EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 January 2016
EMA/467700/2014
Human Medicines Evaluation Division

Lessons learned from the review of the labelling of centrally authorised pandemic vaccines

1. Background

The 2009 pandemic outbreak experience showed that due to the urgency of the situation and the logistical constraints that pharmaceutical companies faced to make vaccines available in a very short time, the review of the labelling (outer/immediate packaging) and the package leaflet was a challenging exercise.

Applicants prepared labelling material in advance hence, modifications affecting the labelling and the package leaflet which arose during the EMA review process were very difficult to implement. Labelling material which had already been printed could not be easily changed without incurring delays to the supply of the vaccines.

Furthermore, package leaflets were quickly outdated and did not contain the most up-to-date approved information. Modifications affecting the labelling were submitted in a very short period of time and this led to multiple versions of labelling being reviewed up to the latest stage of the approval process.

Some applicants opted to use, on the vial labels, a 'generic' name such as "*<Pre-pandemic> <Pandemic> Influenza Vaccine*" (only the outer carton and the package leaflet displayed an invented name). This raised significant issues, in particular with regards to the traceability and identification of the vaccines.

The experience during the 2009 pandemic outbreak also showed that the display of the critical information on the outer and immediate labelling was affected by various factors. Some of these factors are not specific to pandemic vaccine labelling and could affect any type of medicine labelling. However, it is the particular nature of a pandemic situation (i.e. mass vaccination, vaccines available from different manufacturers, different handling instructions…etc.) which required a careful review of factors which could have potentially affected the readability of pandemic vaccine labelling.

2. Scope

The scope of this document is to provide guidance on the preparation of labelling for pandemic vaccines, in the light of the experience acquired during the 2009 pandemic outbreak.

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3. Legal basis

This document has to be read in conjunction with:

- Articles 54, Article 55 and Article 59 of Directive 2001/83/EC laying down the information that must appear on the outer and immediate packaging information and the package leaflet of medicinal products.
- The revised checking process of mock-ups and specimens of outer/immediate labelling and package leaflets of human medicinal products in the centralised procedure (EMEA/305821/2006).
- Guideline on clinical evaluation of new vaccines – Annex: SPC requirements (EMEA/CHMP/VWP/382702/2006).
- Guideline on the readability of the labelling and package leaflet of medicinal products for human use (Revision 1, 12 January 2009).
- Recommendations for the implementation of the exemptions to the labelling and package leaflet obligations in the centralised procedure (EMA/276177/2015 rev.2*, 13 May 2015).

4. Definition

As stated in the Readability guideline, a mock-up is "*a copy of the flat artwork design in full colour, presented so that, following cutting and folding where necessary, it provides a replica of both the outer and immediate packaging so that the three dimensional presentation of the label text is clear*".

5. Problem statements

5.1. Printing of final labelling material

During the 2009 pandemic outbreak, pharmaceutical companies stockpiled sufficient quantities of vaccines in order to be ready once the vaccination campaigns started. This led to a situation where all the pharmaceutical companies had already printed labelling material prior to the submission to the competent authorities of a variation to include the pandemic strain. Thus, changes requested by the Agency could not fully be addressed.

Outcome:

The timing of the submission of labelling mock-ups is a key factor. Mock-ups should be submitted for review to the Agency prior to the printing of labelling material. Taking into account the urgency of the situation, the Agency will offer as early as possible reviews of the mock-ups to ensure that no delays occur in the delivery of vaccines. Due to the particular nature of a pandemic situation where many modifications can occur and in a very short time, the possibility that once the Commission Decision is granted, these draft versions of the mock-ups may not be in line with the latest approved Annexes.

It is important to note that any review of labelling mock-ups prior to the approval of the product information is intended to help pharmaceutical companies in the development of the labelling mock-ups and to streamline the review by the Agency of the labelling mock-ups during the evaluation procedure. It is not a 'pre-approval' by the competent authorities. Only the product information attached to the Commission Decision can be considered as authorised by the competent authorities.

