"Evaluation of design and layout of folding boxes of centrally approved medicinal products using a decision matrix developed from legal requirements and available guidance documents".

Wissenschaftliche Prüfungsarbeit

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GLOSSARY

Agency Directive 2001/03/EC TITLE 1 DEFINITIONS Article 1/27	European Medicines Agency (EMA) established by Regulation (EC) No 726/200424.
Blue box "BLUE – BOX" REQUIREMENTS Doc. Ref: CMDh/258/2012/Rev.1 March 2013 Notice to Applicants Volume 2 C – Regulatory Guidelines of The Rules governing Medicinal Products in eht European Community, Guideline on the packaging information of medicinal products for human use authorized by the Community August 2007 – Section A – Label – 4.	Boxed area in the labeling for centrally authorised products with a blue border, aimed at containing information specific for each Member State. Label information which may be required by Member States under article 57 of Directive 2001/83/EC as amended and Label information which has become established in Member States allowed under article 62 of Directive 2001/83/EC as amended.
Braille Guidance concerning the Braille requirements for labelling and the package leaflet ENTR/F2 D(2005)	Internationally widespread reading and writing system for blind and partially-sighted people. The system was founded in 1825 by Louis Braille (1809 – 1852), who lived in France and himself was blind. It is not a language but another way to read and write a language. It consists of arrangements of dots which make up the letters of the alphabet, numbers and punctuation marks. Basic Braille symbol is called Braille cell. Due to the reason that there are differences in Braille in different countries, the type of Braille letter (size of Braille cell) has to be standardized. The use of Marburg Medium is highly recommended. The uncontracted Braille system should be used. The contracted Braille system with letter-combinations should not be used, except in small volume packaging (up to 10 ml volume).
Common name Directive 2001/03/EC TITLE 1 DEFINITIONS Article 1/21	International non-proprietary name recommended by World Health Organization, or, if one does not exist, usual common name.
Dots per inch (DPI)	Within the DPI-system the number of individual dots are measured that can be placed in a line within the span of 1 inch (= 2.54 cm). Printers with higher DPI produce clearer and more detailed output.
Ecipients Guideline Excipients in the label and package leaflet of medicinal products for human use July 2003 ENTR/F2/BL D (2003)	Constituents of the pharmaceutical form that is taken by or administered to the patient, other than the active substance.
Immediate packaging Directive 2001/03/EC TITLE 1 DEFINITIONS Article 1/23	Container or other form of packaging immediately in contact with medicinal product.
Labelling Directive 2001/03/EC TITLE 1 DEFINITIONS Article 1/25	Information on immediate and outer packaging.
Manufacturer	Manufacturer means the holder of the authorization referred to in Article 16 of Directive 75/319/EEC on behalf of whom the

Directive 92/27/EEC Article 1(2)	qualified person has performed the specific obligations laid down in Article 22 of that Directive.
Mock-up GUIDELINE ON THE READABILITYOF THE LABELLING AND PACKAGE LEAFLET OF MEDICINAL PRODUCTSFOR HUMAN USE Revision 1, 12 January 2009	A copy of a flat artwork design in full color, presented so that, following cutting and folding where provides a replica of both outer and immediate packaging so that necessary, it three dimensional presentation of label text is clear. A Mock-up is generally referred to as a paper copy and not necessarily in the material of the sales presentation.
Name of the medicinal product Directive 2001/03/EC TITLE 1 DEFINITIONS Article 1/20	Name given to the medicinal product which may be either an invented name or a common or scientific name, together with a trade mark or the name of the manufacturer; the invented name shall not be liable to confusion with the common name.
Outer packaging Directive 2001/03/EC TITLE 1 DEFINITIONS Article 1/24	Packaging into which is placed immediate packaging.
Package leaflet (PL) Directive 2001/03/EC TITLE 1 DEFINITIONS Article 1/26	A leaflet containing information for user which accompanies the medicinal product.
Pixels per inch (PPI)	Monitors do not have dots, but they have pixels. Another concept, as the DPI-system, the PPI-system (Pixels per inch) is relevant. The display resolution of a digital computer monitor is the number of distinct pixels in each dimension that can be displayed. The displayed resolution is controlled by different factors and is usually quoted as width × height, with the units in pixels: for example, "1024 × 768" means the width is 1024 pixels and the height is 768 pixels.
Specimen GUIDELINE ON THE READABILITYOF THE LABELLING AND PACKAGE LEAFLET OF MEDICINAL PRODUCTSFOR HUMAN USE Revision 1, 12 January 2009	A sample of actual printed outer carton, immediate packaging material and package leaflet.
Strength the of medicinal product Directive 2001/03/EC TITLE 1 DEFINITIONS Article 1/22	The content of the active ingredient expressed quantitatively per dosage unit, per unit of volume or weight according to dosage form.
Tallmann lettering	Tallman lettering (or Tall Man lettering) is the practice of writing part of a drug's name in upper case letters to help distinguish sound-alike, look-alike drugs from one another in order to avoid medication errors. For example, in Tallman lettering, "prednisone" and "prednisolone" should be written "predniSONE" and "prednisoLONE", respectively. The Office of Generic Drugs of the U.S. Food and Drug Administration (FDA) encourages manufacturers to use Tallman lettering labels to visually differentiate their drug´s' names, and a number of hospitals, clinics, and health care systems use Tallman lettering in their computerized order entry, automated dispensing machines, medication admission records, prescription labels, and drug

	product labels.
Typometer	A truly indispensable, high precision tool for the accurate measurement of type and font sizes up to 340 points, DIN formats, line spacing in pica-points, line thicknesses and angles. It has be developed specifically for the graphic design, pre-press and print industries. But normally the scientist of a health authority evaluating the Mock-ups do not use typo meters.

List of Abbreviations

AMTS	Arzneimitteltherapiesicherheit, German term to describe the potential risk of the entire process of medication, in short translated as medication safety
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BGM	Bundesgesundheitsministerium
CA	Competent Authority
CDER	Centre for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CMS	Concerned Member State
CP	Centralized Procedure
DCP	Decentralized Procedure
D	Depth (of a folding box)
Dir 2001/83/EC	Directive 2001/83/EC of the European Parliament and of the Council of 6 November2001 on the Community code relating to medicinal products for human use
DPI	Dots per inch
EC	European Commission
EMA (previously EMEA)	The European Medicines Agency
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEA	European Economic Area comprises the countries of the European Union (EU), plus Iceland, Liechtenstein and Norway
EU	European Union
FMH	Federal Ministry of Health (Germany)
HHRC	Helen Hamlyn Research Center
FDA	Food and Drug Administration Agency (US)
HMA	Heads of Medicines Agencies
INN	International Nonproprietary Name
L	Length (of a folding box)
MA	Marketing Authorization
MAA	Marketing Authorization Application

MAH	Marketing Authorization Holder
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MRP	Mutual Recognition Procedure
MS	Member States
NHS	National Patient Safety Agency (UK)
NRG	Name Review Group
PIL	Patient Information Leaflet (UK-term)
PL	Package leaflet (EU-term)
PPI	Pixels per inch
QRD	Quality Review of Documents
OTC	Over-the-counter
RMS	Reference Member States
SmPC	Summary of Product Characteristics, previously abbreviated as SPC
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
W	Width (of a folding box)

1 Introduction

Especially for human medicinal products the safe use is very important because medication errors are a substantial threat to patient's safety. Patients may get the wrong medicines, the wrong dosages or do not take the medicine according to the prescribed schedule. There is also a risk for patients taking copies of medicines containing the same active substance as a medicinal product that is already marketed. Similarities in drug names and in medicines packaging can also cause confusion in users.

Therefore it is very important for the safe and appropriate use of a medicine that especially the critical information is legible and easily accessible for the users and that they can easily assimilate this information to minimize any risk of confusion and medication error. Regarding the "Guideline good pharmacovigilance practices" of 22 June 2012 and as stated on the European Medicines Agency (EMA) Homepage "Medication errors are unintentional errors in the prescribing, dispensing, or administration of a medicine while under the control of a healthcare professional, patient or consumer. They are the most common single preventable cause of adverse events in medication practice" [1].

Health-care professionals like doctors, pharmacist and for example nurses get the information on how a medicine should be used in the Summary of Product Characteristics (SmPC). Patients and consumers are provided with this information on the label and mostly in the Package Leaflet (PL), often known as Patient Information Leaflet (PIL) according to the UK term in use.

The intake of a prescribed medicinal product can be explained by the doctor and the pharmacist. But patients must be able to distinguish different medicinal products from each other at home. Therefore a clear, unambiguous identification of the medicine must be guaranteed and all users must be able to understand the information and act on this information. This has to be ensured by good pack design and clearly legible labeling and best use of the space available to avoid too small font sizes.

Patients can obtain medicinal products via self-medication from a retail outlet like a supermarket or in a pharmacy. If the patient is customer in a pharmacy the pharmacist can advise the patient how to use it and can control the medication process to some extent. Therefore, also using non-prescription medicines the clear identification and selection of the appropriate medicine is particularly important especially, if there is no pharmacist intervention. In those cases good quality patient information should supplement but not replace the advice given by a doctor or pharmacist.

To define labeling Wikipedia may provide some ideas: "Package labeling (American English) or labelling (British English) as any written, electronic, or graphic communications on the packaging or on a separate but associated label".

