Some comments about the Draft Key Principles for electronic product information

July 25th, 2019

Electronic product information for human medicines in the EU – draft key principles.

A response:
sixty six comments leading to seven suggestions

A collaboration of EMA-HMA-EC started a public consultation on January 31st, 2019. The aim is to collect comments about these Draft Key Principles for the development of electronic Product Information (ePI). [Link to original document - a copy is attached at the end of this report]

This response consists of four parts:

1. ***Sixty six comments***. These are line-by-line comments of the Draft Key Principles (page 13 to 41).
2. The sixty six comments are grouped into ***seven categories*** (page 4 to 12)
3. The seven categories lead to ***seven suggestions*** (page 3).
4. ***A summary*** of this response (page 2).

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1. Summary

A line-by-line analysis of an EMA-HMA-EU public consultation document on electronic Product Information (ePI) prompted sixty six comments (page 13-41). These comments were grouped into seven categories (page 4-12) and have lead to seven suggestions (page 3).

The Draft Key Principles do not make clear who the ***users*** of ePI are (suggestion 1). The document provides ***unfounded characteristics of information*** (suggestion 2), and is unclear about ***the aims*** of ePI (suggestion 3). It makes many ***unsupported assumptions*** (suggestion 4), and does not fully explore potential ***benefits of digital information*** (suggestion 5). The suggested ***process*** is in conflict with other recommendations of the European Commission (suggestion 6), and it is questionable if the ***standardization*** of existing information is really the most beneficial approach (suggestion 7).

It would be very disappointing for all stakeholders if the implementation of the six recommendations of the European Commission (2017) has only lead to this 'proposal for a mark-up language' as a first step.

There is an urgent need to modify information about medicines and embrace the digital realm. The shortcomings in the provision of analogue information about medicines have been formally recognized in 2010. Prescribing errors, dispensing errors, administration errors, and low adherence require swift attention. The correct, safe, and efficient use of medicines are probably the main aims for ***users of information***. The current regulatory process is complex, costly, error prone, and time consuming for ***developers of information***. Both sides could benefit substantially from the development of electronic Product Information - to be used in both analogue and digital formats.

Information about medicines must focus on what people need to achieve. The development of information must strive for inclusion and accessibility for all. In the absence of measures to ensure different user's needs are taken into account, only those of the dominant group are served. Therefore, it cannot be based on a rigidly standardised information content or the current limitations of digital technology.

The next version of the Draft Key Principles should address the aims, approaches, and processes that are required to develop information about medicines that really 'enable people to act appropriately'.

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2. Seven suggestions

These suggestions are based on the seven categories that group the sixty six comments.

Suggestion 1: It is important to clarify who the users of electronic product information are and how they should benefit. All user groups must be involved in the development of ePI; none of the actual user groups should be excluded.

Suggestion 2: People who use information decide if they can trust it and apply it to their situation. Information does not have 'inherent qualities'. It is therefore necessary to find out which information people trust and use before adding more information in an alternative format.

Suggestion 3: Clarify what the aims of electronic Product Information are for each of the user groups. Set performance based standards for every action that needs to be enabled with the support of electronic product information.

Suggestion 4: Investigate assumptions before using them as a basis for decisions.

Suggestion 5: Digital information is not sequential nor text based. It can be modular, visual, and interactive. Users can modify its language, format, mode, structure, and design according to their needs. Allow for these continuously evolving digital opportunities.

Suggestion 6: Make sure that all six recommendations of the EU can be implemented. The development of ePI as suggested in the Draft Key Principles makes it very difficult to consider other recommendations. It seems essential to reconsider the priorities, and start with scoping and benchmarking studies.

Suggestion 7: Standardizing the current legally required information, which is known to have shortcomings, might not be the best option.

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3. Seven categories

The detailed comments are mentioned on pages 13 to 41. In this section, the sixty six comments are grouped into seven categories.

Category 1: Who are the users?

(This category is based on comments 16, 18, 21).

Throughout the Key Principles document, the people who would benefit from electronic product information (ePI) are not clearly defined. The descriptions below show that at least seven different groups are involved. It is unclear if these different descriptors of the various user groups are intentional and indicate different meanings.

The seven groups are:
1. Healthcare professionals: healthcare professionals (line 52); healthcare professionals who travel and work in several EU countries (line 116); users (line 263).

2. Patients/consumers: patients/consumers (line 53); patients and consumers of medicines in the EU/EEA (line 118-119); citizens (line 190); EU citizens (line 171, line 329); patients/consumers with diverse abilities (line 185); blind and partially sighted people (line 186); those with low literacy levels (line 186-187); patients/consumers with low digital literacy (line 211); patients/consumers with limited internet access (line 212); patients who travel and work in several EU countries (line 116); users (line 263).

3. Industry: industry stakeholders (line 69); the pharmaceutical industry (line 79); other companies (line 246); micro, small or medium-sized enterprises (SMEs) and companies producing generic medicines (line 307-308); pharmaceutical companies (line 319); MAHs (line 246, line 272, line 281).

4. Authorities: regulators (line 69, line 280); regulatory authorities (line 221, line 259); national competent authorities [NCA] (line 137); national authorities (line 335); EMA and NCAs (line 174); Members of the European medicines regulatory network (line 245-246); EU authorities (line 258); HMA and EMA (line 302, line 311-312).

5. Combinations: companies, not-for-profit organisations or patient/consumer groups (line 193); patients and healthcare professionals who travel and work in several EU countries (line 116); all parties involved (line 245); users (patients/consumers and healthcare professionals) (line 263); all stakeholders,

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including pharmaceutical companies and regulators (line 299); regulators and stakeholders (line 111, line 142).

6. Non-healthcare: academia (line 69); not-for-profit organisations (line 69); Member States (line 306).

7. Unclear: stakeholder (line 62, 310); third-parties (line 267); third-party providers (line 276).

The inconsistent and vague descriptions of people who have to handle ePI cannot be used as a starting point because these make it impossible to define performance expectations and select criteria for success.

It is important to clarify who the users are and how they could benefit. Make sure that all user groups are involved and that none of actual user groups is excluded.

Category 2: Contents of an ePI?

(This category is based on comments 2, 20, 23)

The description of the information in the ePI varies substantially throughout the Draft Key Principles document. Each of these descriptions asserts that information can have specific characteristics that can be established independent from the users or context.

The Draft Key Principles document mentions the following characteristics of information:

- scientifically validated information (line 54)
- up-to-date information (line 65)
- authorised, statutory product information for medicines (line 86)
- electronic authorised information (line 118)
- trusted information (line 123)
- unbiased, up-to-date, regulator-approved product information (line 149)
- the latest information (line 151)
- the latest authorised information (line 157)
- regulator-validated ePI (line 170)
- an authoritative source of scientific and evidence-based information on medicines (line 171-172)
- regulator-approved information only (line 218)
- regulator-approved medicine PI only (line 220)
- the latest version of the PI approved by regulatory authorities (line 221)
- validated, non-promotional information (line 235)
- as a trusted source for reliable medicines information (line 284)

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There are several phrases that might have a similar meaning:
- authorised, statutory, regulator approved, regulator vaiidated, authoritative;
- scientifically validated, evidence-based;
- up-to-date, latest.
However, it is not clear if 'regulator approved' and 'regulator validated' are identical, or if 'latest' and 'up-to-date' are identical.

A combination of all these descriptors provides the following characteristic of ePI:

> ***'ePI provides electronic, authorised, regulator approved, regulator validated, authoritative, trusted, unbiased, up-to-date, latest, scientific, evidence based, non-promotional, reliable information.'***

However, there is little evidence - if any - that this information is perceived like this by people who need to read product information about medicines. The problem is that it doesn't matter if competent regulatory authorities aim to provide this, *it is the reader who decides if information conforms to their criteria of reliability and trustworthiness*. Even if it is scientifically validated and approved, it might not be trusted.

People who use information decide if they can trust it and if they can apply it in their situation. Information does not have 'inherent qualities' that can be assessed outside its context of use. It is therefore important to find out which information people trust and use before disseminating the same information in another format.

Category 3: Aims?

(This category is based on comments 7, 8, 12, 14, 15, 17, 19, 22, 26, 31, 34, 35, 38, 44, 46, 47, 49, 50, 51, 66).

The aims of the development of electronic Product Information are not clearly stated. It is not clear what exactly needs to be achieved through the provision of electronic product information about medicines.

Instead, the Draft Key Principles document mentions at least nine aims. The aims described throughout the document seem to be beneficial for different user groups, which makes it difficult to assess if they can be achieved. The nine aims are:
- 'it will ensure patients have timely access to up-to-date information.'
- 'to offer possibilities to streamline, simplify and speed up the regulatory process in the creation and updating process.'
- 'to create the technical foundation for the dissemination of trusted information in the electronic world.'
- 'possible to rapidly update ePI, … expected to increase support to patients/

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consumers in informed decision-making, … should facilitate patient/consumer-healthcare professional interactions and discussions about medicines.'
- 'The structured nature of ePI will offer new opportunities to better tailor product information to the needs of individual patients/consumers.'
- 'ePI can be handled electronically and read by machines, ePI information can flow to other systems, such as electronic health records and e-prescribing systems.'
- 'facilitating targeted delivery of the right information to the right patient/consumer at the point of need.'
- 'EMA and NCAs should work towards ePI to fulfil their mission to protect public health.'
- 'The most up-to-date ePI version should be always easily available.'

