Mr Xavier Prats-Monné
Director General, DG SANTE
European Commission

Brussels, 2.12.2015

Dear Mr. Prats- Monné

RE: The **regulatory implications of the future implementation of safety features**

Although the implementation process of the Falsified Medicines Directive covers quite a broad spectrum of consequences, we are writing to you to address **one particular aspect of the implementation process- the regulatory pathway to implement safety features by the Marketing Authorisation Holders (MAHs).**

We would like to express our concern regarding the regulatory impact of the implementation of the safety features (2D matrix code and tamper verification feature) according to the Falsified Medicines Directive. We call for the implementation **process to be carried out without variations or formal notification process in accordance with Art 61.3 of Directive 2001/83/EC.**

The industry recently learned of the intended decision for the implementation of the unique identifier to be included with the next regulatory action concerning product information (including renewals). If there is no regulatory action within 3 years of publication of the delegated act, then a notification in accordance with Art. 61(3) of Directive 2001/83/EC should be submitted.

The industry is very concerned by the magnitude of the workload for both authorities and the Marketing Authorisation Holders created by choosing a notification under Art 61.3 of Directive 2001/83/EC as a way of implementing safety features and **calls on the European Commission, the EMA and the EU MS to revise their position and to avoid a notification as the regulatory pathway to implement a unique identifier/ 2D barcode.**

The industry proposal

- The industry calls on the European Commission and all MSs to waive the notification process in accordance with Art 61.3 related to the implementation of the unique identifier and tamper verification features on the packaging at both European and national levels.

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- The industry calls for a very pragmatic and burden-free process avoiding administrative workload for both authorities and the industry based on
  - the self- responsibility of the industry to implement the unique identifier on the outer packaging in a way that does not negatively affect the readability of the text on the box
    - In case of doubt, the MAH will proactively approach the competent authorities to agree on a new layout

In view of the extremely high number of marketing authorisations that are affected by this measure, the implementation process should not result in any unnecessary workload burden affecting the industry and national competent authorities.

The industry would be happy to discuss with the EU Health Authorities the most practical and simple way of informing them about compliance with the legal obligation to implement safety features (if absolutely necessary from the Authorities' point of view), but the Art 61.3 notification proposal is clearly too burdensome and resource consuming for both industry and authorities.

We are very much looking forward to your support in applying a pragmatic solution to the implementation process which does not place any unnecessary burden on the authorities and industry.

Yours sincerely,

CC :
Andrzej Rys, DG Sante, Director Health Systems and Products
Stefano Soro, DG Sante, Unit D6
Sabine Jülicher, DG Sante, Unit D5
Guido Rasi, Excecutive Director, EMA
Peter Bachmann, Chair of the CMDh
Klaus Cichutek, Chair of the HMA Management Board

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Annex 1

Justification

The industry calls for the avoidance of notification under Art 61.3 as a regulatory pathway to implement safety features.

1. Reference to the notification guidelines

In view of the legal provision to Art 61.3 in Dir 2001/83 and the relevant CMDh SOP on Art 61.3 Notification: "*leaving the decision on changing the layout of information on packs to local national arrangement*", **all MSs can waive the notification process related to implementation of the unique identifier on the packaging at national level** as contradictory to pursue their primary objectives by investing their resources in protecting public health and assessing the Quality, Safety, and Efficacy of medicinal products.

2. Self-regulation and legal responsibility of the industry to implement the safety features

The MAH will in any case be obliged to follow the legal obligation of introducing the unique identifier and anti-tampering features as spelled out in the Delegated Act.

The industry calls for very pragmatic and burden less process without administrative workload on both authorities and industry based on self- responsibility of the industry to implement the unique identifier on the outer packaging in a way not affecting negatively the readability of the text. In case of doubts, the MAH will proactively approach the competent authorities to agree on a new layout. The guideline on general compliance principles can be agreed with the industry and be published by the EMA/CMDh.

The compliance can be also checked during the routine inspections or routine and random market surveillance.

In view of the extremely high number of marketing authorisations that are affected by this measure, the process of implementation should not result in any unnecessary burden in view of the workload affecting the industry and national competent authorities.

