that the report encourages further research and development of electronic platforms, and recognises the flexibility this format would give to patients. The same applies for HCPs.
Similarly, pharmaceutical industry supports the statement that there is no ideal PL due to the wide variety of medicines and differing patient needs. However, in our view the reports are too focussed on short-term developments, and look less towards the anticipated changes to systems (particularly with reference to the advances in the technological space) and how patients/citizens/HCPs interact with technology and the internet (e.g. one area that has changed a lot is the wide-spread use of smartphones).

Stakeholders recognise the dual function of the PL: as a communication tool and as a legal tool for industry and regulators; this duality can create conflicting objectives. The PL should be used in conjunction with other information sources, including HCP guidance to the patient, in order to build patients' health literacy. Industry believes that health literacy principles can play a significant role in improving product information. To apply these principles, regulators who review package leaflets and SmPC-contents should be appropriately qualified and trained in health literacy principles.

Pharmaceutical industry recommends that the European Commission

1. **Prioritises the development of a strategy for electronic provision of both the PL and SmPC. As an initial activity, steps could be taken to support the introduction and development of electronic dissemination;**
2. **Concurrently, complements the electronic design format and dissemination strategy with recommended and incremental improvements in the content and layout of the PL – as described in our responses below;**
3. **Explores and researches how the application of health literacy principles and electronic dissemination can address the identified shortcomings in PLs and SmPCs instead of investing these resources in additional "key information sections" on which there are divergent views among stakeholders.**

Each of the conclusions from the NIVEL reports and their associated recommendations are considered in detail below. Where possible, pharmaceutical industry provides additional or alternative approaches and solutions.

1.0 Study on the Package Leaflets and the Summaries of Product Characteristics of Medicinal Products for Human use PIL-S study

NIVEL report conclusion 1: Room for improvement of the PIL more so than for SmPC Recommendations:
• *Focus on improvement of the PIL rather than on the SmPC. Small font size, narrow line spacing and the length of the PIL are the primary problems.*

PHARMACEUTICAL INDUSTRY views

Pharmaceutical industry agrees with the report's conclusion that change to the PL is of highest priority. However, pharmaceutical industry proposes that provision of comprehensive, accurate and up-to-date information for both patients and healthcare professionals is of great importance. In addition, as the PL is based upon the SmPC, any solutions proposed should consider both documents and aim for an enhanced information system.

Pharmaceutical industry also concurs that the primary problems patients experience are small font size, narrow line spacing and the overall length of the PL. To improve readability, the NIVEL report suggests font size and line spacing should be increased; however this will inevitably enlarge the size of the product information since all content required by legislation must remain.

Pharmaceutical industry believes that an overall reduction in length of the PL is possible within the current EU legislation if the interpretation of the legislation in the readability and guidelines is adapted with less rigid requirements[3]. The EPAR summaries for the public show how complex details can be explained very concisely in lay language.

Increasing the font size and line spacing will impact the leaflet size and potentially have an impact on the overall pack size – this would have major cost implications. There would also be potential negative impact for the supply chain, in that larger pack sizes would mean fewer packs could be stored in the same space e.g. in warehouses/pharmacies/fridges. This could present logistical issues that could potentially lead to stock-out situations in some countries/HCP facilities/hospitals.

Pharmaceutical industry suggests that a better solution to these issues is,in the interim, to review, if the SmPC, readability and Quality Review of Documents (QRD) template guidelines can be adapted (see NIVEL report conclusion 2) and further to move towards an electronic approach to provision of information (see NIVEL report conclusion 5) to avoid unnecessary extra work for industry/regulators and additional costs.

• *There is a lack of benefit information in the PIL. The report suggests (voluntary) research and user testing of benefit information.*

PHARMACEUTICAL INDUSTRY views

Pharmaceutical industry agrees that there is a lack of benefit information in the PL. Patients and HCPs have suggested that benefits and risks must always be communicated together to improve the benefit-risk perception for patients. Pharmaceutical industry encourages further and timely research on this point – cooperation with Health Literacy experts should be sought to provide solutions on how to convey benefit /risk messages appropriately.

[3] **An analysis and evaluation of the development of the QRD human product information template used in package leaflets;** Dissertation, 2015 from the Faculty of Mathematics and Natural Sciences at the Rheinische Friedrich-Wilhelms-University Bonn; Wolf A

NIVEL report conclusion 2: Adapt guidelines and QRD-template rather than legislation to enhance readability of package leaflets **Recommendations:**
• *Consider reformulating the guidelines so that they include more principles of good information design.*
• *Recommendation: Consider allowing for more flexibility in the information recommended in the QRD template between medicines as long as legislation allows it.*
• *Recommendation: Include guidelines on translation that go beyond the principle of faithful translation, in order that the lay language introduced through user testing in the original language is not lost during translation.*

PHARMACEUTICAL INDUSTRY views

Pharmaceutical industry welcomes the potential for revisiting the QRD template to allow greater flexibility and encourage evolving guidance which includes more details on the principles of good information design in which content and layout are jointly considered. The QRD template should be adapted alongside electronic approaches (rather than before) to avoid double work for products that are already on the market.