At the moment, without reliable benchmark data, it is not possible to state what the current situation is. For example, which specific groups of patients at the moment do not have access to any information, and how many do not have access to up-to-date information?

It seems necessary to clarify what the aims of electronic Product Information are for the different user groups. This can only be done through scoping and benchmarking studies that lead to setting performance based standards.

Category 4: Assumptions?

(This category is based on comments 1, 3, 4, 25, 36, 37, 39, 40, 43, 45, 55, 56, 62, 64, 65).

The document mentions several unsubstantiated assumptions. These need to be investigated befoe they are used as a basis for decisions. Two questions about each assumption need to be answered: 'What is the evidence? (is it really true?)' and 'to which extent? (who or what is excluded?)'.

There is very little evidence that supports the following assumptions:
- 'pivotal.'
- 'assists healthcare professionals in prescribing and dispensing the medicine.'
- 'informs patients and consumers about its safe use.'
- 'the electronic format is the most pressing priority.'
- 'Semi-structured' … 'structured elements (e.g. fixed headings and vocabularies)' … 'some unstructured elements (i.e. free text).' 'Unstructured formats.' [= can information be separated in this manner?]
- 'which will allow patients/consumers and healthcare professionals an additional and tailored approach on information for medicines according to his/her need and/or wish by using suitable (electronic) output forms and platforms.'

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- ‘multiple different standards … would generate unnecessary complexity, impede access to information and require multiple interfaces between standards, restricting flow of data.’
- ‘the benefits this format can offer for public health.’
- ‘will support … provision of the latest information on a medicine’s safety, benefits and its conditions of use.’
- ‘will support … better delivery of information so that the right information is available to the right patient/consumer at the point of need.’
- ‘will support … informed decision-making by patients/consumers and healthcare professionals.’
- ‘Patients/consumers and healthcare professionals using ePI can be fully confident that they hold the latest information.’
- ‘to increase support to patients/consumers in informed decision-making about their treatment.’
- ‘and help them to adhere to their medication regimes, ultimately contributing to optimal outcomes.’
- ‘Availability of regulator-validated ePI will counterbalance.’
- ‘often widely spread through online and other forums’.
- ‘the paper PL is particularly important for patients/consumers with low digital literacy.’
- ‘as trusted source for reliable information.’
- ‘may be a significant burden.’

There is very little reliable evidence supporting any of the abovementioned assumptions. The correctness of these assumptions need to be verified before any system can be developed.

Thorough scoping and benchmarking phases are essential to find out if these assumptions are correct, and if they are correct in all contexts. Further empirical research is necessary to provide reliable evidence for decisions.

Category 5: Digital opportunities?

(This category is based on comments 6, 9, 13, 24, 32, 33, 48, 52, 53, 54).

The digital opportunities can be subdivided into five main groups:

a. Mark-up Language

Line 138 and 139 indicate that the ‘mark-up language’ will be the only available technical feature for electronic Product Information. The other two features - ‘interoperability’ and ‘controlled vocabularies’ - still need to be developed.

A mark-up language is a very narrow focus, and this does not really make much use of digital opportunities. It mainly goes back to the xml-based *‘patient information management’* (PIM) system which was halted in 2011 (PIM, 2011). It might be beneficial to evaluate how the experience of the PIM-project

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could benefit the development of the electronic Product Information before embarking on a new xml-adventure. Existing digital formats, such as Adobe PDF and Microsoft Word (and a range of related software applications) include more and more features that integrate a standardised mark-up language too. Choosing the most beneficial standard will require substantial research.

b. Accessibility

Providing information in a digital format requires the adherence to European legislation and international web-standards. The European Accessibility act (2016/2102) provides a good starting point. A harmonised European standard was recently published (ETSI, 2018), and the W3C-Consortium (https://www.w3.org/WAI/) lists the international requirements. These need to be followed, because they are based on empirical evidence how people access digital information. These standards also support people with diverse abilities to use electronic resources.

c. Information contents & key information section

The obligatory order of information in package leaflets will be modified in digital formats. This is unavoidable in a digital environment where information is modular, layered, and top-level information needs to be shown first. The idea of a 'key-information section' as suggested by recommendation 6 (European Commission, 2017, page 8) is essential for electronic Product Information because that is exactly what people expect on the highest hierarchical information level. This addition will lead to a difference between the printed package leaflet and its digital version in both sequence and the number of sections. It is furthermore likely that the digital environment will require more visual information in the form of pictograms, illustrations, and colours.

d. Adding information

The digital environment will add other information to the ePI, because the addition of meta-data is essential for digital use. This consists of digital wayfinding (menu's, hyperlinks, colours), search engine support, and links to other information sources. Without these, an ePI will not optimally use of digital opportunities. Suggesting that it is possible to make information electronically available ***and*** prohibit the addition of information (line 227-228, comment 61) is simply incorrect.

e. Sharing hyperlinks

One of the main features of electronic information is the ability to link to other digital resources and social media. The limited information in the highly condensed texts in SmPC and package leaflet will be linked to a range of other resources. These links could be really helpful for people to find more information about a medicine.

All five above-mentioned topics are not options: they are an integral part of digital information. Mark-up languages, accessibility standards, variable

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contents on different levels, adding meta-data and search engine support, and including hyperlinks are standard and must be used as a basis for the development of digital information about medicines. Ignoring these will reduce and limit the functionality.

Category 6: Process?

(This category is based on comments 5, 10, 11, 27, 28, 29, 30, 41, 42, 58, 63).

Much of this ePI approach is in conflict with 'the principles of good information design' (Sless and Shrensky, 2006; Black, Luna, Lund, and Walker, 2017).

a. Start from what is available: scoping

Most of the information about medicines is already available in a digital format. Not only in PDF and Word on the EMA-website, but also in many digital pharmacopoeia, medicines compendia, and repertories used by doctors and pharmacists. These are all based on standardised digital structures. Ignoring these existing digital resources, and developing yet another one might not be effective. A first step - as the principles of good information design suggest - is to find out first how different people cope at the moment. This 'scoping' will reveal the activities that go well, and those that are more problematic.

b. Find out how well people coop at the moment: benchmark

The activities that are problematic need attention first. These cause the errors, additional costs, increase waste, and intensify anxiety. The assessment criteria and measurement-units need to be established before small scale benchmark tests can be conducted. The test results will provide the data that can be used afterwards to evaluate if a change has really lead to an improvement. Without the benchmark scores, it is impossible to evaluate what the effects of a change are.

c. Involve people right from the start

The Draft Key Principles document implies that it is possible to start the development of a semi-structured format (line 91) without the involvement of patients, consumers, and healthcare professionals. The scoping and benchmarking phases are simply skipped. This is in conflict with the 'principles of good information design' that are mentioned as recommendation 2 of the European Commission (2017).

d. Consider all six EC-recommendations

This above-mentioned three points show a direct conflict between the development of electronic product information and recommendations 2 and 3 of the European Commission (2017). Recommendation 2 suggests to rely on 'principles of good information design' and recommendation 3 states that 'patient input should be further improved'. Developing the ePI as it is suggested in the Draft Key Principles document will make it very hard to implement recommendations 2 and 3.

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These four points indicate that a reconsideration of the priorities for the development process of electronic product information about medicines is essential. The combination of both analogue (printed) and digital information (on screens) needs to focus on 'enabling the user to act appropriately', as it required in Directive 2004/27/EC, article 63 paragraph 2. Not involving people, and not applying principles for good information design is in conflict with the recommendations of the European Commission.

Category 7: Standardising the right thing?

(This category is based on comments 57, 59, 60, 61).

Two questions need to be asked:

a. Is a 'semi-structured format' appropriate?

The European Commission detected 'shortcomings' in 2010, and the NIVEL PIL-report (2013) showed that *'patient's comprehension of the package leaflet and its readability can be improved.'* The PIL-report further concludes: *'Guidelines should include more details on the principles of good information design in which the content and layout are jointly considered.'* The standardisation of the information into a 'semi-structured format' (line 91) is in conflict with this conclusion because it separates the contents from the layout. The semi-structured format should not be developed without taking the visual presentation of information into account. This combination of contents in a semi-structured format and visual presentation must be developed in cooperation with people who are going to use this information: patients, consumers, and healthcare professionals.

b. Is the information content suitable for all circumstances?

The Draft Key Principles state that the legislation will remain the same and that the contents of the information will not change. Line 227 and 228 state that other information cannot be included in the electronic Product Information. It is therefore likely that the electronic Product Information is very similar, or identical to, the information that appears now in package leaflets, in the SmPC and on packaging.

This information is however not suitable in all circumstances. Patients require different types of information in for example hospitals, elderly care homes, and in emergencies. The variation in medicines, and in contexts in which medicines are prescribed and dispensed also require more variation in information about medicines. Standardizing information that has proven to have 'shortcomings' needs to be avoided. It would be more beneficial to consider the users, required actions, and required performance levels first before standardized information is supplied.

The Draft Key Principles suggest that it is possible to develop a 'semi-structured format' without considering its visual presentation. This

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approach is in conflict with the results of the recommendations of the European Commission, and with the principles of good information design.

