EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Mock ups and specimen review

Labeling Review and Standards Office

Labelling is important…

Labelling / packaging

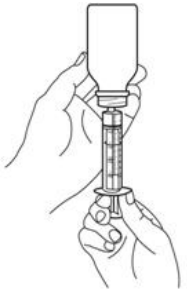
First point of interaction

Potential end user

Selection

Read and understand the label

Are labels always easy to read?



Clozapine – indicated in patients with severe schizophrenia

Medication errors

- Nurse mistakenly thought that each 14ml bottle of clozapine contained 50 mg – but there was 50 mg for every millilitre.
- Patient was given 6 bottles for a 300 mg dose.

- **Labelling issue?**
  - Strength displayed as 50 mg and total volume not prominently displayed?

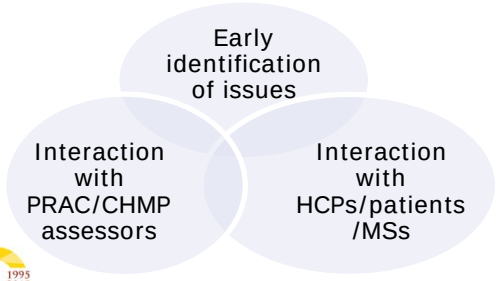
Mock ups and specimen review
Timelines (new applications and extensions)

1st mock-ups review

2nd mock-ups review

Review of all outstanding comments (on average **3-4 rounds of mock-ups reviews**)

Review of **specimens** prior to launch



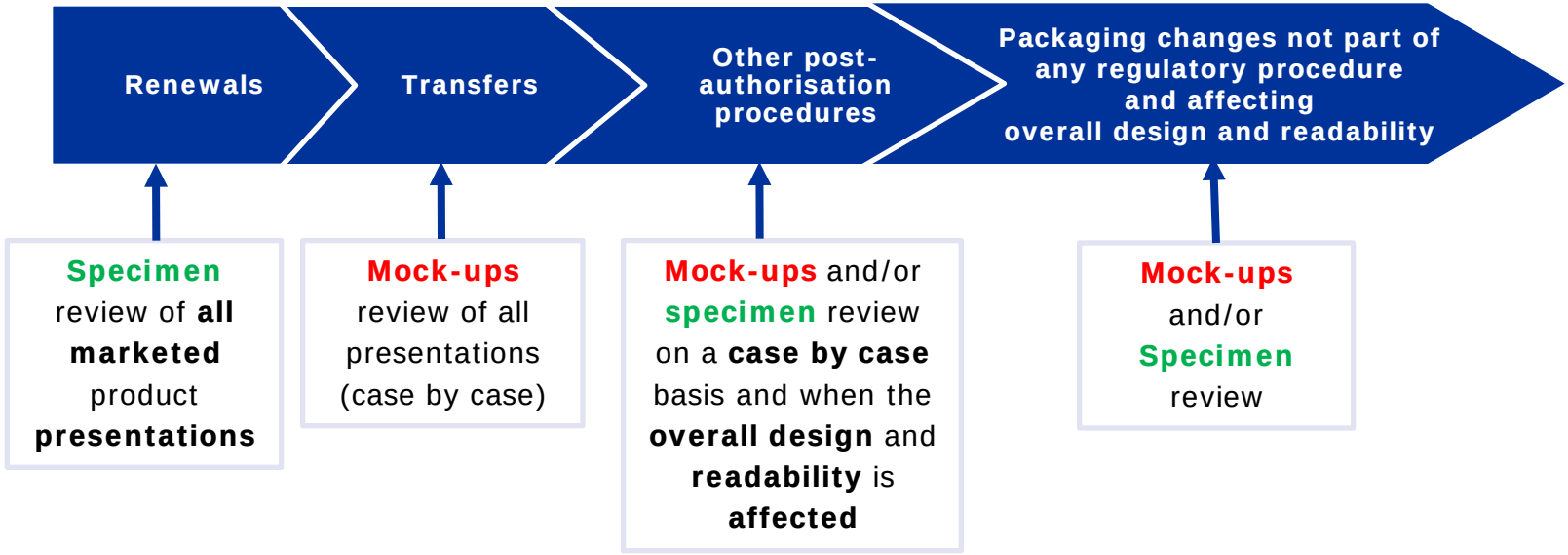
Mock-ups

- Mock-ups reviewed **in parallel** to scientific assessment.