5.2. 'Generic' labelling

During the 2009 pandemic outbreak, some pharmaceutical companies opted to use, on the vial labels, a 'generic' name such as *<Pre-pandemic> <Pandemic> Influenza Vaccine* (only the outer carton and the package leaflet displayed an invented name).

The rationale for the use of these labels presented by these companies was that the 'generic' name supported the use of the vaccine during either the pre-pandemic or the pandemic phases and that the label was developed with the intention of being used globally.

However, during the review performed by the Agency, the use of a generic vial label which did not display the invented name was considered to have some implications regarding batch traceability and correct identification. This is particularly important in the light of the different clinical use of the pre-pandemic and pandemic influenza vaccines.

To overcome the traceability and identification issues and as an interim measure, a recommendation was included as risk minimisation measure to use peel-off stickers displaying the invented name and the batch number.

The number of peel off stickers matched the number of vaccine doses in the carton. In some cases, the vaccine cartons were not big enough to also contain the peel-off stickers hence these were provided in separate cartons. However, this was considered an additional source of errors and confusion as mix-ups could be possible at the time of vaccine administration when the vials are taken out of their original outer carton, especially in mass vaccination centres where large amount of vials from different batches are stored.

As the number of stickers had to be the same as the number of doses in the carton, when further data showed that a half dose could be administered for some products, the number of peel off stickers in each box had to be adjusted which proved to be very difficult and yet again another source of errors.

Outcome:

The use of generic labelling is not accepted by competent authorities as it does not display the invented name, the type of vaccine and, therefore, does not allow the correct identification of the vaccine (in particular by the healthcare professional administering the vaccine). This also affects the correct use of the vaccine, its traceability and the reporting of adverse reactions. Furthermore, pre-pandemic and pandemic vaccines are two separate marketing authorisations which could cover different strains and which, therefore, require different labelling.

The use of generic labelling can also be a source of confusion between different vaccines from different manufacturers which can be available on the market, notably within the same vaccination centre. Healthcare professionals might never know the invented name of the vaccine they are using and they will report adverse reactions attributed to just "a pandemic influenza vaccine".

The use of peel-off labels for traceability purposes is common practice and recommended for vaccine labels. In general, these labels are composed of two parts, one part which remains affixed to the vial and another part that can be peeled-off and affixed onto the patient record. These peel-off labels always display the invented name on both parts of the label and never come as separate sheet of peel-off stickers.

It has to be noted though that in case of multi-dose vials and to allow attachment to a number of patient records, separate sheets of peel-off stickers mentioning the information described above will have to be included in the cartons.

5.3. 'English only' labelling

According to Articles 54, Article 55 and Article 59 of Directive 2001/83/EC, the particulars for labelling shall appear in the official language or languages of the Member State where the product is placed on the market. However, during the 2009 pandemic outbreak and due to the urgent situation, pharmaceutical companies were not in a position to supply the labelling and the package leaflet in all language versions. Some pharmaceutical companies wanted to develop an English only vial label and were asked to liaise directly with the Member States for the acceptability of such label.

Outcome:

The EU legislation provides specific provisions to permit exemptions from labelling requirements. According to article 63 of Directive 2001/83/EC, where the medicinal product is not intended to be delivered directly to the patient, or where there are severe problems in respect of the availability of the medicinal product, competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet. They may also grant a full or partial exemption to the obligation that the labelling and the package leaflet must be in an official language or official languages of the Member State.

On this basis, the Guideline on the packaging information of medicinal products for human use authorised by the Union (Revision 14.2, April 2015) foresees that:

• Requests for exemption regarding language should be addressed to concerned national competent authorities.

• Requests for exemption regarding particulars to appear on the labelling must be addressed to the Agency.

5.4. Outer labelling

According to Art.54 of Directive 2001/83/EC, the full requirements should be displayed on the outer labelling. Moreover, the pack design should also take into account recommendations as given in the readability guideline.

The 2009 pandemic outbreak experience showed that considering the particular setting of mass vaccination centres, key information to help healthcare professionals to correctly administer the vaccine was not displayed prominently enough on the outer carton.

The risk of medication errors was considered to be higher in these particular settings also due to the fact that healthcare professionals within the same vaccination centre could be handling different vaccines from different manufacturers and the handling/administration of the vaccines might not always be the same.