The purpose of packaging is physical and barrier protection and the containment or agglomeration of small objects together in an efficient manner. With help of the packages the users should also be informed about the use, the transport, recycling or dispose of the package or product. The packages can also be used for Marketing or to reduce security risks of shipment. This description applies in general and is not specific to medicinal products [3].

Medicinal products for human use are products where the design process involves detailed legal regulatory requirements. The labeling process of medicinal products has become much more complex following the adoption of European Directives. Because regarding European law all medicines have to be accompanied by outer and immediate labeling texts and a PL (see TITLE V LABELLING AND PACKAGE LEAFLET Article 54, Article 55 and Article 59 of "Directive 2001/83/EC of the European Parliament and of the Council of November 2001 on the Community Code relating to medicinal products for human use (hereinafter: "Directive 2001/83/EC")". These articles provide the information required for labeling and PL and need to be considered when designing folding boxes for medicines [4].

Further information on the presentation of the content of the labeling and PL and on design and layout concepts is provided in the "Guideline on the packaging information of medicinal products for human use authorized by the Community - Revision 13, February 2008 (hereinafter "Guideline on Packaging Information")". The Guideline was published by the European Commission (EC) and gives further information on the presentation of the content of the labeling and PL and on design and layout concepts [5].

Furthermore the "Guideline on the readability of the labeling and package leaflet of medicinal products for human - Revision 1, 12 January 2009 (hereinafter "Readability Guideline")" published by the EC in accordance with Article 65 of Directive 2001/83/EC includes further advice and gives the details regarding the display and readability of information on the printed material [6].

Additional recommendations regarding the design can be found at the Homepage of the EMA [1]. There are templates available that provide Applicants with practical advice on how to draw up the product information. Especially the template "QRD recommendations on pack design and labelling for centrally authorized non-prescription human medicinal products – Draft, 10 March 2011 (hereinafter "QRD recommendations on pack design and labelling")" gives helpful advice [7].

In the last years in some MS like for example in Germany and the United Kingdom (UK) additional national recommendations were developed.

The Federal Ministry of Health of Germany initiated 2007 a first Action plan for the improvement of medication safety (in german: Arzneimitteltherapiesicherheit (AMTS)) [8, 9]. International experiences were incorporated and necessary activities for a better medication safety summarized.

As a reaction in January 2012 the Industrial Forum Action plan medication safety established recommendations for a safe design of folding boxes “Praxisbezogene Anforderungen an ein sicheres Design von Fertigarzneimittelpackungen”, of 08.02.2012, which have to be considered in combination with the European recommendations [10].

In the UK the MHRA Regulating Medicines and Medical Devices has also published on 31 May 2012 a guidance for all the parties involved in the design and layout of labeling the “Best practice guidance on the labelling and packaging of medicines” (Advertising and promotion of medicines in the UK) [11].

Further the National Patient Safety Agency (NHS) published in the UK as a result of a design research collaboration with the Helen Hamlyn Research Centre (HHRC) a design for patient safety series. The publication of 2007 in a second edition “Design for patient safety - A guide to the graphic design of medication packaging” gives useful concrete and helpful advice designing packaging material [12].

Prescrire declares being an independent, non-profit continuing education organization, founded in the 1970´s in France by French doctors and pharmacist, and wants to improve the information given to patients regarding their drugs. On 29 November 2012 Prescrire published the document “Safety and usability of packaging and labelling: assessment is required prior to marketing authorisation for all medicinal products, not just for copies of existing drugs (hereinafter “Safety and usability of packaging and labelling”)” [13].

It seems to be important, that critical information and really important information should be located more prominently on the labeling than less important information. Regarding warnings only critical warnings necessary prior to the administration of the medicinal product should appear on the front of the pack. It is also important, that statutory information must be placed subordinate to non-statutory information.

In all cited recommendations lots of points to be considered when designing packaging material are repeated and most of them address the need for further improvement of better packaging design. Therefore, a relevant potential for improving the design of labeling within the current regulatory framework seems to be obvious. More efficient and additionally streamlined checking processes for packaging material and recommendations easier to understand and to implement must be worked out. On the other hand the pharmaceutical industry must come to a more self-regulated labeling process. It has to be considered also, that different users of medicines require and use the information on all labeling components differently.

The objective of this thesis is to evaluate a set of different sample mock-ups with the help of the before mentioned existing legal requirements for labeling and European recommendations and to investigate to which extend the Applicants adhere to them.

Therefore the European recommendations and legal requirements were analyzed and assessed in terms of packaging design to create a decision matrix to focus on

the points relevant for the overall layout and design of the folding boxes and providing an easy to use tool to facilitate the respective assessment at Applicant or Agency side.

After analyzing how the mock-ups are presented by Marketing Authorization Holders (MAHs) proposals for the improvement for mock-ups presentation will be drawn up. The chosen approach should also verify whether the decision matrix is a valuable tool to support Regulatory Affairs staff.

2 Legal requirements and recommendations for labeling

2.1 Legal requirements

In the EU more than 27 countries were unified to provide a single market for the pharmaceutical industry. The EU Law is a body of treaties and legislations and consists of three sources: primary law (with the Treaties establishing the EU as main source), secondary sources (which include Directives and Regulations based on the Treaties) and supplementary law [14].

Large parts of the pharmaceutical legislation have been harmonized with the objective to eliminate technical and scientific obstacles on the way to the European single market. The EU law consists of many Directives and Regulations which have direct or indirect effect on the laws of the European MS. They outline the requirements for the development, manufacturing and marketing of medicinal products for human and veterinary use. They are mandatory rules (laws). Directives must be implemented by MS into national law, what means that they do not apply directly, while regulations are directly applicable, what means that they are directly legally binding in all MS.

The criteria on which the legislation for human medicinal products is founded are safety, quality and efficacy. Therefore high standards of quality, safety and efficacy have to be met in order to obtain a Marketing Authorization (MA). Several parties are involved in the development of the legislation as outlined next.

Beside the Institutions Council of the European Union and the European Parliament, the European Commission (EC) has legislative power inside the EU. The EC is responsible for the overall Community Systems and for the legal framework for the MA.

The EMA is a decentralized organization providing a central procedure for accessing the EU market. The EMA is also responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU. The EMA supervises medicinal products for human use in the EU and provides advice on measures to ensure the safe and effective use of medicines and promotion of public health.

The Committee for Medicinal Products for Human Use (CHMP) prepares on behalf of the EMA opinions and recommendations concerning medicinal products for human use. On the other hand the individual MS with their National Authorities share responsibilities and provide resources for the assessment of applications and compliance monitoring.

The first European pharmaceutical Directive was established as a reaction to the Thalidomide tragedy in the early 1960s [15]. The aim was to set out harmonizing standards for the approval of medicines within the EU. The Directive requires that a medicinal product could not be marketed within the community without prior Authorization of the Competent Authority of at least one MS.

On 31 March 1992 the first community measure was the publication of the Council Directive 92/27/EEC on the labeling of medicinal products for human use and on package leaflets [16]. Directive 92/27/EEC gives patients clear, precise information on medicinal products so that they use them correctly. Directive 92/27/EEC supplements and clarifies the given list of particulars on labeling in Directive 65/65/EC and was integrated into Directive 2001/83/EC which provides the current legislative framework in regard to labeling of medicinal products [4].

Article 54(c) of Directive 2001/83/EC requires that all excipients have to be declared on the labeling, if the medicine is an injectable, a topical or an eye preparation.

In addition Article 54(1)(c) requires that excipients which are known to have a recognized action or effect have to be declared on the labeling of all other medicinal products. Article 65 requires the publication of a guideline. The EC therefore published in Notice to Applicants Volume 3 B the Guideline “Excipients in the label and package leaflet of medicinal products for human use (hereinafter: “Excipients-Guideline”)” of July 2003 [17]. A list of all excipients which should be stated on the labeling according to the annex to this guideline.

Article 60 of Directive 2001/83/EC requires that MS may not prohibit or impede the marketing of medicinal products within their territory on grounds relating to the labeling or PL if these comply with the provisions of the Directive.

Article 57 provides, notwithstanding Article 60, that MS may require certain forms of labeling that make it possible to indicate for example the price of the medicinal product, reimbursement conditions, the legal status or the identification.

As provided in Article 8(3)(j) and in Article 61(1) of Directive 2001/83/EC an Application for a Community MA must include one or more specimens or mock-ups of the outer packaging and of the immediate packaging of the medicinal product, together with the draft PL.

In Article 62 is specified that the outer packaging and the PL may include symbols and pictograms to clarify information’s required regarding Article 54 and 59(1) and other information’s compatible with the SmPC useful for the patient. Further it is laid down that elements of promotional nature have to be excluded.

Directive 2001/83/EC always takes precedence although in different MS regulations exist that are always specific for the country. Directive 2001/83/EC includes the entire range of drug production and supply of drugs, including the non-centralized Community MA procedures.

That means that the Directive establishes a Community code in which all provisions in force governing the placing on the market, production, labeling, classification, distribution and advertising for medicinal products for human use were brought together. The Directive therefore is the legal basis for the safe and appropriate use of medicinal products and there is also listed the information that should be included on the labeling and PL.

In the EU no medicinal product (apart from special exceptions) may be placed on a market of a MS unless an Authorization has been issued by the Competent Authorities of a MS or by the EMA. Another requirement to place a product on the market is that an Applicant has to be established in the Community.