The MAHs would be happy to discuss with the EU Health Authorities the most pragmatic and simplified way of informing them about the compliance with the legal obligation to implement the safety features (if absolutely necessary from the Authorities' point of view), but the proposal of the Art 61.3 notification is clearly too burdensome in the sense of resource consuming for both industry and authorities

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3. Negative consequences of Notification: increased burden on Competent Authorities and practical hurdles for implementation of the safety features by industry

Although "notification" seems to be a less burdensome, straightforward solution and stipulates very limited regulatory activities, in reality it has significant implications on authorities and companies. The practical consequences are as follows:

3.1Workload for the authorities

The number of regulatory actions concerning the product information submitted each year to the competent authorities is insignificant compared to the total number of marketing authorisations of medicines in the EU. Based on statistics of the Art 57 database (500.000 MAs in total , thus probably around 350.000 MAs in the EU for prescription medicines), this would mean that, for a period of 3 years, the EU competent authorities would receive 1 notification per minute to be assessed for the implementation of the safety features. This will completely block the system from assessing changes and will divert resources necessary to assess changes important from a public health/patient perspective to assessment of changes irrelevant from public health, quality, safety and efficacy perspectives.

3.2. Workload for the industry

As a part of the notification process, the submission of an application form and a mock-up is usually expected for each pack of each MA. The mock up will include a "fake 2D barcode" as the "real one" will differ for each pack released to the market.

There is no real benefit from the patient/public health perspective to submit this massive number of notifications. Member States will be able to assess only the "space for the 2D barcode" (or the location of the "fake code") on the pack of a medicinal product as the unique identifier will be "unique" for each pack. Thus, the implementation of safety features through a formal regulatory process creates a huge unnecessary administrative burden for both industry and regulators, and yields no public health benefit.

Different requirements among the MS related to submission of mock-ups will add even greater complexity to the process.

Due to the characteristics of Article 61 (3) procedures, i.e., grouping/worksharing, typical for the variation process, use of such submissions will likely be impossible for a notification process.

3.3 Link to another regulatory process

Significant amount of MAs (especially non-CAP) will not be able to benefit from the next regulatory action concerning product information (including renewals and changes to

product information). The majority of MAs in the EU have already been renewed. For generic medicines with well-defined safety and efficacy profiles, changes related to the product information are less frequent than for newly authorised NCEs (mainly via CP), thus the chance to link the implementation of 2D barcode to a variation affecting product information is much lower. In addition, the linking the process to variation will have a big impact on manufacturing environment (see point 2.4). Thus, the negative impact on the generic medicines industry, with a traditionally large portfolio and large number of MAs, will be very significant.

3.4. Impact on manufacturing and technical operations

From a practical point of view, manufacturers will be ready to implement the safety features on packs once the packaging line is upgraded. Packaging lines are not dedicated to a single product but to several products and operate according to supply requirements. These processes can take place internally, but also externally (e.g., with a third party manufacturer). Once a line is adapted, all products packed on that line should be preferably packed to include the safety features.

Different pack sizes/ pharmaceutical forms are likely to be packed at different packaging lines, so the implementation of the safety features for the various packs of the same product/MA will be possible at different times, as this is related to the readiness of the production line to implement the safety features.

The MAH has an obligation to implement a “new version” of amended PIL/ packaging at the next round of printing or in 6 months (whatever comes first) which creates some logistic challenges in manufacturing environment.

Relying on another regulatory process (variation to the PIL/ SmPC, which is still very unpredictable from the timeline perspective and varies significantly in practice between MS) will create huge complexity in handling the production in practice (a pack for product X will already have a unique identifier for country A but not for country B; product Z will be “ready” to bear safety features but Product Y still not, although they will be manufactured on the same production line). In practice, it will be impossible to check for each and every product whether the implementation has already been notified or not and whether the pack has been approved as a part of another regulatory process.

For the supply of medicines in Europe, the generic medicines industry alone operates 12.000 packaging lines (see EC impact assessment on the FMD). To upgrade the lines, it would be extremely complex to take into account the regulatory status of a product for the adoption of the safety feature on the pack of the medicinal product.

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3.5. External readiness of the European / National systems to control safety features

The implementation of the unique identifier on each box will be also highly correlated to the readiness of the system on country level to scan 2D barcodes and to connect to the database (EU Hub) which is again a very challenging to combine with the regulatory status of each outer packaging of medicinal product.