Outcome:

In order to avoid potential medication errors in additional to the critical information (invented name, pharmaceutical form, common name), the following other key information should always appear prominently displayed on the main panel of the outer labelling:

Other key information
1. Route of administration

Other key information
2. Total volume of the vial
3. A statement on the fact that it is a multi-dose vial
4. Shelf life after mixing/reconstitution
5. Mixing/reconstitution instructions (e.g. “suspension to be mixed with X before use.”)

Pharmaceutical companies should also use the package design/lay-out to make prominent the above information.

5.5. Small immediate labelling

During the 2009 pandemic outbreak, it was noted that the readability of the information on small immediate labelling was affected by factors such as the use of very small size labels, the amount of information and number of languages displayed on these labels and the type of label (e.g. concertina label, etc…).

When a vaccine was presented as an adjuvant vial + antigen vial, the risk of confusion between the two vials was higher. This was especially significant when the design used on the outer carton was not carried over to the vials and when the two containers were very similar.

Outcome:

The choice of the size of the label is often dependant on the type of containers commonly used for vaccines i.e. small vials and pre-filled syringes and it is acknowledged that the space available on these small containers can be very limited.

It is important that the biggest size label suitable for the concerned vial/pre-filled syringe is always used to ensure that readability is not impaired.

However, the use of a large label might not be enough to fully address the lack of readability and may prevent inspection of the vaccine’s appearance. As the 2009 pandemic outbreak proved, there may also be a need to simplify as much as possible the text of the minimum requirements to be displayed as stated in Art.55(3) of Directive 2001/83/EC. It must be noted that the simplification of the wording of the minimum requirements is only possible as long as the full requirements are available on the outer labelling (Art.54 of Directive 2001/83/EC).

According to Art.55(3) of Directive 2001/83/EC the minimum requirements to be displayed on a small immediate labelling are:

- *Name of medicinal product (including common name), if necessary, the route of administration*
- *Method of administration*
- *Expiry date*
- *Batch number*
- *Contents by weight, by volume or by unit.*

As vaccines are to be only administered by healthcare professionals and that additional information is also distributed to healthcare professionals in other formats (i.e. specific training material, instructions for use sheets, …etc.), the option to simplify the wording of the minimum requirements to be displayed on small labels in order to improve readability can be considered.

Particular attention should also be given to the location and the prominence of the minimum requirements displayed on the labels as this will also contribute to the appropriate selection of the vaccine and the clear differentiation between different vaccines available within the same vaccination centre.

During the 2009 pandemic outbreak, the Agency consulted the Vaccine Working Party to propose some text simplification and it was agreed that the information to be displayed on the antigen vial label and on the adjuvant vial label should at least contain the following information and if space permits other information could be included:

a. Antigen vial label:

Minimum requirements for the antigen vial	**Core labelling**
1. Name of the medicinal product	Antigen for {(INVENTED) NAME OF PRODUCT} {pharmaceutical form}
	<Pandemic Influenza vaccine {strain}> or <Pre-pandemic Influenza vaccine {strain}> **Examples for the display of the strain:** *{A/California/7/2009 (H1N1)v X-179A}* *{A/California/07/2009 (H1N1)}* *{H1N1}*
	{Route of administration} *(Full term as per Standard Terms, space permitting, otherwise abbreviation)*
2. Method of administration	Mix <with><into><adjuvant vial> before use
3. Expiry date	EXP
4. Batch number	Lot
5. Contents by weight, by volume or by unit	x ml <After mixing with <adjuvant vial>: <x dose><x doses of y ml>>
6. Other	Storage conditions *(space permitting)* Shelf-life after reconstitution *(space permitting)* <After mixing: use within {x}<hours> <days>>
	MAH name *(full name, space permitting, otherwise MAH logo)* <Address> *(space permitting)*

b. Adjuvant vial label:

Minimum requirements for adjuvant vial	**Core labelling**
1. Name of the medicinal product	Adjuvant for (INVENTED) NAME
	{Pharmaceutical form}