With regards to a revision of the content of the QRD template, a more balanced approach of benefit versus risk would be welcomed. In addition, some administrative details from the QRD template are burdensome in the way that any minor change (such as change of a country detail in the Centralised Procedure or of a RMS/CMS licence in MR/Decentralised Procedure) requires a change of the leaflet.

Any proposed changes to improve the content and layout should be recommended in consultation and cooperation with citizens of different age groups, representatives of patient organisations as well as HCPs, industry and association representatives and other stakeholders. Ideally the gathered recommendations would be further strengthened from a range of countries with different healthcare systems.

Flexibility in translations is definitely welcomed. It is more important to convey the respective messages for the users/patients rather than insisting on correct, "mechanical" translations. This flexibility will allow achieving appropriate lay expressions in the target languages in a much better way than the current more rigid standards that have to be met over a short time period.

A similar approach is recommended in the report on the European Medicines Agency's workshop on risk minimisation measures[4]:

- Make optimal use of current regulatory tools – optimise PL and SmPC and adapt them to the needs of their audience (and their health literacy).
- To better describe benefit and risk to readers.
- Increase collaboration between regulators, HCPs and patients.
- Increase understanding of the factors that affect adherence to risk minimisation measures by patients and HCPs – cultivating a 'critical trust' culture NOT a blind trust/no trust paradigm.
- Move beyond paper-based communications.
- Measure the effectiveness of current risk minimisation practices – better engage patients and patient registries.

These new approaches could first be applied for new medicines. For products already on the market a transition period should be foreseen to allow the parallel introduction of electronic dissemination of product information and new labelling requirements.

[4] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/12/WC500198810.pdf

NIVEL report conclusion 3: Strengthen patient input in developing and testing of PILs Recommendations:
• *Make the user testing process more iterative.*
• *User test changes in information required by regulators after the initial user testing.*

PHARMACEUTICAL INDUSTRY views

Significant improvements in readability and user friendly language have been made to the package leaflet since the introduction of user testing in 2005. Pharmaceutical industry are concerned that this recommendation by NIVEL was made based partially on the use of older (pre-2005) leaflets in NIVEL's assessment of readability of the PL. In addition, given the NIVEL assessment was based partially on older leaflets, pharmaceutical industry question the inference that increased user testing will result in any significant further improvement.

Whilst strengthening input from patients is welcomed, pharmaceutical industry are concerned that additional user testing may cause delays to the MA and variation assessment timelines and the consequent provision of up-to-date safety information to patients.

Pharmaceutical industry questions how NIVEL considers the activities of writing, designing and testing of PLs as such entirely different activities that they have contributed to the unsatisfactory results as stated in the NIVEL report. The current approach to PL development integrates all stages of the process, so that they cannot be seen as 'stand alone' activities. Many of the difficulties encountered in PL development arise due to the QRD template effectively imposing a 'one size fits all' format. Furthermore, a new QRD template as well as the readability and the SmPC-guidelines developed in dialogue between citizens, patients, HCPs, industry, regulators and policy-makers will likely have a greater impact on improving the provision of up-to-date, accurate information that allows the patient to obtain, identify and use the information necessary to meet their individual needs.

This should be developed concurrently and in consultation with a robust strategy on electronic provision in context with the overall EU strategy on digital health literacy and eHealth[5].

<u>Suggested alternative</u>

Rather than investing efforts in user-testing at the end of the process - which cannot change the underlying regulatory decision and the wording of mandated text - increasing involvement of patients and assessment in the regulatory decision-making-process itself would be a more efficient way to improve the user-friendliness further. The example of the preparation of the EPAR summary for the public could serve as a model.

A group of non-specialists (citizens with representative levels of health literacy) may be established at European Medicines Agency (EMA) and work together with the scientific bodies at EMA to prepare adapted language for decisions affecting the package leaflets. In order to allow these people to dedicate sufficient time to this task a model e.g. similar to the "national experts" for a limited time period employment/secondment from other authorities (non-health), a kind of voluntary "social work" (like in Germany the "Bundesfreiwilligendienst") or national programmes for unemployed people may be considered.