The information content and digital structure must be considered together, based on the results of benchmark tests with actual users. Parts of the process can be standardized in a protocol. The outcomes cannot be standardized because they depend on people who need to undertake specific actions in a context. However, acceptable performance levels for each action can be standardized.

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‘Background’ (line 50 to 74).

Comment 1: Line 54. ‘the pivotal source’.
The word ‘pivotal’ needs to be reconsidered. It is questionable if product information about medicines in Europe can be seen as ‘pivotal’ in all circumstances for all users.

There are three main groups who use SMPCs and PILs:

Group 1: Prescribers use an SMPC to prescribe medicines. There is conflicting evidence about this statement. There is some evidence that healthcare professionals do not use SmPCs to prescribe and use other sources (Raynor 2013; Vromans 2013). The first study concluded: *“Qualitative comments showed that in their current format, SmPCs are of low perceived value to prescribers and are not central to the clinicians’ prescribing behavior. Current content and presentation of SmPCs, while meeting regulatory approval standards, contribute little to the safe and effective use of medication in practice.”* The second study concluded: *“Physicians confirmed the importance of SmPCs as a comprehensive source of medicinal product information, but were moderately satisfied with the current SmPCs, utilised it infrequently and were more likely to engage additional sources of information.”* An EMA-survey in 2016 shows the opposite. It concluded that 95% of healthcare professionals across Europe use the SMPC (Brassart and Peppard, 2016). The Nivel stakeholder survey (PIL-S report, chapter 5, page 71) did not ask or investigate if SmPCs are actually used by healthcare professionals.

Group 2: Pharmacists dispense medicines. The information on the pack that pharmacists must read to dispense is pivotal: there is no other source at the moment of dispensing. A 2014 report by the EMA shows how problematic this information currently is. Between 2% and 49% of the dispensed medicines in hospitals is incorrectly dispensed. This leads in 10% of cases to irreversable harm to patients, and it was lethal in 5%. (EMA, 2014).

Group 3: Patients and consumers use PILs about safe use. (van Beusekom 2016; Leemans, 2011). The first study concluded: *“Patient information leaflets were considered discouraging to use, and information difficult to find and understand. Many rely on alternative information sources.”* The second states: *“We can conclude that the actual PIL is read too little. In order to make the PIL more appealing and even more patient friendly than it is actually, taking patients’ needs into account should be a priority.”*

In some studies, prescribers, pharmacists, patients, and consumers seem to have serious problems using SMPCs and PILs, while in other studies these documents don’t cause any problems. The view of the European Commission is that there are ‘shortcomings’.

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Alternative: This first paragraph needs to be rephrased to do justice to the factual use of these documents. There is little evidence that SMPCs and PILs can be characterized in general as 'the pivotal source'.

Comment 2: Line 54-55. 'scientifically validated information'.
The words 'scientifically validated information' need to be reconsidered. Several sections in the QRD-template are based on fear, not on evidence (QRD-template, version 10, 02/2016). Three examples in the text for the package leaflet that are not supported by evidence are:

- [Page 27] *'Do not pass it on to others'*. Although patients might give their medicines to others, the scale of this behaviour is unknown. It is a fear that is not supported by evidence.
- [Page 27] *'Keep this leaflet. You may need to read it again'*. Apart from the superfluousness of this statement - what are the other reasons to keep a leaflet? - it is an advice that is not supported by evidence. If this was important, than it is essential to make it easy to put the package leaflet back into its box.
- [Page 28] The annotated template states that: *"the benefit(s) of taking the medicine could be summarised. … This would be particularly important to encourage adherence to the treatment, e.g. for long-term and prevention treatment"*. There is no evidence that there is a direct relation between the provision of information and actual adherence. This statement is not supported by any validated scientific evidence.

Alternative: Delete the words 'scientifically validated information'. These are incorrect.

Comment 3: Line 55. 'assist healthcare professionals'.
This is an unsupported assumption. The actual use of these documents by different types of readers - medical doctors and pharmacists - is to a large extent unknown.

Alternative: Before a new approach is introduced, it is essential to benchmark the current performance. This 'benchmarking' will show how well actions are performed at the moment, and how well practical use is enabled by specific types of documents. This baseline data is essential to check later if a modification can be seen as an improvement. It is highly likely that there is a substantial variation of the use of SMPCs by healthcare professionals. Not all healthcare professionals are assisted to the same extent in a similar manner.

Comment 4: Line 56. 'informs patients and consumers about its safe use'.
This is an unsupported claim. The assumption is that all patients and all consumers need identically structured and standardized information to use medicines safely. It assumes that patients and consumers - even if they use

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the same medicine - are homogenous groups. And it assumes that patients and consumers actually read, understand, and apply the information in the package leaflet. Most of the literature about package leaflets shows that these assumptions are incorrect.

Alternative: The aim of information is to 'enable the users to act appropriately'. Authorized information must be provided in formats to:
- enable patients to use medicines correctly and safely
- enable consumers to use medicines correctly and safely

Before a new approach is introduced, it is essential to benchmark the current performance. This 'benchmarking' will show how well actions are performed at the moment, and how well practical use is enabled by specific types of documents. This baseline data is essential to check later if a modification can be seen as an improvement. It is highly likely that there is a substantial variation of the use of package leaflets by patients and consumers. Not all patients and consumers are informed to the same extent in a similar manner.

Comment 5. Line 62-63: 'identifying stakeholder needs and mapping ongoing initiatives'.

Identifying and mapping are essential but not sufficient. These are just the first steps to prepare for systematic scoping and benchmarking phases. Identifying needs and mapping initiatives do not provide the right kind of data that can be used as a basis for an information development proces. It is essential to identify and verify what the most problematic issues for ***all*** the ***different*** stakeholders are. A focus on stakeholder's will reveal conflicts between different stakeholders and within stakeholder groups, but it will not help to resolve these.

Alternative: A systematic scoping phase and a systematic benchmarking phase are essential.

The **scoping activity** will show how people deal with situations in practice. There will be a substantial variation between people. [Not every prescriber will read an SMPC before prescribing a medicine. Which information sources are used? What is the variation between doctors? How does the SMPC fit into activity-patterns?] The scoping phase will point to those activities that are most problematic in practice at the moment. There are many methods to conduct these contextual inquiries.

Systematic **benchmarking** will show how well an information source performs when it is used for a specific action. [A benchmark test will provide exact data if people can find information, can understand it, and can apply it.] Benchmark data can afterwards be used to check if a change can be seen as an improvement. Identifying stakeholders and mapping initiatives will not provide this data.

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Comment 6. Line 62: 'a future electronic PI'.
The phrase 'a future electronic PI' is confusing because the PI already encompasses combinations of electronic information and analogue information. The product information (PI) consists of an SMPC, labelling, and a package leaflet. At the moment, the SMPC and the Package leaflet are already available in a variety of electronic formats. Only the labelling is guaranteed to be on a substrate such as paper, cardboard, blisters, glass, etc.

> Alternative: The aim of the ePI project might not be to develop 'a future electronic PI' but to 'reconsider the provision of information about medicines to increase the use of digital opportunities'. It is very likely that this will lead to a range of product information that takes the user, context, actions, and situations into account. It is not a single 'future electronic PI', but a system that provides people with reliable information about medicines in formats that are appropriate, relevant, and usable.

Comment 7. Line 64. 'the electronic format is the most pressing priority'.
The assumption that the electronic format is the most pressing might be incorrect.

There are several other issues that are directly related to product information such as 'dispensing errors', 'prescribing errors', and 'adherence'.

An EMA report in 2014 (EMA/20791/2014) revealed major problems in the dispensing of medicines in hospitals across Europe. The literature about prescribing errors is increasing (Cousins, Crompton, Gell, Hooley, 2019).

A second pressing issue is the adherence and self-administration errors. There are many definitions, methods, perspectives, and criteria to describe adherence, but there is a fundamental problem with the ways in which patients do not use their medicines in ways that would be optimally beneficial.

Standardising digital formats for information that is currently available in package leaflets and SMPCs will not do much to alleviate any of these problems. Basically, by focussing on the development of an electronic format, these issues become less important, with a delay in progress as a consequence.

> Alternative: Reconsider the priorities and make clear who would benefit from the introduction of electronic formats. The six recommendations of the European Commission need to be considered simultaneously to avoid that decisions to follow one recommendation block progress in others. It is essential to start from the perspective of different types of users and their needs. Starting from current digital opportunities is likely to be less effective because these opportunities are likely to change very quickly.

Comment 8. Line 65. 'as it will insure patients have timely access to up-to-date information'.
This phrase suggests that patients at the moment do not have timely access to up-to-date information. [Note: it looks as if 'insure' is used, where 'ensure' is

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meant?] It is a worthwhile aim that is worth striving for, but would it help to resolve issues related to adherence, dispensing errors, and prescribing errors?

There are four issues here.

a. Is it really possible to 'insure' that patients have access? This is an unlikely aim because achieving this depends on a practical situation and those are extremely varied.
b. Why does the focus shift to patients only? Shouldn't prescribers, pharmacists and consumers have 'access to up-to-date' information too?
c. What are the current risks of 'not having' up-to-date information?
d. The statement suggests that 'patients' can be seen as a homogenous group, and that this urge for up-to-date information is equally important for all medicines.