In the EU different MA approval procedures exist. Inside the Centralized Procedure (CP) pharmaceutical companies submit a single MA to the EMA which is granted by the EC and covers all EU MS and the EEA. Inside the Mutual Recognition Procedure (MRP) pharmaceutical companies who already hold a MA in one EU MS ask additional MS to recognize the MA that has already been granted. During the MRP one MS serves as “Reference Member State (RMS)” and the others are “Concerned Member States (CMS)”. In between the National Procedure (NP) MAs are granted in each MS by National Agencies on a country-by-country basis.

Therefore different labeling requirements exist. Before issuing a MA for a medicine the Competent Authority must check the immediate and outer packaging and the PL which must comply with Directive 2001/83/EC. The same procedure is necessary when labeling or PL must be changed. The labeling particulars must appear at least in the official language or the languages of the MS where the product is placed on the market.

2.2 Recommendations

2.2.1 Recommendations from the European Commission

The Directorate General Health Consumers (DG SANCO) published within Eudralex the Notice to Applicants “The rules governing medicinal products in the European Union” consisting of 10 volumes to give the MAH further advice [18, 19]. To facilitate the interpretation of the legislation and its uniform application across the EU, numerous guidelines of regulatory and scientific nature have additionally been adopted.

Within Volume 2c The “Readability-Guideline” was published in accordance with Article 65 of Directive 2001/83/EC which provides for the development of guidelines. In Article 65 subsection (c) is laid down that the EC in consultation with the MS and parties concerned shall draw up and publish detailed guidance concerning in particular the legibility of the particulars on the labeling and PL [4].

But what is the difference between readability and legibility? Regarding Wikepedia the readability can be distinguished from the legibility. “Readability is the ease in which text can be read and understood whether legibility is a measure on how easily individual letters or characters can be distinguished from each other. Readability is the result of an interaction between the text and the reader. On the reader´s side readability is dependent on prior knowledge, reading skills, interest and motivation and on the side of the text readability is affected by the content, the style, the design and the organization” [20].

The “Readability-Guideline” sets out helpful advice on the presentation of the content of the labeling and PL (required in accordance with Title V of Directive 2001/83/EC) and on the design and layout concepts which will aid the production of high quality information. It assists Applicants and MAHs preparing specimens or mock-ups of the outer and immediate packaging of the sales presentations or drawing up the labeling or PL [6].

The name of the medicinal product has to be expressed also in Braille format on the packaging. The invented name followed by its strength should be put in Braille. The uncontracted Braille system should be used [6, 21].

2.2.2 Recommendations from the EMA

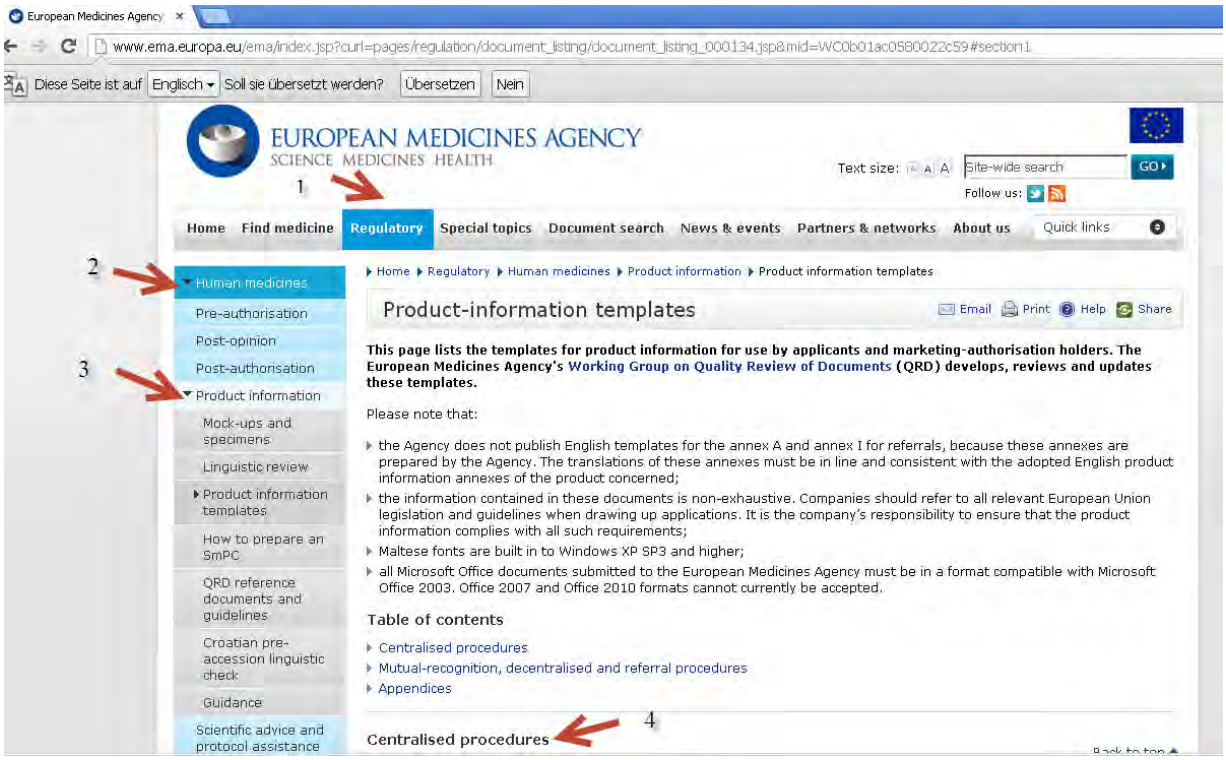
The last years a consultation with MS of the EU has taken place on national practices regarding pack design and labeling for non-prescription medicines. As the supply of medicines differs across Europe also some of the principles of presentation of content of labeling and PL differ among MS. For example the acceptability of symbols and pictograms and the additional information compatible with the SmPC.

Additional requirements may apply in particular MS. Details of those requirements should be checked on the websites of the CMDh [22].

Although a harmonization took place, there are still several items necessary to state on a national basis, e.g. price, reimbursement, legal status, identification and authenticity. For centrally authorized medicinal products this information will be placed in a "blue box" regarding the **"**Guideline on the Packaging Information" [5].

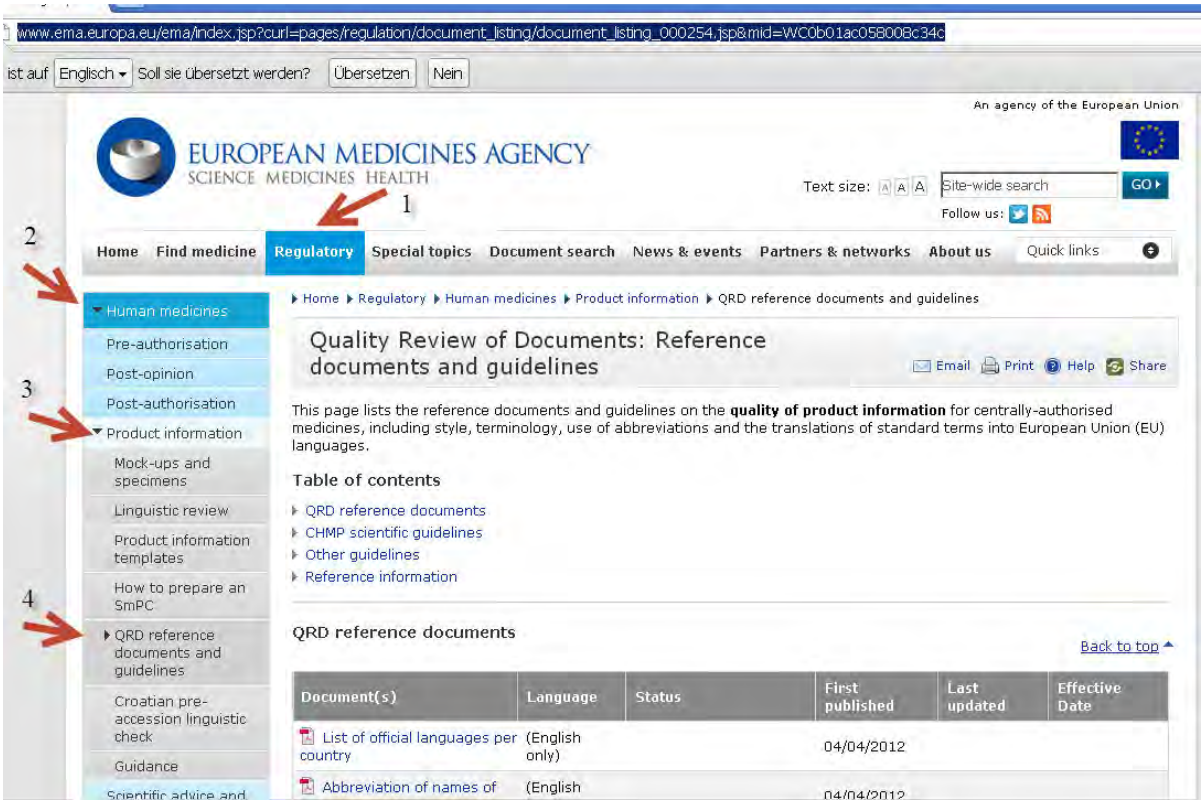
Additionally more specific recommendations regarding the design can be found at the Homepage of the EMA, e.g. templates that provide Applicants with practical advice on how to draw up the product information [1, 3].