3.6. Significant costs still associated with a Notification process

Based on the survey (see annex 3), the notification process for one MA costs up to 4767 EUR per 1 MA/ 1 notification process (if submitted to all EU MS).

In view of the estimated 350.000 MAs in the EU for prescription medicines, the total cost of the notification process for the industry will be still significant (although it is difficult to make an exact calculation, costs for the industry associated with notification process may even reach up to 50 mln EUR).

The industry has already invested 20 mln EUR in the implementation of the verification system by building an appropriate infrastructure to detect falsified packs (European Hub plus national systems connected to the EU hub).

As noted above, for the supply of medicines in Europe, the generic medicines industry alone operates 12.000 packaging lines (see EC impact assessment on the FMD). Upgrading all these packaging lines will cost the generic medicines industry at least € 1 billion EUR.

The notification of changes to packaging entails additional costs (fees plus human resources) with practically no added value for patients/ public health, which is contrary to the principle of better regulation and cutting red tape announced by the EC as one of the key priorities of President Junker's strategy.

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Annex 2:

Legal and guideline provisions

Proposed solution in view of the legal provision to the Art 61.3 in the Dir 2001/83 and the relevant CMDh SOP on the Art 61.3 Notification:

Based on the CMDh SOP related to art 61.3 Notification- leaving the decision on changing the layout of information on packs to local national arrangement - all MS shall waive the notification process at the national level as contradictory to their objectives to spend their resources on protection of public health and assessment of the Q, S, E of medicinal products.

Text		Excerpts
Directive 2001/83/EC, as amended	*Notification*	*Article 61* 1. One or more mock-ups of the outer packaging and the immediate packaging of a medicinal product, together with the draft package leaflet, shall be submitted to the authorities competent for authorising marketing when the marketing authorisation is requested. The results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority. 2. The competent authority shall refuse the marketing authorization if the labelling or the package leaflet do not comply with the provisions of this Title or if they are not in accordance with the particulars listed in the summary of product characteristics. 3. **All proposed changes to an aspect of the labelling or the package leaflet covered by this Title and not connected with the summary of product characteristics shall be submitted to the authorities competent for authorizing marketing. If the competent authorities have not opposed a proposed change within 90 days following the introduction of the request, the applicant may put the change into effect.** 4. The fact that the competent authority do not refuse a marketing authorization pursuant to paragraph 2 or a change to the labelling or the package leaflet pursuant to paragraph 3 does not alter the general legal liability of the manufacturer and the marketing authorization holder.
		EMA: In order for a 61(3) Notification to be valid:

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		• the change must affect only the Annexes IIIA (labelling) and/or IIIB (PL), with no changes to the SmPC and/or the Annex II. In addition, • the changes must affect the English labelling and/or PL text, with consequential amendments to all other language versions. **HMA: (SOP on the Art 61.3 notification)** 3. Changes to information agreed on a national basis, for example the content of the 'blue box' information, or changes resulting from a translation issue, are outside the scope of this procedure and should be agreed with the Member States concerned according to national procedures. 7. Local national arrangements will continue for changes such as changes in the local representative on the PL, layout of information on packs and in package leaflets, translation issues to DC/MR authorised products. Regulatory practice: there is a requirement to provide an application form and mock-up of the proposed sales pack on submission (incl. barcode), but in many cases a fake barcode is used here. The MS have different requirements related to submission of mock-ups.

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Annex 3: Notification in accordance with Art 61 - Costs: overview
Conclusion: Total costs: 4767 EUR per 1 MA/ 1 notification process across the EU

MS	Price in Euro	Remark
AT	0	
BE	761.77	for several MA in parallel 609,42
BG	No data	
CY	No data	
CZ	222	
DE	300	560 in RMS role
DK	0	
EE	0	
ES	1249	366,49 € for any additional one
GR	510	as IA
FI	0	
FR	0	
HR	150	
HU	67	
IS	230 (30.000 ISK)	IS RMS in DCP: 77.000 ISK
IE	250	
IT	0	
LT	158	
LU	0	
LV	142	
MT	0	
NL	0	
NO	0	
PL	96	
PT	0	
RO	250	
SE	0	
SI	100	
SK	0	
UK	282 (207 GBP) first	140 (103 GBP) second strength

Timeline: 90 days; if the authorities do not oppose the change- it can be implemented in practice

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