> Alternative: The interpretation of information varies between people, depends on the situation, and is likely to be partly incorrect. People are very well aware that the information they read might not be the most up-to-date, the most accurate, or the most reliable. Healthcare professionals are trained to check this. Patients gain experience and trust their doctors and pharmacists to provide reliable information. It seems necessary to investigate this in detail in order to provide information that is really effective and beneficial. The general aim to 'ensure that all patients always have access to up-to-date information' might not be attainable.

Comment 9. Line 65-66: 'coordination among the many initiatives ongoing in the EU'.

It is unlikely that the EMA and HMAs can coordinate initiatives of for example Amazon (online pharmacy, PillPack), FaceBook (discussions between patients, advertising), and Google (sequence of answers to searches). Furthermore, this scope excludes initiatives outside Europe. It is really necessary to look globally at this point because electronic information ignores European borders. Patients, healthcare professionals, and consumers do not distinguish where the geographical source of information is, as long as they can find what they need.

> Alternative: Focus on the core activity: providing reliable information about medicines to enable people to act appropriately. It is not possible to coordinate digital initiatives because these initiatives are not bound by European borders.

Comment 10. Line 74. 'to form the basis of follow-up implementation plans for ePI'.

In the light of the sixty six comments in this document, the Draft Key Principles will form a poor basis. The Key Priniciples start from several unsubstantiated assumptions, excludes essential scoping and benchmarking activities, excludes initiatives outside Europe, and ignores non-authorized digital resources.

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Alternative: Please reconsider this statement. In order to have any chance of success, it needs to be reversed:

Step 1 - Start from a thorough evidence base. Scoping studies, contextual enquiries, and literature reviews will provide a more complete description of the situation. The literature gives a clear first indication. There are a few hundred articles about the malfunctioning of package leaflets, and there is not a single article that is moderately positive about its effects. Furthermore, the medical literature as it is available in the medical databases such as PubMed is incomplete, because it does not take other perspectives into account. For example, the financial perspectives (costs and benefits), production perspectives (manufacturing leaflets), and environmental perspectives (waste, sustainability) are not included.

'Shortcomings' was the description of the European Commission in 2010 (2010/84/EU, amendment 18(b)). The current product information about medicines might be more accurately characterized as a 'system failure'. It is not effective for anyone, it is expensive for all, it is environmentally wasteful, and in many cases it is causing irreversible harm or death. There is no data that indicates that the current system of SMPCs and Package leaflets is effective, for an acceptable price, environmentally neutral, and does no harm to patients nor consumers.It only works because there is no alternative. Patients, consumers, and healthcare professionals cannot avoid dealing with poorly designed information and do their upmost best to cope. Unfortunately, despite all good intentions, this leads to high error rates, extra costs, and unnecessary anxiety.

Step 2 – Benchmark the current situation to find the most pressing issues. The selection of the most pressing issues cannot be done without benchmarks-experiments. Benchmarks tests will provide data that can be used afterwards to check if change can be seen as improvements, and if further improvements are required. Without benchmark data, it is impossible to gauge if a change has had any effect.

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Draft key principles on ePI in the EU (line 77 to 140).

Comment 11. Line 77. Key principles.

The Draft Key Principles are not related to the other recommendations of the European Commission (2017). They need to be considered and integrated in order to make sure they don't cause conflicts at later stages. Especially a reference to recommendation 3 *'Improving patient input in developing and testing of PLs'* is missing in the Key Principles document. Standardizing a 'semi-structured format' which is based on the order stated in Directive 2001/83/EC,

article 59.1 is in conflict with the recommendation of the Commission because it does not improve patient input.

Alternative: Integrate the key principles for digital information about medicines within a larger strategy that encompasses the other recommendations of the European Commission.

1.1. ePI

Comment 12. Line 88. 'and allows dissemination via the world wide web, e-platforms and print.'
This part of the definition is strange for two reasons.
1. it specifies media instead of aims.
2. it includes an undefined word 'e-platforms'. This word does not have a univocal meaning and will lead to confusion.

> Alternative: Describe the aim as '… and allows dissimination to optimally enable the users to act appropriately'. In this phrasing, there is a direct relation with the text of article 63 paragraph 2 of Directive 2004/27/EC, but it extends its scope from package leaflets only to all product information for medicines. The information in electronic format will not replace the information on paper: all formats need to be considered together.

Comment 13. Line 91-93: 'Semi-structured format', 'some structured elements (fixed headings and vocabularies), and some unstructured elements (i.e. free text)'.
The assumption is that the structure is provided in a sequential text format (= in words). Lines 103 and 104 state that '*this initiative should not be understood to change the interpretation of the European legislation*.' Lines 119 - 121 repeat this. The legislation for package leaflets states that information in the package leaflet *'must be given in the following order'* (Directive 2001/83/EC, article 59.1). If the 'semi-structured format' will not create new interpretations, than it is unavoidable that this semi-structured format will follow the sequence of the information elements in the package leaflet as it is now.

Three assumptions are made by the choice of this format.
1. 'information is sequential'. The order is set in a Directive. However, digital information can modify the sequence of information according to algorithms based on characteristics and previous behaviour of users.
2. 'information is presented at a single level'. Digital information makes it also possible to present information in different layers.
3. 'conventional text structures are the basis'. The 'fixed headings and vocabularies' are only available as words. Interpretation of digital information is guided by visuals such as pictograms, illustrations, colours, and patterns.

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Starting from the opportunities of electronic information, a set structure in text only might not be effective. A flexibility in structure, modularity on different levels, and the visual basis are common digital standards.

> Alternative: It seems essential to start from the activities that people need to perform when they must handle medicines. This includes at least prescribers, pharmacists, nurses, patients, and consumers. It also includes the people who develop and check information, such as the pharmaceutical industry, suppliers, and regulatory authorities. None of these need 'all the information' at the same time in the same format.
>
> Information needs to be divided in relevant 'chunks' that are presented in a sequence that is relevant to the user, on different levels, and guided by a visual structure.

Comment 14. Lines 91, 92, 93: 'Semi-structured format', 'some structured elements (fixed headings and vocabularies), and some unstructured elements (i.e. free text)'.

Starting with a list of structured elements in text is in conflict with both the 'principles of good information design' as well as with article 63 of Directive 2004/27/EC that states that information *'must enable users to act appropriately'*. One of the principles of good information design is to start from the activities that people need to perform. A semi-structured format with fixed headings and vocabularies cannot – as we have seen in the last 27 years for patient inserts – provide information that is suitable for all patients, in all languages, for all therapies, in all contexts, and for all medicines.

> Alternative: In order to have any chance of success, these need to be changed. In order to 'enable the users to act appropriately' (as is the current legislation), and to follow recommendation 4.2 of the European Commission, it is essential to figure out:
>
> a. what the actions are
>
> b. who the people are that must undertake these actions
>
> c. how these people can be supported to enable them to undertake these actions
>
> d. set performance based standards to verify if the action is executed appropriately.
>
> Standardizing a 'semi-structured format' is unlikely to enable people. It is essential - as one of the priniciples of good information design - to start from the different perspectives of different users.

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1.2. Common EU electronic standard.

Some comments about the 'Common EU electronic standard' (line 105 to 140).

Comment 15. Line 111: 'controlled vocabularies'.

In the definition, the words 'controlled vocabularies' are ambiguous. They can relate to a mark-up language such as sgml or xml where a limited number of words can have a meaning. Or they can relate to human languages where only a limited number of words can be used, and others are excluded. Only a mark-up language can have a controlled vocabulary. Standardising human languages is always detrimental for clarity over a longer period of time.

> Alternative: Clarify the phrase 'controlled vocabularies'. If 'human languages' are intended than it is not part of the 'technical features'. However, it is possible in the digital domain to modify the language according to the characteristics of the reader.

Comment 16. Line 111: 'regulators and stakeholders'.

In the definition, the 'regulators' and 'stakeholders' are distinguished from eachother. The group 'stakeholders' is not further defined and it is not clear which groups are incorporated.

> Alternative: It would be useful to see 'regulators' as one of the stakeholders. A statement like 'agreed by all stakeholders' would be more accurate. It might be easier to delete 'agreed by regulators and stakeholders' because it seems a superfluous statement. Any standard has to take the perspectives of all stakeholders into account.

Comment 17. Line 116: 'as well as'.

The words 'as well as' suggests that the standard consists of two systems: one to support the interlinked regulatory networks, and one for the dissemination of information for healthcare professionals and patients. This combination is not likely to be functional because the reasons to use a standard vary substantially between these two groups. The regulatory networks, in cooperation with the pharmaceutical industry, develops and controls ***the development*** of information. The second group '***uses the information***' to achieve their aims.

> Alternative: It might be more efficient to separate both systems: one that optimally support the registration of medicines in Europe. This system aims to optimally support the development. And a second system that makes information about medicines optimally accessible for those who need it. This system aims to support the use of information. At least, it is necessary to motivate why a single standard is preferred above two separate ones.

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Comment 18. Line 116: 'meeting the expectations of patients and healthcare professionals who travel and work in several EU countries'.
It is not clear why 'patients and healthcare professionals *who travel and work in several EU countries*' differ from 'patients/consumers and healthcare professionals' who do not. Is it really necessary to make this distinction? If this distinction is essential, on which basis was it established? Is it really consistent throughout Europe? Are 'patients and healthcare professionals who travel and work in several EU countries' a homogenous group?