Figure 1: EMA Homepage: "Regulatory / Human medicines / Section Product information / Product information templates for centralised procedures"



For the context of the thesis: "QRD recommendations on pack design and labeling for centrally authorized non-prescription human medicinal products – Draft, 10 March 2011" (hereinafter "QRD recommendations on pack design and labelling") is the most relevant available document [7].

Figure 2: EMA Homepage:" product information / Quality Review of Documents / Reference documents and guidelines"



Several more recommendations have been developed and published under the auspice of the Quality and Review of Documents (QRD) Working Group.

The QRD Group established in June 1996 provides assistance to the EMA`s scientific committees and to companies on linguistic aspects of the product information for medicines. This includes SmPCs, labeling and PL`s. The Group is chaired by an EMA representative and is composed of two experts per MS (one for human and one for veterinary products), selected by the National Competent Authorities. They have appropriate expertise in regulatory and linguistic areas, as well as in product information and labeling for medicines. The Agency's Secretariat also participates in the work of the group.

The tasks and the mandate of the Working Group are to ensure linguistic clarity, consistency and accuracy of the medicinal product information; verifying the terminology used in translations and their consistency with the original versions; promoting legibility of patient information; reviewing and updating templates for opinions of the scientific committees and for product information, to ensure compliance with EU rules on medicinal products and taking practical experience into account; contributing to the development of a common understanding on the implementation of legislation and guidelines in relation to product information and labeling.

The areas of activities of the QRD Group are product specific or general issues, user testing (patients review of the PIL from a readability point of view), updates of

legislations and guidance and reference documents, translations services and most important the Product Information Quality Review.

Important in the context of this thesis are the following documents: “QRD recommendations on pack design and labelling”, “Compilation of QRD decisions on stylistic matters in product information” of 31 May 2012 [23] and the “QRD recommendations on the expression of strength in the name of centrally authorized medicinal products (hereinafter “QRD recommendations on the Expression of Strength”)” of 18 November 2009 [24, 25].

All the QRD recommendations are based on the “Guideline on Summary of Product Characteristics” of September 2009 [26].

2.2.2.1 QRD recommendations on the Expression of Strength

It is very important for the correct use and the correct identification of the medicine to state the quantity of the active substance consistently. The quantity of the active substance should be declared in line with the qualitative and quantitative composition and with the posology and the method of administration of the medicinal product. The Applicant should design labeling and packaging material in a way that the prominent and unambiguous identification of the key information for the correct use of a medicine is guaranteed. Among the MS different practices for labeling exist especially for parenteral preparations and products with a multidose preparation which contains a quantity of the preparation suitable for two or more doses.

The legal requirements regarding labeling on packaging do not clearly define the way in which the strength of a medicinal product is to be indicated, especially for medicines with liquids, particularly for parenteral use. Especially for those products there should not be any chance to use different ways of expressing the strength and one single form of expression should be adopted.

Regarding the findings from medication error programs the expression of strength in the name as concentration (x mg/ml) rather than total content/total volume (z mg / y ml) has led to medication errors. It does not exist a uniform way to express strength regarding the quantitative composition (particularly for injectable drugs). When there are several registered presentations for the same product, the use of concentrations in the name increases the possibility for errors in identifying the different presentations. Then it is better to use in the name of the medicinal product the total content/total volume (z mg / y ml) and the per ml amount. So a harmonized approach is welcome.

In a table at the end of the “QRD recommendations on the expression of strength” proposals can be found for preferred presentations of the strength in the name with given format for different pharmaceutical form`s like oral preparations; parenteral preparations; implants; cutaneous, transdermal, rectal, vaginal, oromucosal and

gingival preparations; preparations for inhalations and eye, ear and nose preparations [24, 25].

These recommendations for different pharmaceutical forms were made in order to archive harmonization across similar medicinal products and pharmaceutical forms and especially to make improvements to labeling to ensure correct and safe use of human medicines and to avoid and minimize medication errors.

2.2.2.2 QRD recommendations on pack design and labeling for centrally authorized non-prescription human medicinal products – Draft

Overall, the QRD recommendations are designed to ensure that both the labeling and PL are suitably presented and easy to understand. Some of the basic elements which contribute to the optimization of the pack design such as the use of a clear layout, font type, the use of color or graphic design and recommendations on such elements are addressed jet in the “Readability guideline”.

The recommendations also highlight the type of information that must be featured (by Article 54 of Directive 2001/83/EC) and deemed critical for the safe use of the medicine, which includes the usual suspects of medicine name (invented name + strength + pharmaceutical form), active substance, route of administration, indications and instructions for use. Such important information should be brought together on the pack in the same field of view in clear large font. Because of the location and prominence of this critical information will contribute to the appropriate selection of the medicine, and will aid the differentiation between different medicines and within presentations of the same range (e.g. umbrella brands).

For non-prescription medicines there is also other important information (e.g. therapeutic indication, dosage, warnings, instructions for use etc.), which contributes to the appropriate selection and safe use of the medicine. Where possible this information should also be brought together in the same field of vision and using a sufficiently large type size on the packaging in order to aid users.

What is not to be included? The recommendations advise against using italics and capital letters for entire sentences because they are hard to read (bold type is usually better). Also, careful consideration needs to be given to the color of the package to ensure that it does not impact readability.

Companies will also need to take care when using symbols or pictograms. Although these are allowed (if relevant), they must not be confusing; for example, the number of tablets shown must not mislead about the dose. Images that are not allowed include those of leaves and fruits (text is considered sufficient to identify a medicine’s flavor), children, toys, balloons or other images that may cause confusion with other types of products.

The template “QRD recommendations on pack design and labelling” summarizes the basic recommendations and national practices of the MS of the EU regarding pack design and labeling. The “QRD recommendations on pack-design and labelling” and the “Readability Guideline” give guidance to Applicants and MAHs preparing mock-ups and specimens required by Directive 2001/83/EC for non-prescription medicines authorized within the CP.

In addition, following the consultation with MS on existing national guidance for non-prescription medicines, it became apparent that further emphasis and guidance on some of these recommendations was thought to be important for inclusion in this document.

The intended scope for this guidance is to apply these principles only to non-prescription medicines authorized via the CP. In addition, due to the differences in the way non-prescription medicines are supplied throughout the EU, i.e. pharmacy, general sales points etc., the final approach/set of common principles to be agreed upon should be sufficiently generic to cover all possible scenarios, i.e. dispensing with or without the intervention of a pharmacist.

It is supposed that the QRD template for the CP will be adapted also for the MRP, the Decentralized Procedure and Referrals.

2.2.2.3 Checking process of mock-ups and specimens of outer/immediate labeling

Since January 2007 mock-ups and specimens and all printed packaging materials of the outer and immediate labeling of centrally authorized medicinal products as well as of the printed PL must be submitted and reviewed during a general checking process by the EMA before commercialization of the medicinal product in the CP (see Article 8(3)(j) of Directive 2001/83/EC). The EMA has reviewed the experience of this process and still wants to introduce further amendments and simplification in the future. The details of this proposed checking process can be found in the QRD-template: “Checking process of mock-ups and specimens of outer/immediate labelling and package leaflets of human medicinal products in the centralised procedure” of 22 March 2013 [27].

The review takes place in order to check compliance with the requirements outlined in Directive 2001/83/EC. Regarding Article 8(3)(j) of Directive 2001/83/EC Applicants must provide at Day -10 of the submission of the New Applications in Module 1.3.2 of the Application an English color full-size mock-up and one multi-lingual color full-size mock-up (“worst-case”) of the outer and immediate packaging for each pharmaceutical form in each container type (e.g. blister, bottle, vial, pen) in the smallest pack-size. Mock-ups must also be provided for all strength or for all different total contents per total volume, when the strength is expressed as concentration per unit volume. Mock-ups of the PL can be included optionally. For Extensions

Application this will only concern the new strength and/or pharmaceutical form applied for.

By Day 121 at submission of the answers of the list of questions, revised mock-ups of labeling and PL have to be provided in case of comments or if the overall design has be changed.

At the latest 15 working days before Marketing, specimens of all printed outer and immediate packaging materials and the PIL for each strength, pharmaceutical form and container type have to be provided to the EMA. Within 15 working days the EMA will check these documents from the viewpoint of readability and inform the Applicant about the outcome.

The review is necessary because the agreed product information's texts must be implemented correctly in the printed packaging materials and have to be in line with the Commission Decisions and the relevant EU legislations. The EMA does not perform any more a details linguistic check but a general check regarding the readability to guarantee the safe use of the medicine.

At the time of the submission of the Application samples for testing the medicinal products are not required.

This readability/legibility check of the submitted mock-ups and specimens focuses on overall lay-out and design of the packaging and leaflet, font-sizes, positioning of text, use of colors, pictograms, blue-box-location, differentiation between strength, and presentation of critical labeling information. For the readability print size, color and lay-out are the most important factors. Items considered critical for the safe use of a medicine should appear in the same field of vision using a large font. This are the name of the medicinal product, the strength, (where relevant) the total content and the route of administration. Warning and storage conditions are also considered as critical information's.