Specimens

- Shorter specimen review, which facilitates faster launch.

Mock ups and specimen review Timelines (post-authorisation)



Tools and interactions

Tools:

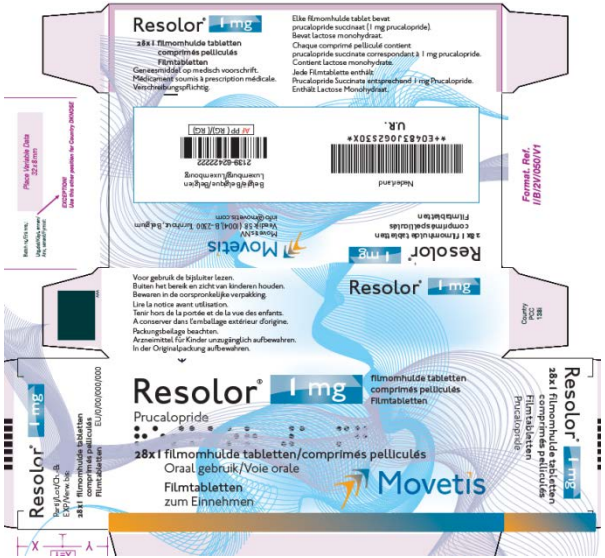
- EU legislation and guidelines.
- Guidance and alerts issued by medication safety organisations (ISMP, NPSA etc.) and other regulatory agencies (MHRA, FDA, Health Canada etc.).
- Product information, RMP, CHMP and RMP PRAC ARs.

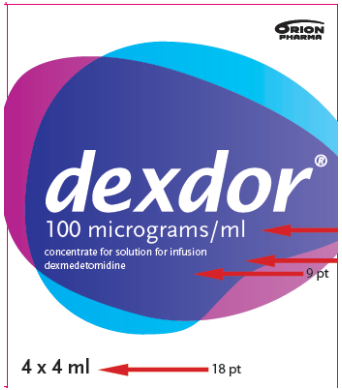
Interactions:

- QRD group and PRAC/CHMP assessors and Rapporteurs.
- Consultations with HCPs, patients and consumers organisations to gather how the medicinal product will be used in ‘real life’.



Readability check (1)

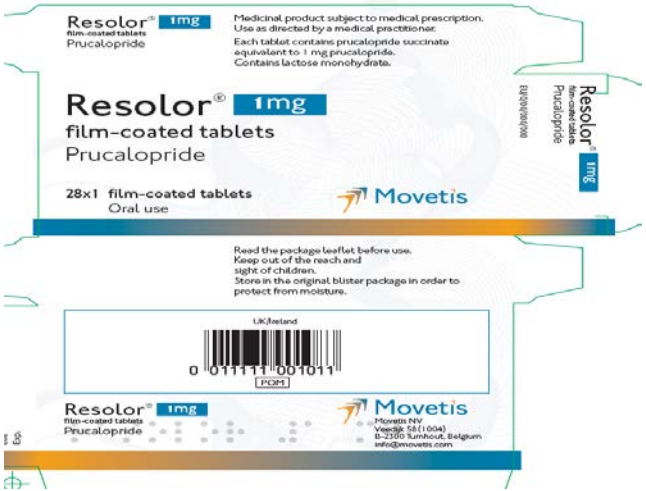


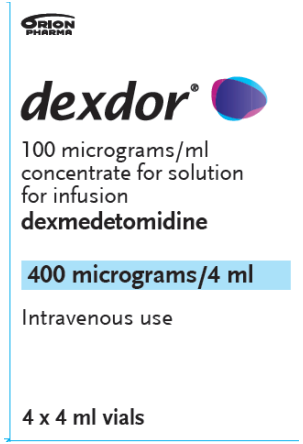


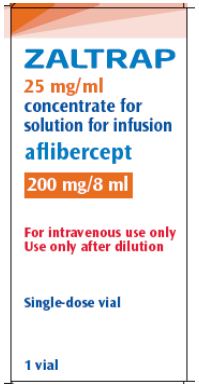
Examples of problematic areas

- **Logos and pictograms** can interfere with the readability of the information.
- Available **space** not used to enhance legibility/readability of information.
- **Poor contrast** between text and background.
- Too much **prominence** on one element can impair visibility of the rest of the information.
- Small **font size** can impair readability.
- Too many **colours** can confuse.