> Alternative: It seems worthwhile to start from the idea that information is used by 'people who live in Europe', without continuously separating 'healthcare professionals', 'consumers', and 'patients'. [In many practical situations, these groups work together to improve health conditions.]

Comment 19. Line 118: 'A common standard enables the generation and dissemination'.
The words 'the generation and dissimination' indicate again that the system will consist of two separate parts. One to enable the development of information. This requires a dialogue between regulatory authorities and marketing authorization holders. The other system disseminates information about medicines to people in Europe. (See also comment 17.)

> Alternative: The benefits of a combined system need to be clarified. The aims of both parts, the people who have to work with it, and the people who benefit from it are very different. Of course, the results from the 'generation part' form the basis for the 'dissemination part' but both are used in very different contexts. The first part is used in a commercial-legal environment. The second is used in a medical-care environment.

Comment 20. Line 118: 'electronic authorised information'
The word 'electronic' is superfluous because a common standard already refers to an electronic standard'.

> Alternative: Delete 'electronic'.

Comment 21. Line 119: 'patients and consumers of medicines in the EU/EEA'
The description of the people who will be using the dissemination part of the system varies throughout the text. In the section 'Background' (line 50-72) the groups were described as 'healthcare professionals' and 'patients and consumers'. Healthcare professionals were further subdivided into those who are 'prescribing medicines' and those who are 'dispensing medicines'. It is not clear why healthcare professionals are not mentioned in line 118-119.

> Alternative: it is essential that all stakeholders are involved right from the start of the development of the standard. This requires a substantial

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'scoping activity' that aims to find out who the different groups of people are, if they can be seen as homogenous groups, and what their main needs and expectations are.

Comment 22. Line 122-129 'The aims of the common standard are:'.
Both parts of the standard - for the generation and dissemination - are clearly described. What is missing is a rationale why these two activities must be based on a single standard (See also comment 17 and 19).

Furthermore, the dissemination of information is not really the problem. The focus should be on the activities that people are enabled to do with this information. The assumption is that the dissemination will be beneficial for patients/consumers and healthcare professionals, because it will allow for an additional and tailored approach. However, the contents of the information will be similar - or identical - to the information that is provided at the moment in SMPCs and Package leaflets. It is not clear what the specific benefits are of the dissemination of the same information in an additional digital format.

It is unlikely that it is possible to provide a 'tailored approach' because the information of the electronic version must be based on the current legislation. The 'tailoring' is in conflict with the legislation, because it is obligatory that the information is 'full and comprehensible' and 'provided in a specific order'.

Alternative: It seems necessary to add a thorough reasoning why these two aims must be combined into a single common standard. It is likely that 'regulators and industry' might need a different standard from 'users of authorized information'.

The benefits of electronic product information must be specified. It is not sufficient to just to claim that this will allow patients/consumers and healthcare professionals an additional and tailored approach. It needs to be made clear what these groups can do with the digital information in addition to the paper versions.

Yes, information about medicines needs to be tailored to needs and wishes of individual users (patients, consumers, healthcare professionals). However, the legislation clearly states that the information for patients needs to be based on the SMPC (2001/83/EC, article 59), must be full and comprehensible (2001/83/EC, recital 40), and must be presented in a specific order (2001/83/EC, article 59). These three issues prevent the possibility to 'tailor information' if the interpretation of the European legislation will not change.

Comment 23. Line 123. 'Trusted information'.
The information is not 'trusted'. It is 'authorised'. Patients taking part in Readability tests often mention that the information in package leaflets is just there to 'cover their backs'. Patients are very well aware that the information in

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package leaflets is written by the pharmaceutical industry, and are suspicious about its reliability and appropriateness.

Alternative: Change 'trusted' to 'authorised'. Probably even 'authorised product information'.

Comment 24. Line 123. 'The aims of the common standard are: ... to create the technical foundation for the dissemination of trusted information in the electronic world.'

The 'creation of the technical foundation' that only consists of a 'mark-up language', and nothing else seems to set a very low standard that makes little use of digital opportunities.

Furthermore, the legally obligatory information has been found to have 'shortcomings'. Using this information that is known to be insufficient as the basis for dissemination seems incorrect.

Alternative: It seems that the aim could be written as: 'The aim of the common standard is to apply a mark-up language to the existing standardised information'.

Comment 25. Line 124 - 126. 'Which will allow' ... 'tailored approach' ... according to his/her need and/or wish ... suitable output forms and platforms'.

This is an unsubstantiated assumption because 'his/her need and/or wish' has not been established. These needs and/or wishes cannot be fulfilled if they are not investigated beforehand. It is not possible to define 'tailored' and 'suitable' without conducting systematic scoping and benchmarking activities with a variety of stakeholders. And it is very likely that there is a substantial variation within each group of stakeholders. Assuming that 'all patients', 'all consumers' and all 'healthcare professionals' have similar needs and wishes is probably incorrect. The Draft Key Priniciples document seems to suggest that it is possible to develop a common standard without involving patients, consumers, and healthcare professionals.

Furthermore, this approach will make the implementation of point 2 and 3 of the EMA action plan impossible. Basically, the development skips the first two steps of an information design process.

Alternative: Involve patients, consumers, and healthcare professionals in the development of electronic product information before unsubstantiated assumptions are used as a basis. This involvement also complies with recommendation 2 ('principles of good information design') and 3 ('improving patient input') of the European Commission (2017).

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Comment 26. Line 127. 'to offer possibilities to streamline, simplify and speed up the regulatory process'.

This is a very positive approach because it acknowledges that it is necessary to streamline, simplify and speed up the regulatory process. In order to do that, it seems essential to find out through scoping and benchmarking studies where the processes are not sufficiently streamlined yet, not simple enough yet, and slower than necessary. It is possible that digital technologies can be helpful, but it seems unlikely that these three aims can be achieved by introducing a mark-up language for electronic product information only. This raises the expectations too high because it suggests that the development of an ePI could really streamline, simplify, and speed up registration processes. Without looking at other potential factors in scoping studies, this is a high risk approach.

> Alternative: Both the regulators (= the European medicines regulatory network (line 115-116)) and 'the pharmaceutical industry' are not homogenous groups. It is likely that a scoping study will reveal that there is a substantial variety within these groups. Line 136-137 indicates this variety by mentioning the centralised and national levels. Asking a variety of stakeholders in these groups about the possibilities to streamline, simplify, and speed up the regulatory process is likely to reveal many suggestions. A mark-up language is likely to be one, but there will be many other ways too.

Comment 27. Line 130: 'Agreement of a common standard.'

It needs to be made clear who needs to agree on this common standard. If all relevant stakeholders need to agree, than it is essential to make sure that all stakeholders are directly involved. In the absence of measures to ensure that needs of different stakeholders are taken into account, only those of the dominant groups are served.

The double aim of dissemination and improving the regulatory process shows for example a different geographical scope. The regulatory process is only applicable in the European Union and some countries that might or might not apply it (Turkey, UK, Norway, Switzerland, Ukraine). The dissemination process is immediately global because healthcare professionals, patients, and consumers will search the internet and select the most likely reliable source. They are unlikely to distinguish what the geographical origin of information is.

> Alternative: It is necessary to make clear who needs to agree on this standard. There are different stakeholders and different processes that need to be separated because the 'needs' and 'expectations' vary substantially between stakeholders and within stakeholder groups. It is especially important to find out which stakeholders will be 'excluded' by this agreement.

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Comment 28. Line 131- 133. 'which would generate unnecessary complexity, impede access to information and require multiple interfaces between standards, restricting flow of data.'

Is there any evidence that these consequences will occur, or are these mainly 'based on fear'? It is of course beneficial to have a single standard, but multiple standards are very common in most areas and adding yet one more will only increase the complexity. How can EMA be sure that this 'new common standard' will not add to complexity, impede access, and require multiple interfaces'?

> Alternative: Although it is hard to predict the practical consequences of the introduction of a new standard, it is clear that there are both benefits and risks. It seems worthwhile to investigate which standards are currently used to develop electronic product information about medicines. Most countries do have a national pharmacopeia or compendia which are commonly used by prescribers. The pharmacy-information-systems include information for patients too. All are based on standards. Ignoring these existing standards will make it unlikely that potential digital cooperation will be optimal.

Comment 29. Line 136-137 'compatible with use at centralised and national levels.'

The first step is an agreement between centralised and national level. This first step therefore intentionally excludes patients, consumers, and healthcare professionals. It is therefore likely that this standard does not take their needs into account. Trying afterwards – after the standard has been established – to make it suitable for patients, consumers, and healthcare professionals is very likely to lead to failure. It is also in conflict with the second recommendation of the European Commission (2017).

> Alternative: The first steps in any design process are the scoping and benchmarking activities. These are essential to find out which stakeholders are involved, to find out how they cope at the moment, and to get actual data how successful the current performance is. Excluding stakeholders in the first steps is unlikely to be a good start of any project.

Comment 30. Line 138-139. 'available technical features, including those from the EU Telematics projects.'

The ePI project starts from the 'available technical features'. This is questionable. It would be more beneficial to start from the performance levels that need to be achieved through the provision of information: a reduction of errors, an increase in adherence, a reduction of waste, longer term sustainability, etc.