The check will be performed by dedicated EMA staff in the Medical Information sector in close liaison with the Product Team Leader and the QRD secretariat. From this situation it becomes obvious, that the development of a tool to harmonize and to speed-up the assessment should be valuable.

2.2.3 Recommendations in Member States like for example Germany (DE), United Kingdom (UK) and France (FR) as well as from the United States of America (USA)

In some MS, for example Germany and England, national recommendations were developed in the last years.

DE

The Federal Ministry of Health of Germany initiated 2007 an Action Plan for the improvement of medication safety (in German: Arzneimitteltherapiesicherheit (AMTS)) [8, 9] which involves all parties in the medication process. International experiences were incorporated and necessary activities for a better medication safety were drawn up. Measure 24 of that Action Plan is aimed to minimize the risk of medication errors due to “sound-alike” or “look-alike” medicinal products.

Since April 2007 pharmacist in Germany are legally obligated to replace prescribed medicines though cheaper alternatives containing the same active ingredients. Medicines with the same active ingredients may look similar, but the dosage could be different. This may cause medication errors. Also the Corporate Design Strategy of pharmaceutical companies can lead to the confusion of “look-alike” medicines.

According to the Action Plan it is also important that patients are well informed for a better compliance. Patients should therefore get the information about the correct use, risks and potential harm that could be caused by the medicinal product. In 2008/2009, and 2010/2012 the Action Plan was maintained as progress of several actions was achieved [8, 9].

One favorite outcome are recommendations for a safe design of folding boxes agreed on by an industrial forum composed of several stakeholders in the area of medication [10].

Specific recommendations based on this document are below:

Clear Font**:**

The package has to be labeled over the longitudinal axis of the package; a sanserif font with same type sizes must be used; the name of the medicine should appear in one line; the characters should be 7 mm high; The name of the active ingredient has to be regarding type size in a balanced proportion to the type size of the name of the medicinal product.

Information of the quantity of the active ingredient:

The quantity of the active ingredient per divided pharmaceutical form must be written in the same type size as the registered trade name; different strength of a medicinal product with the same registered trade name should be presented in different colors or the quantity of the active ingredients should be deposited with different colors; packages for solutions for infusion or injection should contain information on the quantity per unit volume and the total quantity per total volume and the concentration of the active ingredient; on the packages of other liquids or semisolid pharmaceutical forms must be stated the concentration of the active ingredient normally as mg/ml respectively mg/g.

Information of the pharmaceutical form:

The pharmaceutical form has to be regarding the declaration in the European Pharmacopoeia.

Figure for scorability:

The outer packaging of not scorable tablets must be provided with the advice: “not scorable”; tablets which should only be scored for eased swallowing should be provided with the advice: “scoring only for easier swallowing and not for division into same dosages”. If the tablets are not scorable no pictogram of a tablet should be presented on the package so that scorability could be suspected.

Use of colors:

Colors can aid users to differentiate between different medicinal products. But colors should be used in a manner that the legibility of labeling elements is not affected, or that the appearance of the medicinal product is not extenuated and that the complete design does not lead to misuse, especially from children.

USA

Similar to the point “Figure for scorability” from the specific German recommendations in the USA a draft guidance for industry was published from the U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) “Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation” in August 2011 [28].

The Food and Drug Administration Agency (FDA) sees a need for consistent scoring between a generic product and it´s Reference Drug. The pharmaceutical form of a tablet can be manufactured with a score(s) or without a score(s) to facilitate the splitting into fractions. Then it is possible not to take the whole dose of one tablet. For the FDA there is a need for consistent scoring so that a patient is able to adjust the dose of a tablet by splitting it in the same manner as the Reference Drug. In the past it happened, that by splitting tablets of different manufacturers there were differences in content, weight, disintegration or dissolution with effects on absorption of the active ingredient.

UK

Also in the UK some really helpful and useful recommendations were worked out.

In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) has published guidance’s for all the parties involved in the design and layout of labeling. The MHRA is an executive of the Department of Health and responsible for the regulation of all medicines and medical devices. The intended scope of the guidance is to help to improve the way in which labeling information is presented to health care professionals and to patients. This guidance applies to medicinal products available on prescription and also for non-prescription (over the counter) medicines.

For example in the **“**Blue Guide – Best practice guidance on the labelling and packaging of medicines (Advertising and promotion of medicines in the UK)” comprehensive guidance can be found about the interpretation of the legal

requirements for advertising medicines in the UK and how such advertising is regulated [11].

Also in the UK, the National Patient Safety Agency (NHS) as an Arm's Length Body of the Department of Health takes the mandate to lead and contribute to improved, safe patient care by information, support and influence of organizations and people working in the health sector. The "Design for Patient Safety series" want to give advice on how better design can reduce the risk for patient and how the working environment can be improved for those relating with medicinal products for human use [12].

The "Design of Patient Safety series" want to help to avoid mistakes people make because the systems, tasks and processes they work within are poorly designed. The idea of the series is, that effective design has to lead to products and processes and environments that are intuitive and simple to understand and to use, convenient and comfortable. The still existing knowledge and methods from the design world could be used to improve labeling design.

As a result of a design research collaboration between the National Patient Safety Agency (NPSA) and the Helen Hamlyn Research Centre (HHRC) at the Royal College of Art, London a "Design for patient safety - A guide to the graphic design of medication packaging" was first published in 2006, the second edition in 2007 [12].

This guide is written to help designers to understand quickly and simply how and why good packaging design and the clear labeling of medicinal products can lead to improved patient safety. The needs and capabilities of the widest range of potential users (especially older, partially sighted persons and children) should be taken into account when designing packaging. But also the needs of the pharmacist which have to identify, classify and differentiate between medicinal packages are very important. Therefore in this guide current medicines packages were analyzed over a one-year period regarding common problem factors and as a result design solutions were proposed. In the guide a fully illustrated set of design considerations with good and bad examples can be found.

A "Packaging design checklist" with key factors with impact on patient's safety and design recommendations for primary packaging and secondary packaging design are presented. Further it is recommended in the guide that pharmaceutical companies should, with the help of designers, use own methods testing their packages on users.

Specific recommendations - based on this document - are "highlighted" below:

> A clearly defined space for "dispensing labels" with a minimum size of 70 x 35 mm and the generic name and strength of the medicine should appear directly above or beside the space provided for the dispensing label.
>
> The critical information should appear on at least three (if possible on more) non-opposing faces of the secondary packaging: on the top, on the bottom and on the side faces.

The text on every face excluding the ends should be orientated in the same direction.

The generic name should be in 16 point size or bigger because when the patient is given different brands of the same medication this could lead to confusion.

In medicines names “Tallmann lettering” should be used to emphasize the differences between “look-alike” and “sound-alike” medicines names.

Medicines strength should stand out through type face, type weight, color or shape.

Minimum recommended type size should be 12 points but 14 points should be more accessible for patients with sight difficulties.

Capital letters should not be used for generic medicines names, brand names or paragraphs.

Sanserif type faces should be used such as Arial, Helvetica or Univers. Serif type faces should not be used for medication packaging where clarity, accuracy and legibility are very important.

Bold or semi-bold type should be used and lightweight type avoided because it reduces legibility what is especially important for partially sighted patients.

Condensed type face should be avoided because legibility is reduced.

Lines of text should not be squashed together. If text is in 12 point, the leading should be 16 point. The text between lines should not be adjusted because this would enhance legibility.

Text should be aligned to the left hand margin and text should not be justified because an irregular amount of space between words affects legibility.

Opposing, meaningless colors should be used to distinguish between medicines with similar names in a Manufacturer`s range. An awareness of users with limited color perception should be developed.

The products primary and secondary packaging should have an identical or linked visual style created through, for example color.

Further on some new ideas are discussed like putting small products in larger packaging or matching machine-readable codes on packaging and dispensing labels.

FR

Since the end of the 1970s in France exists Prescrire situated in Paris, an independent, non-profit continuing education organization, committed to better patient care. This organization was founded by some French doctors and pharmacist which had the ideas to provide independent information by and for healthcare professionals and to publish a reliable and independent journal adapted to the needs of primary care. From 1981 to 1987 the organization received an annual grant from France´s Health Ministry. The aim is also to give the patients clear, comprehensive and reliable information about their drugs, drug-therapies and diagnostic strategies.

On 29 November 2012 Prescrire published the document “Safety and usability of packaging and labelling: assessment is required prior to marketing authorisation for all medicinal products, not just for copies of existing drugs (hereinafter “Safety and usability of packaging and labelling”)” [13]. With this publication Prescrire asks for the assessment of packaging and labeling of new medicinal products as part of the evaluation of Marketing Applications and also the packaging of all existing medicines should be re-exanimated by European and National Authorities.

For Prescrire poorly designed packaging expose patients to the risk of medication errors. Therefore pharmaceutical companies and Drug Regulatory Agencies granting MA must give the packaging (outer packs, PL, blisters, child-proof caps, etc.) more importance regarding patient safety and medication errors that could be avoided. Findings of risk of error associated with the packaging a medicinal product should be published in a medication error public assessment report at the beginning of the registration process so that it would be possible to implement improvements before granting the MA. Also the mock-ups of all packaging items should be publicly accessible.