Readability check (2)







Focus:

- Presentation of critical information (balanced and cohesive display).
- Critical information displayed in primes places.
- Differentiation between strengths/total contents.
- Font sizes, positioning of the text, line spacing.
- Special warnings.
- Use of colours/pictograms/logos.
- Overall lay-out and design.

Multilingual packaging - Challenging area

TRADENAME 200 U

5000 U/ml, j./ml, E/ml

Injekčný roztok /Roztwór do wstrzykiwań

Oldatos injekció /Injekční roztok

Intramuskulárne použitie/Podanie domięśniowe/
Intramuscularis alkalmazásra/Intramuskulární podání.

1 x 0,5 ml injekčná liekovka/ fiolka/ injekciós üveg/ injekční lahvička

Intramuskulárne použitie/Podanie domięśniowe/
Intramuscularis alkalmazásra/Intramuskulární podání.

Zloženie/Skład/Összetétel/Složení:

Jeden ml obsahuje 5000 U botulínového toxínu typu A (2500 U v jednej injekčnej liekovke)

1 ml zawiera 5000 j. toksyny botulinowej typu A (fiolka zawiera 2500 j.)

Milliliterenként 5000 E/ml A típusú botulinumtoxint (2500 E injekciós üvegenként)

Jeden ml obsahuje 5000 j. botulínového toxínu typu A (2500 jednotek v injekční lahvičce)

EU/0/00/000/00EU/0/00/000/00EU/0/00/000/00

Dinátriumsukcinát, chlorid sodný, ľudský sérový albumín, nátriumkaprylát, nátriumacetyltryptofanát, kyselina chlorovodíková a voda na injekcie.

Disodu bursztynian, sodu chlorek, albumina ludzka, sodu kaprylan, sodu acetylotryptofanian, kwas solny i woda do wstrzykiwań.

Dinátrium-szukcinát, nátrium-klorid, humán szérum-albumin, nátrium-kaprilát, nátrium-acetil-triptofanát, sósav és injekcióhoz való víz

Dinatrium-sukcinát, chlorid sodný, lidský sérumalbumin, natrium-oktanoát, sodná sůl acetyltryptofanu, kyselina chlorovodíková a voda na injekci.

1 x 0,5 ml injekčná liekovka/ fiolka/ injekciós üveg/ injekční lahvička

2500 U
2500 j.
2500 E

1 flacon / 1 injectieflacon / 1 Durchstechflasche
1 seringue stérile sans silicone / 1 steriele siliconenvrije spuit / 1 sterile silikonfreie Spritze

TRADENAME 250 mg

poudre pour solution à diluer pour perfusion
poeder voor concentraat voor oplossing voor infusie
Pulver für ein Konzentrat zur Herstellung einer Infusionslösung

Active substance/acrive substance/active substance

Pour la reconstitution et la dilution, utiliser la seringue jetable sans silicone fournie dans l'emballage. / Gebruik de siliconenvrije spuiten die inbegrepen zijn in de verpakking voor oplossen en verdunnen. / Benutzen Sie zur Rekonstitution und Verdünnung die silikonfreie Spritze, die in der Packung enthalten ist.

Voie intraveineuse / Intraveneus gebruik / Intravenöse Anwendung

blode kapsler
pehmeät kapselit
myke kapsler
mjuka kapslar

nintedanib/nintedanibi

Hver kapsel indeholder 150 mg nintedanib (som esilat). Læs indlægsseddel før brug. Opbevares utilgængeligt for børn. Må ikke opbevares over 25°C. Opbevares i original pakning for at beskytte mod fugt. Ikke anvendt lægemiddel skal i følge hvor skal bortskaffes i henhold til lokale retningslinjer. Receptpligtigt lægemiddel.