> Alternative: In line 110-111, these features are introduced as the basis of the common standard. In line 139-140 both 'vocabularies' and

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'interoperability specifications' are 'yet to be developed'. So the only thing that remains is the 'mark-up language' augmented by the features of the EU Telematics projects. The focus should be on 'enabling people to act appropriately', not on the available technical features. The first one is a long term vision, the second one will change within months.

2. Benefits for public health.

Some comments about the 'Benefits for public health' (line 142 to 182).

Comment 31: Line 142. 'Because of the benefits this format can offer for public health.'

'Can'? Is it possible to check the expected results first before a new system is implemented on a European scale? It seems essential to clarify the direct relations between the provision of information in an electronic format and 'public health' as a first step.

Alternative: One of the main risks is that the development of the ePI-standard will take a substantial amount of time. During this period, all other initiatives are postponed because there is little point in developing something that might be overruled later by an obligatory system. Based on the experiences with the development with databases and digital resources, in combination with a problematic financial funding system, it is very unlikely that this could take between 5 to 10 years. With sufficient funding, it might be in operation sooner.

This is simply not acceptable for patients. The focus might need to be on these most urgent 'benefits for public health' before embarking on yet another new and costly IT-system. An EMA report describes that medication errors occur in between 2% and 49% of administrations in hospitals based on data collected before 2006 (EMA, 2014). There is no reason to believe that these percentages have changed.

The current legislation states that information for package leaflets must '*enable users to act appropriately*'. Using that legal requirement as a guide for the electronic product information would be a good start. Furthermore, it would be good to develop and implement the database that is required in article 57, 1, l) of Regulation 726/2004. Both these suggestions do not require any changes in legislation, just a stricter adherence to the current legislation. The relations between 'public health' and 'electronic product information' can be investigated simultaneously.

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2.1. Expanding access to information on medicines as a public health imperative.

Comment 32. Line 149. 'because it will expand the dissemination of for all medicines in the EU.'
It is not clear how an expansion of the dissemination exactly benefits public health. There are very substantial 'shortcomings' in the current information, and making the same information available in a digital format might not result in the expected benefits. Just adding more-of-the-same information is unlikely to improve the shortcomings, and benefit public health.

> Alternative: One of the major benefits of information in an electronic format is that it can be modified by the reader so that it better answers their questions. This modification can affect the structure (sequence and level, links), language, and mode (verbal, visual, aural, or combinations of these). There is not much point in providing exactly the same information (as required by the legislation) in the same structure (order) and the same mode (text) in an electronic format.

Comment 33. Line 150. 'among other functions.'
This phrase does not provide enough detail. It needs a concise list of these other functions or at least give some examples which functions are meant.

> Alternative: The following functions could be used as examples:
> a. Reducing the risk of confusability of outer packaging. At the moment, it is likey that both pharmacists and patients have problems to differentiate different medicines because the design of packaging looks too similar. Electronic verification might be beneficial but is not always available.
> b. Integrating information on packaging and package leaflets with electronic information. The 2D barcode might be a possibility, or a specific url-code for medicines.
> c. ePI could check interactions between medicines, contra-indications, and suggest administration schedules based on data-mining across large groups of patients.

Comment 34. Line 151. 'Provision of the latest information on a medicine's safety, benefits and its conditions of use.'
Regulation 726/2004 (article 57, 1, l) already asked for a website with a very similar aim in 2010. It would be essential to find out what is happening with this now, and how it could be made to work for this purpose. This website is mentioned as *'the future European Medicines web portal'* on page 13 in line 348, but it is unclear how ePI will exactly be related to this website.

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Alternative: Integration of digital information is essential to reduce investment costs, maintenance costs, and confusion among users (patients, consumers, healthcare professionals).

It is essential to conduct a thorough scoping and benchmark study to establish what is available and how well, or how poor, this functions at the moment. Before it is possible to speak of an improvement, it is essential to find out how patients, consumers and healthcare professionals find, understand, and apply the latest information on safety, benefits, and conditions of use. This might not be equally important for all medicines in all contexts, and these differences could be used to develop appropriate standards and templates.

Comment 35. Line 152 – 153. 'Better delivery of information so that the right information is available to the right patient/consumer at the point of need'.
This statement suggests that patients cannot access the right information at the point of need at the moment, or not in all situations. Is there any evidence to support this assumption? Is it absolutely guaranteed that electronic product information will achieve a 'better delivery' of 'the right' information, to 'the right' patient/consumer, at the 'point of need'? Is there any evidence to support this assumption?

Alternative: Before a statement as 'better' can be made, it is essential to have benchmark data that can be used as comparison. Without benchmark data, it is not possible to be sure that a changed situation can be categorized as 'better'.

Comment 36. Line 154. 'Informed decision making by patients/consumers and healthcare professionals'.
This sentence suggest that this support is not available at the moment. It might be worth looking at practice how 'informed decisions' are taken at the moment, and which role the package leaflet and the SMPC play in that decision. It is correct that paper package leaflets are not available at the conversations between patients/consumers and healthcare professionals. Patient-prescriber, patient-pharmacist, customer-pharmacist, patient-hospital nurse, patient-hospital pharmacist, are some examples of these dialogues. However, the Draft Key Principles document assumes that a single electronic format - that is identical to the current information in the package leaflet and SMPC - will affect treatment decisions.

Alternative: This assumption really needs to be investigated thoroughly before it is suggested that these decisions 'will be supported'. If patients, consumers, and healthcare professionals are not able to make informed decisions, or must make 'better informed decisions', than we need to have accurate benchmarks first. Without benchmark data this suggestion might not be helpful because informed decisions could be influenced by very different information sources.

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Comment 37. Line 158. 'Patients/consumers and healthcare professionals using ePI can be fully confident that they hold the latest information about benefits, risks and use.'

It is essential to examine the current situation and find out how confident healthcare professionals, patients, and consumers are with the current supply of information. Is it really essential for these groups to be absolutely sure that they have the latest version? At the moment the websites of, for example MHRA, EMA, Electronic Medicines Compendium, BCFI, and Farmaceutisch Kompas all link to different versions of the same package leaflet of the same medicine.

> Alternative: It needs to be investigated how important it is for patients/consumers and healthcare professionals to be confident that they hold the latest information about benefits, risks and use? How do they check?

Comment 38. Line 157 'it will be possible'; line 161: 'is thereby expected'; line 163: 'should also facilitate.'

Can we accurately state the expected performance levels, and stop using indefinite phrases that make it very hard to check if any progress has been made?

> Alternative: Make accurate performance based indicators for these vague statements. Without measurable indicators, it is not possible to establish if a change can be seen as an improvement. For example:
>
> a. Modified ePIs will be updated within 24 hours after a change has been approved.
> b. ePIs support patients and consumers to make informed decision about their treatment. The criteria are relevant argument-structures, individual satisfaction, and an increased knowledge about a treatment.
> c. ePIs enhance interactions and discussions between patients and consumers and healthcare professionals. All groups are able to provide a structure for dialogues, use checklists, and a list of questions to check if information has been understood.

Comment 39. Line 161. 'to increase support to patients/consumers in informed decision-making about their treatment.'

This statement differs from the statement in line 154. 'Increasing support' indicates that there is support at the moment, but that this can be increased. The baseline level of support needs to be established through benchmark studies. It is likely that this varies according to the situation, context, and type of medicine.

> Alternative: It is really essential to have accurate benchmark data before these statements can be made. Furthermore, it is necessary to be absolutely sure that ePIs really can deliver this. Decision-making about a

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treatment is a fairly complex activity in which many information sources are required. The addition of ePI might not be the most effective way to support this process.

Comment 40. Line 162. 'And help them to adhere to their medication regimens, ultimately contributing to optimal outcomes.'
This is an unsubstantiated assumption. There is no evidence, not a single scrap, that there is a direct relation between the provision of information and adherence to medication regimen. The provision of information might lead to better outcomes, but this cannot be stated as a general statement. It really depends on the patient, the regimen, the context, the situation, and the expected outcomes.

Alternative: It is essential to have accurate benchmark data before these statements can be made. Investigating the direct relation betwen the provision of information and treatment outcomes has proven to be elusive. Although information is an essential ingredient of every medicine, it is not directly related to the activity of taking medicines safely.

Comment 41. Line 165. 'The structured nature of ePI will offer new opportunities to better tailor product information to the needs of individual patients/consumers.'
This looks at the provision of information from the wrong perspective. It suggests that it is possible to design a structure of information in such a way that it will benefit individuals afterwards. This is an incorrect assumption because the needs of patients/consumers must lead a variation of structures provided by ePI. It is also in conflict with the EU-legislation that states that information in package leaflets must be 'given in the following order' (2001/83/EC, article 59).

Alternative: Principles of good information design suggest that it is essential to start from the perspective of the user in order to 'enable the users to act appropriately'. Starting from a standardized structure of information is in direct conflict with this approach because it will not be suitable for all patients in all situations. It is unlikely that the same structure will benefit the activities of healthcare providers

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Comment 42. Line 166-168. 'Also, because ePI can be handled electronically and read by machines, ePI information can flow to other systems, such as electronic health records and e-prescribing systems.'
This looks at the provision of information from the wrong perspective. In order to flow to other systems, it is essential to establish first what these existing electronic health records and e-prescribing systems do and need to do. Without this scoping exercise, it is very unlikely that a new ePI structure can be easily integrated.