With the submission of the Application dossier an evaluation of the packaging material should be provided. For this reason the Authorities must strengthen their teams, resources and expertise in packaging analysis. It is proposed to extend Readability test to all information on the packaging materials of medicinal products. Graphical information that has been deemed unsatisfactory in tests should be prohibited.

In the document “Safety and usability of packaging and labelling” in Proposal 2 quality and safety standards for packaging are given. Specific recommendations based on this document are “highlighted” below:

(1) The international nonproprietary name (INN) and dose strength must be prominently and legibly displayed on labeling and PL`s to ensure that medicines are identified by their real name; the brand name should have less prominence than the INN;

(2) The essential information must be clearly displayed on at least 3 surfaces of the secondary packaging, leaving adequate space to systematically add patient-specific information about the treatment, either handwritten or in the form of a “dispensing label”;

(3) Font sizes must be large enough to be read easily

(4) Clear descriptions of dose strength and concentration must be given;

(5) All medicines whose doses are standardized must be supplied in unit dose presentations that are ready to use or administer;

(6) Unintelligible multi-language packaging must be rejected;

(7) Graphics, pictograms and colors have to be evaluated, mainly used to help users discriminate between different dose strengths of the same medicine, paying special attention to color coding that might cause errors by providing a false sense of security;

(8) Bulk bottles for tablets and capsules, beginning with substances that are fatal to children (e.g. iron, methotrexate, quinine) and orodispersible medicines should not be produced;

(9) Each dose of tablets or capsules packaged in blister packs must be individually and fully labeled, and on blister packs a safety film containing particularly dangerous drugs must be presented; a child-proof cap must be provided on bottles of oral liquid medicines, unless accidental ingestion has been shown to be harmless;

(10) Multi-dose oral liquid forms must be supplied with an appropriate dosing device of suitable 5/8 capacity and accuracy (such as an oral delivery syringe graduated in milligrams or units).

3 Proposal of a decision matrix to assess design and layout of labeling

3.1 Development of the decision matrix

To develop the decision matrix all the relevant points for the evaluation of the design of the folding boxes which were found in the European recommendations especially the “Readability Guideline” and the “QRD recommendations on pack design and labelling” were grouped thematically and listed in a table.

The first consideration was to classify the requirements into four higher-level categories:

- “Overall layout and design”
- “Use of colors and pictograms”
- “Other important information for non-prescription medicines” and
- “Presentation and positioning of critical labeling information for safe use of medicines – differentiation between strengths”.

Under the first higher-level category “Overall layout and design” three subcategories were created:

- “Type Size and font”
- “Design and layout of information” and
- “Text positioning and boxing”

Under the second superordinate category “Use of colors and pictograms” also three subcategories can be found like:

- “Print color”
- “Paper” and
- “Use of symbols and pictograms”

The third higher-level category “Other important information for non-prescription medicines” has no subcategories.

The fourth higher-level category “Presentation and positioning of critical labeling information for safe use of medicine – differentiation between strengths” is divided into the information that is especially critical for safe use i.e.

- The “name of the medicine”
- The “strength and (where relevant) the total content”
- The “route of administration” and
- The “active substance".

For each subcategory various criteria have been selected from the European recommendations for pack design, but only those relevant for outer labeling. The items were phrased as questions to be answered with assessment clear “yes” or “no”. When one item is not relevant a specic folding box the assessment would be “not applicable (na)”.

For the answer “yes”, which means that the recommendation has been implemented, a level of compliance was introduced. This provides the opportunity to assess the degree and the quality of the implementation of a specific recommendation. If the recommendation has been implemented very well the level of compliance is 5, when the level of compliance is not that good the value is 3, when it is even worse, the value is 1. In case of “no” the level of compliance is 0, if “not applicable (na)” is stated there will be no value (-).

3.2 Which criterion is provided by which recommendation

For the above mentioned higher-level categories and below criteria the source will be mentioned and the most important information is “highlighted”.

3.2.1 Overall layout and design

3.2.1.1 Type size and font

Readability Guideline, Chapter 1, section A, recommendations for package leaflet, also applicable for labelling [6]

> A font should be easy to read. For this reason stylized fonts should be avoided because they are difficult to read. Furthermore in the chosen font similar letters/numbers, such as “i”, “l” and “1” should be easily distinguished from each other.
>
> The type size should be as large as possible. Especially when the medicinal product is intended for an indication linked to visual impairment and also on small packs. As a minimum 9 points are recommended (measured in font “Times New Roman”, not narrowed). Different text sizes should be used to enable key information’s to stand out and to facilitate navigation in the text.
>
> The space between the lines should be at least minimum 3 mm.

Readability Guideline, Chapter 1, section A, Recommendations for package leaflet, also applicable for labeling and *QRD recommendations for pack design and labeling for centrally authorized non-prescription human medicinal products*

> Widespread use of capitals should be avoided and lower case text should be chosen for larger text blocks. But as method for emphasis capitals could be useful. In addition to capitals also italics and underlining make it more difficult for the reader to recognize the word shape and should not been used.

3.2.1.2 Design and layout of information

Readability Guideline, Chapter 1, section A, Recommendations for package leaflet, also applicable for labelling

Line spaces should be kept clear and the space between one line and the next should be at least 1.5 times the space between words on a line because the line space influences the clarity of the text.

The contrast between the text and the background is also important. Too little contrast adversely affects the accessibility of the information. And also for this reason background images should not be placed behind the text.

Readability Guideline, Chapter 1, section B, Recommendations for labelling

There should be made best use of the space available to ensure that important information is clearly mentioned on prime space and in a sufficiently large type size on outer and immediate packaging.

Special consideration should be given to line-spacing and the use of white space to enhance the legibility of the information provided.

For small packs, where it is not possible to present all information in the same field of view, innovative techniques in packaging design may be used to aid the identification and selection of the medicine. For example the use of wrap-around or concertina labels are recommended and paper labels for ampoules to increase the legibility of the information.

QRD recommendations for pack design and labeling for centrally authorized non-prescription human medicinal products [7]

The largest type size possible should be used on all components.

3.2.1.3 Text positioning and boxing

Readability Guideline, Chapter 1, section B, Recommendations for labelling

Company logos and pictograms can be included on outer and immediate packaging when they do not interfere with the legibility of the mandatory information and if there is enough space.

On multilingual packages there should be a clear demarcation between the different languages where space permits. The information should be grouped per language.

Space for the “prescribed dose” to be indicated must been included on all outer packaging and/or “blue box information” as required by MS. These blue box requirements for Central Approval can be found in the “Guideline on the packaging information of medicinal products for human use authorized by the Community” (Notice to Applicants Volume 2 C).

QRD recommendations for pack design and labeling for centrally authorized non-prescription human medicinal products

To have enough space for the product information the company details should be moved on a side panel.

The information should be grouped per language on multilingual packs. When it is not possible to place all information in different languages on the same panel, each panel can be used per language.

3.2.2 Use of colors and pictograms

3.2.2.1 Print color

Readability Guideline, Chapter 1, section A, Recommendations for package leaflet, also applicable for labelling

Different type sizes and also different colors are a way to make headings or other important information clearly recognizable. Different characters may be printed in one or several colors allowing them to be clearly distinguished from the background.

The relationship between the colors is as important as the colors themselves. As the best possibility dark text should be printed on a light background. To highlight, for example special warnings, it could be considered to use light text on a dark background. Under these circumstances a larger type size or bold text could be useful. For the text and the background there should not be used similar colors as legibility could be impaired.

Readability Guideline, Chapter 1, section B, Recommendations for labeling

Similarity's in packaging and therefore medication errors could be reduced by the judicious use of colors on the packaging. For the same reason the colors of the outer packs should be carried onto the primary packs also.

Readability Guideline, Chapter 1, section B, Recommendations for labeling and *QRD recommendations for pack design and labeling for centrally authorized non-prescription human medicinal products*

Different colors in the name of the product are not recommended because they could maybe impede the correct identification of the product name. But it is strongly recommended to use different colors for distinguishing different strength of a medicinal product.

QRD recommendations for pack design and labeling for centrally authorized non-prescription human medicinal products

With colors on packaging good differentiation between packs is possible but they should not impact on the legibility of information or encourage misuse, especially by children.

Judicious use of colors on packs is important to avoid similarity in packaging which contributes to medication error. As important is it, to consider the number of colors used, because too many colors may cause confusion.

Colors of outer packs should been carried onto primary packaging to aid the user identifying the medicine.

3.2.2.2 Paper

Readability Guideline, Chapter 1, section A, Recommendations for package leaflet, also applicable for labelling

Paper should be sufficiently thick to reduce transparency because otherwise reading would be difficult, especially smaller text. For this reason also glossy paper which reflects the light should be avoided. Uncoated paper should be used instead.

3.2.2.3 Use of symbols and pictograms

Readability Guideline, Chapter 1, section A, Recommendations for package leaflet, also applicable for labelling

Symbols and pictograms are allowed regarding Article 62 of Directive 2001/83/EC provided they do not have an advertising message. They can be useful if their meaning is clear and not confusing or misleading and if they are not too big. They should be generally understood, only clarify messages, highlight important aspects, aid the users and should not replace other important information.

QRD recommendations for pack design and labeling for centrally authorized non-prescription human medicinal products

Symbols and pictograms should not interfere with the legibility of the mandatory, statutory information and should be used to explain the appropriate and safe use of the medicine.