Jokainen kapseli sisältää 150 mg nintedanibia (mesilaattina). Lue pakkausseloste ennen käyttöä. Ei lasten ulottuville eikä näkyville. Säilytä alle 25 °C. Säilytä alkuperäispakkauksessa. Herkkä kosteudelle. Käytämättön valmiste tai jäte on hävitettävä paikallisten vaatimusten mukaisesti. Reseptilääke.

EU/0/00/000/000

Partii nr./ Sērija/ Serija

Kõlblik kuni:/ Derīgs līdz:/ Tinka iki

MM/YYYY

EU/00000000

MAHBMAH MAHMAH/ AMH/MAHa

Tradename

5 mg / active substance
5 mg / active substance
5 mg / active substance

Suukaudne lahus. Šķīdums iekšķīgai lietošanai. Geriamasis tirpalas. Active substance Active substance

50 ml

Suukaudne lahus. Šķīdums iekšķīgai lietošanai. Geriamasis tirpalas.

Suukaudne. Enne ravimi kasutamist lugege pakendi infolehte. Üks kord ööpäevas. Iekšķīgai lietošanai. Pirms lietošanas izlasiet lietošanas instrukciju. Vienu reizi dienā. Vartoti per burną. Prieš vartojimą perskaitykite pakuotės lapelį. Vartoti kartą per parą. Hoida laste eest varjatud ja kättesaamatus kohas. Uzglabāt bērniem nepieejamā un neredzamā vietā. Laikyti vaikams nepasiekiamoje ir nepastebimoje vietoje. Mitte hoida temperatuuril üle 30 °C. Pārsat avamist kasutada 3 kuu jooksul. Uzglabāt temperatūrā līdz 30°C. Pēc atvēršanas izlietot 3 mēnešu laikā. Laikyti ne aukštesnėje kaip 30 °C temperatūroje. Buteliuką atidarius, tinka vartoti 3 mėnesius. Retseptiravim. Recepšu zāles. Receptinis vaistinis preparatas. Lahus sisaldab ka kaaliumsorbaati ja sorbitooli (E 420). Lisainfo saamiseks vaata pakendi infolehte. Šķīdums satur arī kālija sorbātu un sorbītu (E420). Sīkāku informāciju skatīt lietošanas instrukcijā. Suėtyje yra kalio sorbato ir sorbitolio (E 420). Pumba ūks aktivatskoon (ūks allasuunalline pumbavajutus) väljutab 0,5 ml lahust, mis sisaldab 5 mg acetriveklorlidi ja mis vastab 4,16 mg active. Vieno sūkyna izsmidzinājums (vienreiz nospiežot lejupvirzienā darbiāmo sūkni) nodrošina 0,5 mililitru, kas satur 5 mg active hidrohlorīda, kas ir ekvivalents 4,16 mg active. Daugiau informacijos patelkta pakuotės lapelyje. Vienu pompos dozavimu (vienu pompos paspaudimu) išpurškiama 0,5 ml tirpalo, kuriame yra 5 mg acetivesee atitinkančio 4,16 mg active

Chaque ml de solution pour inhalation par nébuliseur contient lévofloxacine hémihydrate équivalent à 100 mg de lévofloxacine.
Chaque ampoule contient 240 mg de lévofloxacine, chlorure de magnésium et eau pour préparations injectables.
Solution pour inhalation par nébuliseur 56 x 2,4 ml ampoules.
Voie inhalée. A usage unique seulement.
Lire la notice avant utilisation. Tenir hors de la portée et de la vue des enfants.
Pas de précautions particulières de conservation concernant la température.
À conserver dans l'emballage d'origine à l'abri de la lumière.
Médicament soumis à prescription médicale.

Jede ml Lösung für einen Vernebler enthält Levofloxacin-Hemihydrat entspricht 100 mg Levofloxacin.
Jede Ampulle enthält 240 mg Levofloxacin, Magnesiumchlorid und Wasser für Injektionszwecke.
Lösung für einen Vernebler 56 x 2,4 ml Ampullen.
Zur Inhalation. Nur für einmaligen Gebrauch.
Packungsbeilage beachten. Arzneimittel für Kinder unzugänglich aufbewahren.
Für dieses Arzneimittel sind bezüglich der Temperatur keine besonderen Lagerungsbedingungen erforderlich.
In der Originalverpackung aufbewahren, um den Inhalt vor Licht zu schützen.
Verschreibungspflichtig.