[5]https://ec.europa.eu/digital-agenda/en/news/ehealth-action-plan-2012-2020-innovative-healthcare-21st-century

NIVEL report conclusion 4: Best practice should be promoted **Recommendations:**
• *Make best practice examples of aspects of leaflet design (anonymised) available for pharmaceutical companies and include not only the end product but also information on the process of development where possible.*

PHARMACEUTICAL INDUSTRY views

Pharmaceutical industry supports the introduction of best practice examples as a further method of enhancing patient information.The development process for EPAR summaries for the public should also be included in this exercise.

Health literacy experts and regulators should work jointly to ensure that health literacy principles are applied best to product information. In particular Pharmacovigilance Risk Assessment Committee (PRAC) decisions should be reviewed by an independent body of national non-experts (see conclusion 3) regarding the meaningfulness for patients.

NIVEL report conclusion 5: Development of a strategy for electronic PILs **Recommendations:**
• *Examine the potential to use electronic media in the (near) future as an increasing number of EU-citizens get access to these media.*
• *Explore opportunities these media offer for optimizing the PIL in terms of flexibility of information provided and design.*
• *Explore and research the opportunities for the PIL to be part of the care process rather than a stand-alone source of information.*
• *Consider how mechanisms to alert patients taking long-term medicines to changes in the PIL could be developed through electronic media.*

PHARMACEUTICAL INDUSTRY views

Pharmaceutical industry agrees with the conclusion that the development of a strategy for electronic product information is required. Pharmaceutical industry strongly suggests, however, that this be given the highest priority.

There are three different settings to be distinguished:

1. Hospital-only products where the electronic information already replaces the paper leaflet in daily practice and the paper leaflets included in the packages are often thrown away.
2. Prescription-only products where paper could stepwise be replaced by electronic information (see below).
3. Non-prescription medicinal products ("Over-the-counter/OTC" products) need to be regarded separately. As the patient may have no or little interaction with a healthcare professional, information provided directly with the pack will continue to be required but could be complemented by possibly a more user-friendly electronic information. In this case, electronic availability of the leaflet may help people to get information before buying a non-prescription medicine and, by that, help them choosing the appropriate product or addressing questions to a healthcare professional.

Electronic dissemination will be helpful to ensuring rapid updates to product information and in presenting the information to address the different needs of patients and HCPs. A patient-friendly benefit of such an electronic system would be the ability to highlight any critical changes (e.g. new warnings) to the product information.

Pharmaceutical industry proposes that the electronic provision of the PL and SmPC in a structured database/website will make a more significant contribution to addressing the shortcomings of the paper based approach outlined in the NIVEL studies.
Electronic information:

- Allows for flexibility in font size and line spacing;
- Enables patients to search for information in a tailored fashion to meet their own needs;
- Addresses the issues associated with multi-language packs (see NIVEL report conclusion 6);
- Allows enhanced device-related instructions for the application of medicinal products (e.g. video instructions for asthma sprays, pre-filled syringes)
- Addresses needs of people with disabilities;
- Most importantly, enables rapid availability of new efficacy / safety information to patients and HCPs.

Pharmaceutical industry encourages the European Commission to explore the possibility of addressing the above opportunities for both patients and HCPs via one electronic solution. The information for patients and HCPs on all authorised products could be made available electronically through a **single trusted source** in a way that allows quick access to the preferred level of information and in a more user-friendly format.

Pharmaceutical industry finds that in this context, enhancing existing member state level platforms, and the introduction of new technological platforms for providing product information should be further explored and introduced in the European Economic Area (EEA), while keeping in mind access to information must also be ensured for patients who do not (yet) have access to electronic media[6].
Reduced impact on the environment is another advantage of electronic dissemination. Paper labelling has a significant impact on the environment. With each routine labelling update comes a tremendous amount of paper waste due to the fact that outdated labels must be disposed of each year. Besides the waste being created at the industry's side, there are the hundreds of thousands of PLs that HCPs, who obtain their information through other means like electronic compendia, are being routinely discarded.
With the use of e-labelling, this potential negative environmental impact would be minimised while allowing rapid access to up to date information to patients and healthcare providers.

Platform requirements:

- Facilitate the presentation of information that is specific to the needs of patients and HCPs, and is available anywhere at any time, comprehensive, and up to date. Also addresses needs of people with disabilities and special requirements for information representation (e.g. permits audio versions, font size flexibility, use of videos, charts etc.)
- For those patients who do not use or cannot access the internet it has to be ascertained that they can get the corresponding "product information" for prescription medicines printed in the pharmacy or via other technologies
- Links in the table of content can make information easily accessible (if needed and the possibility to select parts of the information by search functions)
- As a mid-term task, a web-based information system should be designed and installed that is easily accessible also from mobile devices[7]
- Electronic information should be complementary to many other health applications[8] available on the internet

[6] A pilot project to explore such a system is currently in preparation and expected to start in Q2/2016.
[7] Platform requirements are dependent on future technical developments such as e.g. ISO IDMP
[8] Results from the European programmes on Digital Health Literacy and other eHealth related initiatives should be taken into consideration