Medicines should be clearly distinguishable from other medicinal products and from non-medicinal products with the help of symbols and pictograms and they should be useful to identify individual medicines.

3.2.3 Other important information for non-prescription medicines

QRD recommendations for pack design and labeling for centrally authorized non-prescription human medicinal products

For the appropriate selection and the safe use there is other important information for non-prescription medicines like the authorized therapeutic indication, dosage, contraindication(s), warnings, instruction for use (“Read the package leaflet before use”).

This information should appear on the packaging in the same field of view in a clear font and a sufficiently large type size. It has to be evaluated for example, for small packs or multilingual packages, if this information can be accommodated within the same panel or not.

3.2.4 Presentation and positioning of critical labeling information for safe use of medicines – Differentiation between strength

3.2.4.1 Name of medicine (Art. 54(a) Directive 2001/83/EC)

Readability Guideline, Chapter 1, section B, Recommendations for labelling

> For the correct identification of the medicinal product the outer and the immediate packaging should include the name of the medicinal product, with its strength and its pharmaceutical form and, if appropriate, if it is intended for babies, children or adults.
>
> When a medicinal product contains more than tree active ingredients, the INN / common name(s) of these active ingredient(s) should be stated after the full name for safety reasons.

QRD recommendations for pack design and labeling for centrally authorized non-prescription human medicinal products

> The invented name and strength may appear in the same line. If they appear as a cohesive unit it is possible that invented name, strength, pharmaceutical form and active substance appear in different lines.
>
> The name of the medicine should appear prominently, on prime space, especially on the front panel, using a sufficiently large font type. For better identification on the shelf it should appear on at least three non-opposing sides of the outer carton.

3.2.4.2 Strength and (where relevant) total content

Readability Guideline, Chapter 1, section B, Recommendations for labelling

> Under certain circumstances, especially for safety reasons (for example for injections, solutions or suspensions), the packaging should contain the quantity per unit volume and the total quantity per total volume.
>
> Also for safety reasons micrograms should be spelt out in full, not abbreviated. Only if there is not enough space on the package this is acceptable, if there are no safety concerns.
>
> Different strength of a medicinal product should be expressed in the same manner. 250 mg, 1000 mg and not 1 g. Trailing zeros (2.5 mg and not 2.50 mg) and decimal points or commas (250 mg and not 0.25 mg) should be avoided.

QRD recommendations for pack design and labeling for centrally authorized non-prescription human medicinal products

> The strength should be preferably stated only once on each side of the package and within the name of the medicine. When further repeated it should not be confused with the pack size.

3.2.4.3 Route of administration

Readability Guideline, Chapter 1, section B, Recommendations for labelling

> Only standard abbreviations should be used like i.v., i.m. or s.c. and other non-standard routes of administration should be spelled out in full.

QRD recommendations for pack design and labeling for centrally authorized non-prescription human medicinal products

> The route of administration should appear in the same field of vision as the rest of the critical information.

3.2.4.4 Active substance

QRD recommendations for pack design and labeling for centrally authorized non-prescription human medicinal products

> The active substance should appear on the front of the pack in the same field of view as the name of the medicine. If active substance and name of the medicine are presented in different lines they must appear as a cohesive unit. This is especially important, if different active substances are included in the same umbrella brand of a range of medicines.
>
> The names of the active substance(s) must not been repeated on the sides or flaps but were the names are included; the type sizes should be in the same relative proportion to the name of the medicine as they are on the front pack.

3.2.5 Braille

Readability Guideline, Chapter 2, specific Recommendations for blind and partially sighted patients

> Regarding Art 65(a) of Directive 2001/83/EC the name of the medicinal product must also be expressed in braille format on the packaging for the clear identification for blind people.
>
> On multilingual packaging the name in Braille must be included on the packages in all different languages.
>
> Further information or the name in Braille on all packaging components can be presented on bigger packages on a voluntary basis. On smaller packs contracted Braille systems can be used.

3.3 Decision matrix template

On the following pages the decision matrix template is presented. This template has been used for evaluation of the samples and was a matter of review on its own.

Figure 3: Proposal for decision matrix developed from legal requirements and available guidance documents – Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. xx - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = 0; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?		
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?		
	• Type size as large as possible used?		
	• Is space between lines at least 3 mm?		
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?		
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?		
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)		
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?		
	• Is related information standing together?		
	• Is there enough contrast between text and background?		
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)		
	• Is dark print on light background considered where small type sizes have been used?		
	• Multi-lingual packaging (if relevant):		
	- Is clear demarcation between different languages infixed where space permits?		
	- Is information per language grouped when feasible?		
	- When space does not allow display of all information in different languages on same panel is each panel per language used?		
	- Is content of all languages versions identical?		
	• Is space for prescribed dose included to be indicated?		
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)		

Figure 4: Proposal for decision matrix developed from legal requirements and available guidance documents – Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. xx - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = 0; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! **Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.**	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?		
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)		
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?		
PAPER			
	• Was uncoated carton used?		
	• Was highly glossy, metallic or reflective packaging avoided?		
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?		
	• Are no elements of promotional nature used?		
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?		
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?		

Figure 5 Proposal for decision matrix developed from legal requirements and available guidance documents – Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. xx - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = 0; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?		
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?		
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?		
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?		
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?		
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?		
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!		
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?		
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?		
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?		
	• Were micrograms spelt out in full and not abbreviated for safety reasons?		
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?		
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?		
	• Does route of administration appear in front of pack in same field of vision as name of medicine?		
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?		
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?		
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).		
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?		
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?		

4 Results from evaluation of the Example-Mock-ups

Nineteen example mock-ups were evaluated. Mock-ups one to twelve were mock-ups of centrally approved medicines and mock-ups thirteen to nineteen of not centrally approved medicinal products.

4.1 Do all decision criteria apply to all mock-ups assessed?

The “Readability Guideline” [6] gives advice to MAHs, for all MA procedures, for all medicinal products including those available without prescription. Therefore the recommendations apply to all nineteen mock-ups.

The “QRD recommendations on pack design and labeling” [7] give guidance to MAHs across the EU when preparing mock-ups and specimens of sales presentations for non-prescription medicines within the CP. Although national practices on pack design differ across the MS the recommendations of the QRD templates should be considered in this context. As a number of general rules have been defined, these recommendations were used for the evaluation of mock-ups number one to twelve as well.

A number of recommendations from the “Readability Guideline” have been repeated in the “QRD recommendations on pack design and labeling”. But the latter provide some more details about the differentiation of critical and other important information, especially about the presentation of the active substance name, which is missing in the “Readability Guideline”.

4.2 Issues during examination and results after applying the decision matrix evaluating the mock-ups

4.2.1 Overall comments on layout and design

4.2.1.1 Type size and font

First of all the original format of the mock-up respectively the size of the printed folding box is very important. When on the mock-up no dimension for the dimension for the package is given, it is impossible to evaluate type sizes and fonts and the space between the lines correctly. Not on all example mock-ups the formats of the packs were specified.

All companies presented the formats in a different manner and sometimes it was not mentioned that the given data should be understood as the dimension of the folding box. In some of the examples measurement units, like for example millimeter, cannot

be found or it is not specified which number means the Lengths (L), the Widths (W) or the Depths (D) of the package.

Normally, measurements are written according to industry standards clearly mentioning the three dimensions: L, W and D. They should appear in the order (L x W x D) [29, 30]. This was mostly not the fact for the evaluated mock-ups.

For font types it is required, that they should have at least 7 points (or a size where the lower case “X” is at least 1.4 mm in height in case of labeling). Since 1735 the size of font type is usually measured in points what is a unit of length. With the rise of the digital typesetting since approximately 1990 in typography a point is a desktop publishing point and is equivalent to 0,3527 mm. Points are an usual measure for font size which most people prefer but for example Macintosh and Windows computers display points differently because they have different DPI (Dots per inch) [31].

For this reason, when measuring font sizes in points, it is not sure that the font sizes of different mock-ups are equal.

As an example of a serif font “Times New Roman” is mentioned. This is a font with many old style characteristics but was adapted in a way to give excellent legibility coupled with economy. So it is used for many print categories like books, magazines, reports but also for advertising [32]. For labeling items the “Readability-Guideline” does not recommend specific type faces, only that narrowed fonts should be avoided. Serif type sizes like Times New Roman are type faces with small terminal strokes added to the end of the main stroke or line of a character and are harder to read on medication packages [12].

Sans-serif type fonts like Arial here in the text are type faces without serifs and might be better to read in case of short information texts as labeling items used to be.

On all mock-ups analyzed sanserif fonts are used, except Mock-up No. 16.

Generally it would be better to choose a font size that is easy to read. For older people of 65 and over or for people with known visual handicaps the text should have a size from 14 to 18 points. For people in the 40-65 age range 11 to 12 points should be used as for most people. So it is clear that 7 points are not very much. To choose a good type size it is important to know as much as possible about generally accepted guidelines on point-size, x-height, character spacing, alignment and type styles.

On almost all the mock-ups (where it could be evaluated) the type sizes were too small and had not even 7 points. The type size was not used as large as possible. For example on Mock-up No. 09 the smallest type size was 4.5 points or on Mock-up No. 02 where the important information and the product-specific information (like the excipients) is presented in a type size of 5 points.

For legibility and readability line spacing is also very important. In this sense the recommendations given are not very precise.