Alternative: Start with a scoping activity to find out which other systems there currently are and how they are used. This will provide a basis to

benchmark the existing situation. After the benchmark studies, and based on their results it is possible to develop a structure that can be integrated into existing systems.

Comment 43. Line 168-169. 'facilitating targeted delivery of the right information to the right patient/consumer at the point of need.'
This statement suggests that this is currently not achieved everywhere across Europe. It is unknown if this aim can be achieved without making clear beforehand what 'the right information' is, who 'the right patient/consumer' is and what the 'point of need' is.

Alternative: It really is more beneficial to turn this around and start from the perspective of people who need to use medicines information. The needs of patients, consumers, and healthcare professionals vary substantially. This variation is caused by different contexts, different expectations, different activities, different medicines, and different experiences. Ignoring all these, and suggesting that a single structured text format will be beneficial for all is an unsupported dream.

Comment 44. Line 170. 'Availability of regulator-validated ePI will counterbalance unreliable and spurious claims about medicines,'
This needs to be investigated before this claim can be made. Yes, there are unreliable and spurious claims about medicines, but a European approach wil not change this in a digital environment where national borders don't mean much.

Alternative: This really needs more research to find out if this is at all possible. The risk for patients of spurious claims needs to be investigated too. This might be overestimated or underestimated, and it might vary per country or per medicine.

Comment 45. Line 171-172. 'often widely spread through online and other forums,'
Is there any evidence that supports this claim, and are there data what the exact influence is on adherence, medication errors, and prescribing behaviour?

Alternative: There really is little reliable research to support this claim. For example, the complete PubMed database only mentions 'Facebook' six times (May 12th, 2019). Other social media are mentioned even less. This needs to be investigated before this claim can be made. It might not be equally applicable to all medicines in all countries.

Comment 46. Line 174. 'EMA and NCAs should work towards ePI to fulfil their mission to protect public health.'
This assumes that there is a direct relation between ePI and public health. This

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relation needs to be more detailed because not all areas of public health can be protected through the implementation of electronic product information.

This sentence also shows that 'regulatory authorities' can be further subdivided into 'EMA' and 'NCAs'. It is not clear why that division is especially relevant at this point.

> Alternative: The relation between 'public health' and the provision of electronic product information needs to be clarified. It might be possible to replace 'EMA and NCAs' by 'regulatory authorities'?

Comment 47. Line 177. 'The most up-to-date ePI version should be always easily available.'

The word 'most' is superfluous. Information is either up-to-date or it is not.

'Easily available' depends on the characteristics of the user. It is likely that there is a substantial variation between people who need to evaluate if electronic product information is 'easily available'. This might be possible for young, higher educated citizen, but less so for poorer educated elderly.

> Alternative: It is essential to set performance based standards together with all the other stakeholders. It will take substantial discussions to find a generally acceptable description of 'easily available'. The description is likely to differ according to the situation, for example in hospitals or elderly homes.

Comment 48. Line 178-179. 'To achieve this principle, ePI should be made available through various technologies and applications, including mobile scanning technology (such as a 2D barcode) on the medicine package.'

This is very odd because the information on the inner and outer packaging are part of the ePI. This would mean that the information on the inner and outer packaging must be made available through a 2D barcode on the outer packaging? Why is this necessary?

Furthermore, this would make original packaging essential to access digital information. This availability really depends on the context. A patient in a hospital with a tablet or phone does not have the medicine package. The name of the medicine might be handwritten or printed or on a label on an infusion bag and the 2D barcode is not there.

> Alternative: It is essential to explain 'various technologies and applications'. What exactly is meant? Does this include a website, or a modification of existing websites. Again, it is essential to start from the perspective of the user. Who needs to use information about medicines, what needs to be achieved, and what is considered to be a success? Just stating that 'various technologies and applications' make information available does not help much. Are patients, consumers, and healthcare professionals really able to use a 2D barcode to search for information in all circumstances? Who is excluded?

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2.1. Expanding access to information on medicines as a public health imperative.

Comment 49. Line 183. 'Accessibility to patients/consumers with diverse abilities.'
Shouldn't this include accessibility for healthcare providers too? Or do all prescribers, pharmacists, and nurses have perfect eye-sight, work in perfectly illuminated conditions, and have high literacy levels in all European languages?

> Alternative: A detailed scoping activity is necessary to make sure that the practical issues are correctly mapped out. The World Wide Web Consortium (W3C) has very detailed guidelines and advice on how to achieve this. Please follow these W3C recommendations.

Comment 50. Line 185-187. 'accessible to everyone, including patients/ consumers with print impairments such as blind and partially sighted people (e.g. use of large font size) and those with low literacy levels (e.g. audible formats).'
It is a fallacy that the accessibility of information needs to be based on the 'exceptions' who do not have 'sufficient eye sight' or have not acquired 'sufficient literacy levels'. The whole movement towards an 'inclusive society' - which is one of the key European principles - is ignored by this statement.

> Alternative: It is not really an 'option': it is absolutely essential to make sure that ePI follows the fundamentals of an 'inclusive society'. As stated earlier: In the absence of measures to ensure different user's needs are taken into account, only those of the dominant group are served.

Comment 51. Line 190. 'Current PDF and print copy formats of PI'.
Although the key principles exclude the use of PDF and print copy formats, and characterize these as 'unstructured formats' (line 93 - 94), they have proven to be useful in some situations.

> Alternative: Although it is correct to state that PDF and print copy formats of PI do not well serve all citizens equally, they certainly have their purpose. From the perspective of a patient or consumer, a PDF-document, or a document in Word are also 'electronic product information'. Suggesting that these formats are not part of the ePI creates an unnecessary and confusing division. All information needs to be available in all sorts of formats: whatever suits the user.

Comment 52. Line 192-194. 'In contrast with current PDF and print copy formats of the PI, the availability of ePI will allow third-parties, such as companies, not-for-profit organisations or patient/consumer groups, to convert the PI into accessible formats.'.

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This statement suggests that PDF and print copy formats cannot be converted into accessible formats. That is incorrect. There are several software solutions to make sure PDFs can be transferred into different formats related to accessibility. Patients/consumers are not the only groups who need accessible digital formats. Nearly all stakeholders would benefit from more accessible digital documents.

> Alternative: PDF and print copy formats can be converted into accessible formats in a standardised manner (example: Ghent Workgroup). This is not a reason to abandon these formats. There will be plenty of PDFs and print copy formats used outside the medical product information domain. People will be very used to these.

Comment 53. Line 196. 'ePI will be accessible by design.'
It is nice to see this phrase in a document like this. However, there are several other terms that should be mentioned here. The approach to develop ePI does not stand on its own. It is part of several societal movements that have specific names. A few of these are the World Wide Web Consortium standards for accessiblity (W3C), 'universal design', 'Inclusive societies', and the European Accessibility act.

> Alternative: It seems essential to relate ePI to these developments. Ignoring these is not really an option. Information about medicines really needs to follow the same principles as all sorts of other types of digital information.

3. Existing legislative framework

Some comments about the 'Existing legislative framework' (line 198 to 251).

3.1. Complementing paper package leaflet

Comment 54. Line 205. 'Since the current legislation does not require the use of an electronic version of PI, the use of ePI will not constitute a new legal obligation.'
The EMA-QRD template includes an optional statement: "Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu <, and on the website of {name of MS Agency (link)}>." Line 205 implies that it is possible that a marketing authorization holder does not provide, or does not allow, to publish the product information on the EMA-website?

> Alternative: The ePI does not really add much new information to information that is provided on the EMA-website for centrally registered medicines. For many medicines - and may be even all? - the information

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on the EMA-website is already available in an electronic format: in PDF-format or in Microsoft Word. Is the ePI just adding yet another format with the same information? It seems necessary to analyse which electronic information is already available on the EMA-website, find out which information about which medicines is required, and find out how people currently use the available electronic product information. Starting afresh, without considering what is available and without consulting current users (patients, consumers, healthcare professionals) first, might not be the most effective way.

Comment 55. Line 209. 'PLs are a valuable tool presented directly in the medicines package and therefore provided to all patients/consumers when they open their medicine.'

This statement is incorrect. Many patients in hospitals, nursing homes, and elderly homes do not receive a package leaflet when their medicines are administered. Furthermore, it is very questionable if package leaflets are really a 'valuable tool'. There is not a single scientific investigation that shows that people appreciate the contents or design. There are several hundred articles that show their shortcomings.

Alternative: The 'shortcomings' report by Nivel (PIL-S, 2014) clearly shows that Package leaflets are not very valuable for patients. In hospitals, they are discarded immediately. If pill pouches for multi drug dispensing are used, they are discarded too. It is likely, but it is essential to investigate this further, that the most vulnarable patients do not receive package inserts.

Comment 56. Line 210. 'The paper PL is particularly important for patients/consumers with low digital literacy (low ability to use digital devices effectively) or limited internet access.'

This is an assumption and a gross simplification of practical realities. There is little evidence for this sweeping statement. The design of the outer packaging and inner packaging is probably far more important for the safe and effective use of medicines by patients and consumers.