Elke verneveloplossing bevat levofloxacinehemihydraat wat overeenkomt met 100 mg levofloxacine.
Elke ampul bevat 240 mg levofloxacine, magnesiumchloride en water voor injecties.
Verneveloplossing 56 x 2,4 ml Ampullen.
Inhalatie. Uitsluitend bestemd voor eenmalig gebruik.
Voor gebruik de bijsluiter lezen.
Buiten het bereik en zicht van kinderen houden.
Voor dit geneesmiddel zijn er geen speciale bewaarcondities wat betreft de temperatuur.
Bewaren in de oorspronkelijke verpakking ter bescherming tegen licht.
Geneesmiddel op medisch voorschrift.

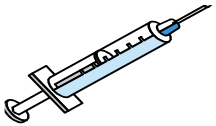
Available tools…

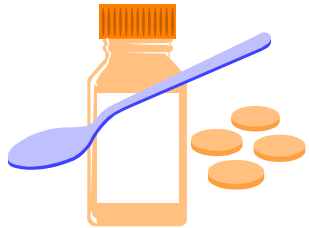
- All the readability principles can be **very difficult to apply, especially on multilingual packaging.**
- **Several strategies are available:**
  - Use of innovative labels
  - Display of one language per panel
  - Use of English or Latin for the active substance
  - Use of short standard terms (pharmaceutical form, route of administration, container)
  - Use of standard abbreviations
  - Exemption - Text simplification (Art.63 of Directive 2001/83/EC)*
  - Language exemption (Art.63 of Directive 2001/83/EC)*
  - To have thorough assessment of the text that will be displayed

*Products not intended to be delivered directly to the patient and orphan products

Mock-ups and specimens review - **Further scope?**

- The readability check performed considering **practical aspects** on how the product will be **prescribed, dispensed, stored and used** to make sure that the proposed **layout** allow the correct **identification** and **safe** use of the product.
  - Introduction of a new device/change of device.
  - Introduction of a new pharmaceutical form (tablets vs prolonged-release tablets).
  - Inclusion of specific warnings (cytotoxic)
  - Introduction of a higher concentration (Insulin).
  - Expression of strength (concentration per ml vs total content per total volume)
  - Potential for medication errors due to pack configuration (complex posology)





Tresiba (new MAA) (1)

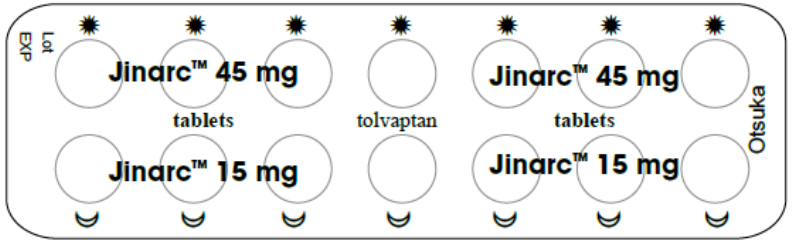
- **New MAA**: Introduction of a new higher concentration insulin (**200 mg/ml**).
  - ➢ Impact on harmonised therapeutic environment (only **100 units/ml in EU**).
- **Issue:** potential risk of mix-ups with fatal consequences (high-risk product).
- **Mock-ups review:**
  - – Similarity in pack design and colour scheme.
  - – Focus on the maximum number of units to be delivered.
  - – Pen delivering “2 units per click”.
- **1st consultation** with patients, healthcare professionals and QRD
  - ➢ **Product information** and **mock-ups.**

Tresiba (new MAA) (2)

- Issues were presented and discussed at **CHMP** and followed up at a **Diabetes & Endocrinology SAG**.
- **2nd consultation** with patients, healthcare professionals and QRD
  - **Revised mock-ups** and **educational materials.**
- **Outcome**:
  - Highlight of the **strength**.
  - Highlight of the **warning** regarding the steps vs. units.
  - Change in **layout** and use of **colours.**

Jinarc (new MAA) (1)

(Indication - cyst development and renal insufficiency of autosomal dominant polycystic **kidney disease**)