Minimum requirements for adjuvant vial	Core labelling
	{Route of administration} *(Full term as per Standard Terms, space permitting, otherwise abbreviation)*
2. Method of administration	Mix <with><into><antigen vial> before use
3. Expiry date	EXP
4. Batch number	Lot
5. Contents by weight, by volume or by unit	x ml <After mixing with <antigen vial>: <x dose><x doses of y ml>>
6. Other	Storage conditions *(space permitting)* Shelf-life after reconstitution *(space permitting)* <After mixing: use within {x}<hours> <days>>
	MAH name *(full name, space permitting, otherwise MAH logo)* <Address> *(space permitting)*

When a vaccine is presented as an adjuvant vial + antigen vial and in order to aid identification of the vaccine, the design used on the outer carton should be carried over to the vial labels.

Moreover, when the vials are very similar, colours should also be used onto the antigen/adjuvant vials flip-off caps to differentiate them.

5.6. Multi-dose vials

Multi-dose vials are not routinely used in the European Union for vaccines. However, due to the large-scale immunisation program during the 2009 pandemic outbreak, pharmaceutical companies delivered the vaccines in multi-dose vials. The information/instructions provided to healthcare professionals on the handling of multi-dose vials did not adequately address key aspects regarding the correct handling of this type of vials. Compared to single use vials, the potential risks for contamination of multi-dose vials is much higher.

During the 2009 pandemic outbreak, it became clear that the pandemic vaccination campaign was organised differently between Member States. In one case, the instructions about the handling of the multi-dose vials had a direct consequence on the national vaccination campaign since fixed-needle syringes were purchased by the Member State while the vaccine instructions required that the dose be withdrawn with a needle that had to be then replaced with a different needle for administration.

Outcome:

When multi-dose vials are used, specific key information about their correct handling should be included as part of the information/instructions to healthcare professionals to ensure the safe use of the vaccine.

The information/instructions should aim to ensure that multi-dose vials are correctly used to prevent transmissions of diseases, to avoid vial contaminations and to minimise potential risk of medication errors.

During the preparation of the information/instructions for the handling of the vaccines, early discussions with Member States should also be envisaged, ideally with the participation of healthcare professionals. This will make sure that from the handling viewpoint, all the above aspects are covered and compatibility with the concerned Member State vaccination scheme is thereby assured.

Pharmaceutical companies are also encouraged to reduce the number of multi-dose vials for use in a potential pandemic and to consider the use of single dose vials.

5.7. Labelling impact for a posology change from full dose to half dose

During the 2009 pandemic outbreak and following the posology change from full dose to half dose (for paediatric population) for some products, pharmaceutical companies proposed not to specify the number/volume of doses on the vial/pre-filled syringe label, but only to display the total volume of the container; this would allow more flexibility to fill/label the vials and pre-filled syringes without any discontinuation in production.

With regard to pre-filled syringes, the posology change from full dose to half dose for some products had an impact on the use of the pre-filled syringe presentations since the marketed pre-filled syringes were not graduated to accommodate the administration of different doses.

Outcome:

Because of the specific nature of multi-dose vials, it was agreed that the fact that half a dose may be used would be clearly stated in the SmPC and the package leaflet while the labelling would only display the total volume of the vial.

For pre-filled syringes, similar to the practice for seasonal vaccines and in view of the possibility that a half dose could be administered, a mark on the syringe barrel should indicate up to where the contained volume should be discarded, prior to administration. Information on the need to discard volume from the syringe for particular doses should also be clearly mentioned in the SmPC and package leaflet.

5.8. Package leaflet

During the 2009 pandemic outbreak and due to the on-going scientific assessment, the package leaflets included in the packs were quickly outdated and did not contain the most up-to-date, approved information by the competent authorities.

The Agency recommended the inclusion of a statement at the beginning of the package leaflet to refer to the EMA website.

Recommendation:

Pharmaceutical companies should optimise the time to implement in the printed material the authorised changes made by the competent authorities.

The package leaflet should provide a link to the European Medicines Agency website where the most up-to-date information is published. The QRD template standard statement “Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu” should always be included.