Alternative: This might be an incorrect assumption and it needs to be confirmed first through systematic scoping and benchmarking. Without these activities it is not possible to check afterwards if any progress has been made. Is it really possible to correctly identify a group of patients with 'low digital literacy' and ignore the internal variation within this group? Aren't there different levels of 'low digital literacy'?

Comment 57. Line 214. 'Generation of ePI does not involve any change to the content of the PI.'

It is clear that there is no intention to modify the legislation with regard to the information about medicines. However, the response of the EMA to the

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European Commission's recommendation in the 'Shorcomings report' states in 2017: *"This represents a unique opportunity to improve the information patients receive on their medicines, within the boundaries of the current legislation."* (EMA, 2017). The EMA suggests that the main improvements are patient's comprehension of the package leaflet and its readability by changing the language itself and the design and lay-out of the information. If the language and graphic design of the information is the only change, how can the three claims in line 151 to 154 be made? (See comments 34, 35, and 36). What does electronic product information exactly add in comparison to printed product information that these three claims can be achieved?

Alternative: The ePI offers several opportunities to make the legally required information easier to find and understand. There are at least five initial options:

a. It is possible to reduce the length of the product information. There is fairly strong research evidence that patients would appreciate a much shorter text (Fuchs, Scheunpflug, Götze, 2012). A lot of information can be hidden in specific circumstances. In combination with the characteristics of patients sections can be hidden. [For example: experienced patients with a chronic disease could choose to select only the information that is changed.]
b. Information can be made visual through the use of illustrations, pictograms, animations, and infographics.
c. The structure can be offered in a user-determined sequence.
d. External links can be included.
e. It is easy to include language options, so readers can select their own language.

These options can later be augmented by 'patient-to-patient' communication, blogs and newsletters, side effect warning schemes, personalised administration advise, and so on.

Comment 58. Line 216. 'The use of ePI will be a recommended innovation; however it is not mandatory'.

This is surprising. It is very likely that the pharmaceutical industry will wait until the practical value of the standard and ePI has been established. Until that time, very little will happen. Possible innovations will not be initiated or continued because it might not be compatible with the ePI standard. This approach will therefore stall initiatives and delay progress.

It is unclear why this is described as 'an innovation'. The only thing the electronic product information suggests is the use of a 'mark-up language'. This mark-up language can hardly be seen as an innovation: XML has been a recommendation of the W3C since 1998.

Alternative: It doesn't matter if it is 'mandatory' or 'innovative' or not. The pharmaceutical industry has already got the obligation to '*enable*

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users to act appropriately' (article 63 of Directive 2004/27/EC). Before any 'innovation' is recommended, it seems necessary to apply this current legislation.

Furthermore, a strict application of the EMA-QRD template and Readability Guideline has proven to lead to information that has 'shortcomings'. It should therefore be allowed and be stimulated to conduct pilot-tests and develop prototypes to find alternatives that really *'enable the users to act appropriately.'*

Comment 59. Line 217. 'The paper PL should include a statement directing to the ePI as the most up-to-date version of the PL.'.

At the moment, there is already a sentence in the EMA-QRD template. This sentence is: *"Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu<, and on the website of {name of MS Agency (link)}>."* It is not clear if the same webaddress can be used. Especially the language-selection of the ema.europe.eu website needs attention because the current EMA website is only available in the English language. This excludes large numbers of patients in Europe who do not read English sufficiently.

Line 179 mentions the use of a 2D barcode as a possible way to direct patients who read the package leaflets to the most up-to-date information.

And it is likely that many patients (and this needs further research) would select the digital version first, even before considering the paper package leaflet.

Alternative: The accessibility of the website needs to be thoroughly reviewed, designed according to best practice, following web standards and legislation, and tested in detail.

It might be possible to include only the 'most important' information in the package leaflet. This 'most important' information depends on the type of medicine, and the context in which it is used. A very short package leaflet can refer to an electronic version that contains all the required information and is presented in such a way that people can select what they want to see. However, the development of this combination of paper and electronic information needs to follow a normal design process that includes scoping, benchmarking, designing and testing activities.

Comment 60. Line 218. Missing information.

The Draft Key Principles document discusses the package leaflet, but does not include a section on the SMPC and inner and outer packaging. Section 3.1 is about the paper package leaflet. There are no sections on the inner and outer packaging, nor about the SMPC. Although these information sources are an integral part of the product information, they are not further mentioned.

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Alternative: It seems necessary to consider all product information for all types of users. The focus on package leaflets in section 3.1, without similar sections about SMPCs and labelling, does not give a balanced description of the issues related to information about medicines.

3.2. Open access to regulator-approved information only

Comment 61. Line 227-228: 'legislation). 'no additional information — either for promotional or other purposes — can be included in the ePI.'
This makes it nearly impossible to develop any applications or websites because it is neccessary to include wayfinding information to make the structure of the information clear. Menu's, buttons, symbols (home, index), search-functions, bookmarks, digital links, pop-up menu's are all excluded because they add information for a specific purpose.

Alternative: This is really a fundamental issue that cannot be dealt with later. In order to make information about medicines available in a digital environment, it is crucial to add a visual structure. This structure helps readers to find where they are, where they can go, and adds support to make strategic reading decisions possible. The current structure of the SMPC, the package leaflet, and the labelling fails to enable people to act appropriately. In order to make any information 'accessible' it is esential to allow that additional information is included in the ePI.

3.3. Data protection

No comments. This is fine.

4. Processes

Some comments about the 'processes' (line 252 to 323).

4.1. Governance

Comment 62. Line 284: 'The regulator should hold ePI data, as a trusted source for reliable medicines information.'
Before this statement can be made, it seems necessary to ask readers of current product information if the regulator is really seen as a 'trusted source for reliable medicines information'. The current product information is mainly written by marketing authorisation holders (MAHs), and it is likely that prescribers, pharmacists, patients, and consumers realise this. The role of the regulatory authorities is not mentioned, not introduced, and not explained.

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Alternative: In order to make this statement and to be really sure that people see product information on a website of a regulator as 'trusted and reliable', it is essential to investigate this. Without reliable and published data, this remains an unsubstantiated assumption that is unlikely to be correct.

Comment 63. Line 285-286: 'A pan-European medicines web portal.'
Regulation 726/2004 (article 57, 1, l) already asked for this website in 2010. It would be essential to find out what is happening with this now, and how it could be made to work for this purpose. This website is mentioned as 'the future European medicines web portal' on page 13, line 348. [See also comment 34.]

Alternative: The development of this pan-European medicines web portal will take many more years before it is operational. Until that portal is fully functional,digital information about medicines is poorly accessible, hard to understand, and difficult to use. The number of errors in prescribing and dispensing, the muddling of medicines by patients and consumers, and poor adherence figures will not be reduced. A pan-European website would be nice, but it is now essential to design the harmful and lethal events out of the system.

4.2. Flexibility in implementation

Comment 64. Line 299: 'All stakeholders, including pharmaceutical companies and regulators, will commit to implementation of the common electronic standard for creation of ePI for all EU medicines.'
This is in conflict with the text in line 215-216 stating that the use of ePI will be a 'recommended innovation; however it is not mandatory.' It is likely that, without a legal obligation, not all stakeholders will be equally enthousiastic.

Alternative: The approach is very questionable and based on hope, not on facts. It is essential to find other ways to convince stakeholders to join the development of ePI. The investment in time and effort should lead to tangible results with clear benefits for specific stakeholders. These benefits could be related to design and language, to improvements in strategic communication with patients and healthcare professionals, and to improvements in registration processes and standards. Other options are the support of disciplinary practices of nurses, doctors and pharmacists. Probably most prominent should be the search for convincing performance data that show that people are really enabled to act appropriately. And the benefits for a society in relation to sustainability and durability need to be considered. Without considering this range of benefits, it is unlikely that all stakeholder will commit to electronic product information.

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Comment 65. Line 306-308: 'In addition, handling ePI may be a significant burden for some Member States as well as certain companies such as micro, small or medium-sized enterprises (SMEs) and companies producing generic medicines.
Before this statement can be made, it is essential to figure out if the handling of ePI really is a significant burden and for whom. This can be done before ePI is standardised and implemented. The different groups of people need to be observed and interviewed in scoping activities, and benchmark tests will reveal the extend in which this burden exists and is perceived as a real problem.

> Alternative: Base the implementation of the ePI on benchmark data, not on assumptions.

Comment 66. Line 310: 'stakeholders must plan'
The word 'must' seems to be in conflict with the text in line 215-216 stating that the use of ePI will be a recommended innovation which is not mandatory.

> Alternative: Make sure that the stakeholders can rely on the status of EMA-documents. Either it is mandatory or it is not. If it not mandatory, there is no 'must plan' for stakeholders.

5. EU context
Some comments about the 'EU context' (line 324 to 372).

5.1. Multilingual ePI
No comments. This is fine.

5.2. Interoperability with EU and global initiatives
No comments. This is fine.

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Karel van der Waarde frequently publishes and lectures about information design and is on the editorial board of several journals. He is vice president Research and Education of the *International Institute for Information Design* (IIID, Vienna). He has taught in Brazil, USA, Canada, Turkey, India, Australia, and most EU-countries. Currently he is professor Visual communication at Swinburne University, Melbourne (Australia), and visiting professor at the FHNW Basel School of Design in Switzerland.

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