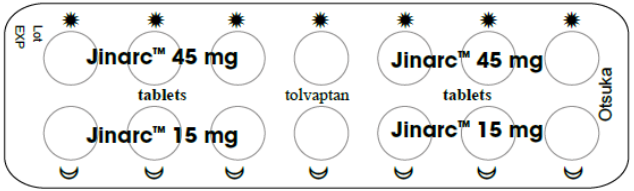
- **Posology**: Total daily doses (**60**, 90, or 120 mg). **To be** taken twice daily **in split dose (**e.g **45 mg + 15 mg**)
- **Potential risk for medication errors:** lack of **adherence** to the treatment due to **blister layout**.
  - High **risk** of medication errors **if tablets are taken randomly**.
  - A simple **blister** containing **two strengths** has **never** been **accepted.**

➢ **Discussion with company:** to consider different packaging to ensure that the right dose is taken.

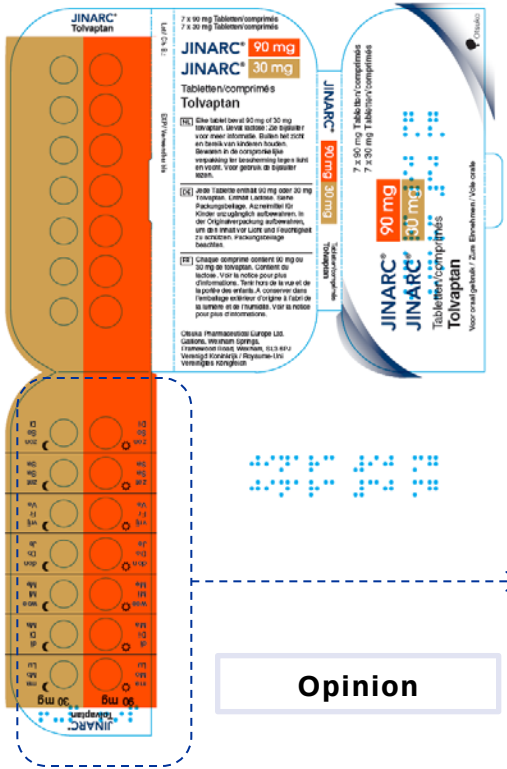
➢ **Concerns shared** and discussed with **CHMP, PRAC** Rapporteurs.

- Issue incorporated as part of the **D180 LoOI** .

Jinarc (new MAA)



Day 1



Opinion

- **Outcome:** change to the blister layout.
  Use of a wallet type blister.

Multipack presentation

MULTIPACK
(carton)

MULTIPACK
(Shrink wrap / bundle wrap)

NOT A MULTIPACK

- The **Commission**, together with **Member States**, in the context of the Notice to applicants provided clarification regarding **multipacks** in the **packaging guideline**:

"Pack composition
The description below provide examples of presentations, that may be covered by marketing authorisation(s), and do not reflect marketing possibilities.
Multi packs: these packs are composed of several single packs of the same strength of a medication product. […]"

Multipack presentations – General principles

- The multipack **outer carton** should display all **legally** required **items** (including **blue box**)
- **Not possible** to **sell** the **inner boxes** within the multipack **as single presentations**
- **Each** individual **inner boxes** should contain **a package leaflet**
- It is expected that **Braille** would be present on both the **outer packaging** and **inner boxes**
- The **labelling** must **clearly** state the **content of the pack** to ensure correct identification in the **supply chain**, to **healthcare professional** and **patients.**
- The current **QRD template** provides detailed **guidance** on the wording and structure of **multipack presentations**.
- **Multipack** presentations should be **register** (i.e. included in the Annexes) even if **not market** in all Member States.
- A **multipack** will be authorised as a **separate presentation** with its own **specific EU sub-number** and will attract a **separate fee**.

Carton vs plastic wrapping (bundling)

- **Preference is for carton**. Use of **plastic wrapping / bundling** should only be **exceptional.**

- A simple **plastic wrap** might not fulfil the requirements for clear identification and **could create confusion.**

  - **Plastic wrapping** often used for **transportation or shipment** (i.e do not constitute a pack size).
  - It is essential to **differentiate** between outer packaging used for **transportation / shipment** and wrapping used to contain a **presentation**.
  - Packs wrapped together to create an **additional presentation** have to be correctly **labelled** to meet the labelling **requirements** for **medicinal products**.