- Easier access to information for patients connected to dose dispensing solutions (like e.g. implanted insulin pumps)
- Options for integration in eHealth systems and electronic medication plans
- Options for small member states to provide product information in national languages
- Consider removing the requirement of (paper) package leaflets for hospital-only used products immediately where feasible, also from an environmental perspective

With regard to internet access and usage, in Europe it is recognised that there is great disparity across Europe. Luxembourg and the Netherlands both report the highest household internet access in Europe of 96%. According to the figures from Eurostat all the Nordic countries have an internet access of 90-96%, hence the Nordic region should be one of the first regions to receive the option for adapted approaches. Bulgaria currently has the lowest household internet access in Europe. However between 2009 and 2014 this increased by 27 percentage points to 57% in 2014 (figures taken from Eurostat). Some countries also have existing and sophisticated databases for electronic provision of SmPCs and PLs (e.g. FASS in Sweden, ePIL in Norway and Denmark). The data format in accordance with the Identification of Medicinal Product (IDMP) standard may also be explored.

In order for those more electronically advanced countries to take early advantage of the benefits of an electronic strategy, pharmaceutical industry propose a stepwise approach should be explored that allows those countries where there are already well established electronic databases and those that are more advanced in using internet technologies, to use these systems in advance of an EU-wide system. An EU-wide system should not replace the well-functioning national systems, but should facilitate the access to them via one single portal.
This flexible and Member State specific approach to the introduction and use of electronic media and its role alongside an option for a paper version should be applied, depending upon electronic access and the value of a paper PL, within the individual EU member states.

NIVEL report conclusion 6: Multilingual PILs can benefit from electronic formats **Recommendations:**
• *Consider those countries with more than one official language in the electronic media strategy.*

PHARMACEUTICAL INDUSTRY views
Multi-language PLs are more lengthy, complex and structurally challenging. It is promising that the report suggests that multilingual PLs may benefit from an electronic strategy, recognising the flexibility that electronic product information would provide. However, throughout the report it is implied that electronic formats should be considered a long-term solution. Pharmaceutical industry recommends electronic formats as a priority solution to the problems experienced by patients.

Pharmaceutical industry disagrees that a key information section should complement multilingual PLs. Alongside our recommendation to develop electronic PLs in the short-term, the introduction of a key information section would be unnecessary (see section 2).

The general comments on key information sections apply also for multilingual PLs (see below).

2.0 Feasibility and value of a possible "key information section" in patient information leaflets and summaries of product characteristics of medicinal products for human use The PILS-BOX study

NIVEL report conclusions:
• *Too early for evidence-based EU-wide introduction of a key information section.*
• *UK experience offers potential for gathering evidence.*
• *EU-wide user tests needed to develop standards for key information section.*

PHARMACEUTICAL INDUSTRY views

The second survey that NIVEL conducted focused on the feasibility of a 'key information section', concluding that the introduction of a key information section into the PL and SmPC is currently premature. Pharmaceutical industry agrees that as there is limited, inconclusive data. Therefore a key information section should not be mandated. Introduction of an additional key information section would add to the length of the documents already criticised. There is very significant concern the patient would not read all relevant information but rather focus on the key information section. This would also raise considerable legal concerns regarding the content of such a section. In addition, there is the challenge of meeting every patient's need and so the question arises which patient group such a key information section should target.

The proposed methods of electronic dissemination discussed in section 1 (Conclusion 5), will allow the users to more easily locate or select product information relevant to them and it is proposed as a better solution than a key information section, given the disparity of perspectives on the possible content of such a key information section. In addition a link to the EPAR summaries for the public should be discussed rather than the development of such key information sections.

Suggested alternative

Rather than investing efforts in research of key information sections increasing involvement of patients and assessment in the regulatory decision-making process would be a more efficient way to improve the user-friendliness further. The example of the preparation of the EPAR summary for the public could serve as a model.

A group of non-specialists (citizens with representative levels of health literacy) may be established at EMA and work together with the scientific bodies at EMA to prepare adapted language for decisions affecting the package leaflets. In order to allow these people to dedicate sufficient time to this task a model similar to the "national experts" for a limited time period, a kind of voluntary "social work" (like in Germany the "Bundesfreiwilligendienst") or national programmes for unemployed people may be considered.

In addition healthcare professionals need to be taken into consideration. A broader concept of product information also for HCPs (e.g. information that could be conveyed during a consultation) that takes into account the available information for patients based on new technologies could bring more improvements than a narrow focus on some specific aspects of the PL. This concept should ideally be developed with all stakeholders.

The application of usability aspects and electronic dissemination will be more beneficial than key information sections.

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