- If **shrink-wrapping** is used, **justification** on why this is the preferred option over a carton should be provided.

  - A **label** displaying all legally required items for outer packaging has to be affixed to the plastic wrap (including blue box)
  - Transparent vs non-transparent wrapping => **EMA no policy** => MAH choice

Packaging material : "Any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment. (**GMP guideline (Eudralex glossary - volume 4**))

Quick Response codes (QR codes)

Legal basis – Article 62 of Directive 2001/83/EC, *"the outer packaging and the package leaflet may include symbols or pictograms designed to clarify certain information mentioned in Articles 54 and 59(1) and other information compatible with the summary of product characteristics which is useful to the patient, with the exclusion of any element of a promotional nature".*

QR code – **content and location**

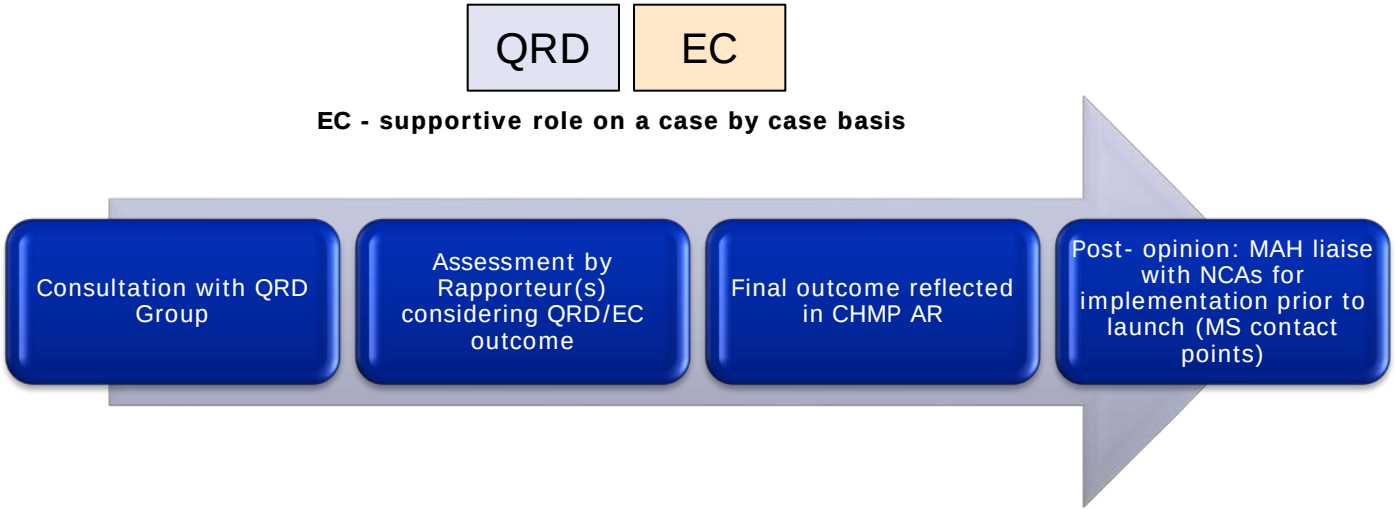
- **Statutory information**: Information from the **approved product information** (SmPC/leaflet)
- **Additional information**: other information that is not included in the product information as such but is **useful** to patients/users and **non-promotional** (e.g. video)
- **Location:** Not affect the readability of statutory information and ideally to be located in an area with minimal or no impact on readability (e.g. inner flap of the carton)

QR Code – **submission and assessment**

- **Submission of request/declaration form**: information regarding QR code content + updated mock-ups + product information (in the context of an assessment procedure – Module 1.3.1)

➢ **For statutory information**: Rapporteur **only** reviews the **declaration form** (acceptability reflected in CHMP AR)

➢ **For additional information:**



Quick Response codes (QR codes)

Guidance

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/07/WC500190405.pdf

Declaration

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000254.jsp&mid=WC0b01ac058008c34c

QRD contact points:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/07/WC500190404.pdf

Thank you for your attention

Further information

Mock-ups and specimens team (muspecimens@ema.europa.eu)
Julien Lormain, Monica Prizzi, Ana Sempere and Maria Bonafonte

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Follow us on **@EMA_News**