If the dimension of a folding box was given the size of the pdf-file of a mock-up was increased in size regarding the given size so that the magnification factor was 100%. Then the mock-up could be printed for example to evaluate the size of the font or the space between lines. If it was too big for one DIN-A4-Page, different pages were printed and must be glued together. After this the type size and the space between the lines were measured with a typo meter or simply with a ruler. The smaller the type size the more difficult it was to measure.

Some pdf´s of the mock-ups had a very bad picture resolution for example Mock-up No. 03, especially page No. 02 with the folding box. And further on Mock-up No. 11 the boxed area with the technical data had such a bad picture resolution that even with magnification it was almost not possible to read the information in the box.

A new and reasonable recommendation in the “Readability Guideline” is that different text sizes should be used to enable key information’s to stand out and to facilitate navigation in the text. In lots of examples the used type sizes were too similar to achieve any advantage.

The space between the lines was very difficult to evaluate and in some examples it was definitely less than recommended.

4.2.1.2 Design and layout of information

If the related information stands together, if white space was used and consideration given to line-spacing and if the space between one line and the next was at least 1.5 times the space between words on a line could not be evaluated for all cases. For all these evaluation criteria the size of the folding box was relevant but not always given.

In most of the examples the critical and other information stands mostly together but in some examples this was not good enough, as of Mock-up No. 03, page 2. In this case the text sizes of the information are too different to impose as related information and, therefore, do not appear as a cohesive unit. A good example in this context is Mock-up No. 04. But this is also an example to show, that too similar colors are chosen and therefore the information given is not clear enough. This is also the fact for the side flaps were the company details do not appear.

The evaluation of the contrast between text and background is a bit subjective and depends also from someone’s personal fancy. But for some cases it is relatively clear, for example black writing on a dark grey background would mean that the contrast is not good enough. Mock-up No. 07 is an example were the contrast between text and background is not good enough and makes it hard to read the

information on the package. But in almost all examples the contrast between text and background was good enough.

4.2.1.3 Text positioning and boxing

The bullet points under this subcategory, like the amount of space for company details, if dark print on light background was considered especially for small type sizes and if “space for prescribed dose to be indicated” was included or a “blue box” for centrally authorized products can be evaluated quite easily.

For the centrally approved medicines only on Mock-up No. 09 no “blue-box” could be found. In the mock-ups of the not centrally approved medicinal products, Mock-up No. 16 to Mock-up No. 19, do not have space for a “dispensing label”. So in lots of cases the recommendations regarding this matter were not considered.

The criteria regarding multi-lingual packages are also clear and can be reviewed without doubts. Only Mock-up No. 08 and Mock-up No. 09 are multi-lingual packages. The information per language is the same in these cases but there are not really clear demarcations between the languages as recommended. In Mock-up No. 08 the other information is grouped in blocks per language and the language in which the information is written appears in the first line of the information. This is useful.

4.2.2 Use of colors and pictograms

4.2.2.1 Print color

The evaluation of the used colors for a package is not so easy because this is again dependent from someone’s personal fancy and is therefore subjective. Furthermore the recommendations given for the colors are not very concise, like the colors chosen should ensure good contrast between text and background and not too many, no similar and good colors should be used. Also the relationship between the colors should be good is a very vague recommendation.

But if different colors in the name of the products are used can be easily answered. In this context no further recommendations exist, for example which colors harmonize well with each other or which provide enough contrast.

One very important recommendation is to use different colors to distinguish different strength. In the examples in which was made use of this possibility it was not solved very successfully. On Mock-up No. 04, Mock-No. 07, Mock-up No. 10, Mock-up No. 11, Mock-up No. 12, Mock-up No. 14, Mock-up No. 15 and Mock-up No. 17. On Mock-up No. 10, Mock-up No. 14 and Mock-up No. 15 the strength is shown twice. One time following the name of the medicine and another time in a colored cycle

symbol what seems to be a bit confusing. Maybe Mock-up No. 11 is a good example but the strength is written in yellow and for this reason the contrast with the white background and the text is not big enough.

In Mock-up No. 12 the strength has another color like the name of the medicine but on the side flaps the strength is directly followed by the name of the medicine and on the most important front flap it stands in the line under the name of the medicine. This is a little bit confusing. Also the space between the name of the medicine and the strength is too big and the colored line underlying the text with the strength too long (longer as the text). So they really do not appear as a cohesive unit.

4.2.2.2 Paper

Uncoated carton should be used and highly glossy, metallic or reflective packaging should be avoided. When a MAH submits only a mock-up with his Application and not a specimen this aspect cannot be evaluated because the auditor cannot proof the original packaging and cannot evaluate the original carton or paper used.

4.2.2.3 Use of symbols and pictograms

First of all there were not many symbols or pictograms used for the evaluated mock-up`s.

If they interfere with the legibility of the mandatory, statutory information, if they are placed behind the text or if there is enough space on the package can be easily assessed. On the examined mock-ups this points were not relevant.

The other recommendations are again very broad and subjective. For example, if symbols and pictograms are useful to identify a medicine or to differentiate from other medicines and from non-medicinal products. Even vaguer are the questions, if their meaning is misleading or confusing or if they help to clarify certain information. So it can be assumed that a company must be very careful in using symbols and pictograms for their folding boxes and other packaging materials.

Generally it must be considered to use larger symbols and pictograms and that they should be relevant to pack design especially, if there is limited space. They should consist of a simple image and give a concrete instruction. This is especially important for non-prescription medicines where no doctor or pharmacist can explain their meaning. It should also be taken into consideration that there may be important cultural differences across the MS of the EU in the ability to interpret symbols and pictograms.

There were not so many pictograms used. On Mock-up No. 10 there is a pictogram used that is hard to interpret. On Mock-up No. 06 can be found an image of the “InnoLet” what must be the injection aid for this medicinal product. This seems to be

useful. On Mock-up No. 04 a little pictogram of a tablet is placed and the information “14 tablets Oral use” is written beside. This could aid users also to recognize that they have to take a tablet orally.

4.2.3 Other important information for non-prescription medicines

For the other important information it is not said which of the other information concretely should be placed on the package, in which order, or with which preference. It is only precisely said, that the information should be brought together in the same field of view.

This is the fact in most of the mock-up`s evaluated. In some cases this information is structured by for example “bold font” so it can be easier understood and important information stands out. For this Mock-up No. 14 is an example or Mock-up No. 18.

The “Guideline on Summary of Product Characteristics (SmPC)” as of September 2009 [26] gives advice about how the full information should be presented in the SmPC. Maybe these instructions could be helpful in certain occasions.

The statements that the font type should be clear and the type size large enough are imprecisely again.

4.2.4 Presentation and positioning of critical labeling information for safe use of medicines – Differentiation between strength

4.2.4.1 Name of medicine (Art. 54(a) Directive 2001/83/EC)

Regarding the name of the medicine it is clearly recommended that the name of the medicine has to appear together with its strength and pharmaceutical form as a cohesive unit. The definition of being a cohesive unit in this sense is not given. As there is guidance available for Applicants the decision will be taken arbitrarily. On the evaluated mock-ups the critical information is brought into the same field of vision but on some examples it is not solved that good because the space between the lines is too big or the font size is too similar for example on Mock-up No. 05. and Mock-up No. 06.. On Mock-up No. 01 the name of the medicine is written in capital letters what is not recommended.

The further recommendations like that the name of the medicine with its strength and pharmaceutical form should appear in a sufficient large font type on prime space, particularly on the front panel permits various possibilities for the implementation. The advice that it should appear on at least three non-opposing sides of an outer carton is clear. This was the fact on almost all evaluated mock-ups except Mock-up No. 05 and Mock-up No. 09.

The recommendation to state the INN/common name(S) of the active ingredients, if there are up to three, after the full name of the medicine could not been evaluated. Because none medicinal product under evaluation had more than three active ingredients.

4.2.4.2 Strength and (where relevant) total content

The recommendations that, under certain circumstances information on both quantity per unit volume and on total quantity per total volume should be given, enables the Applicants to decide by their own what to do or not. As examples to use this possibility, injectable products, solutions or suspensions are mentioned. In some mock-ups this recommendation was not followed, as for example Mock-up No. 01, Mock-up No. 08 and Mock-up No. 16. This recommendation was met for Mock-up No. 02 and Mock-up No. 03. In the other cases it was not applicable because it was not a relevant pharmaceutical form.

The “QRD Recommendations” recommend that the strength should appear within the name of the medicine preferably only once on each side of the package. The “Readability Guideline” gives further concrete advice on the manner of the expression of strength. Different strength should be expressed in the same manner, trailing zeros should not appear, decimal points or commas should be avoided, micrograms should spelt out in full for safety reasons and not abbreviated and strength should not be used as percentage. This is quite easy to evaluate.

The recommendation to spell out micrograms in full for safety reason was never followed by the Manufacturer.

Otherwise in none of the mock-ups appeared trailing zeros. Decimal points or commas were avoided in the expression of the strength. And it was also avoided to formulate the expression of strength as percentage. Therefore, these recommendations were taken into account.

4.2.4.3 Route of administration

The route of administration has to be in accordance with the SmPC. Generally accepted abbreviations can be used but it is in question, if patients understand for example the abbreviation i.v., or it is disputable, whether the abbreviations i.m. and s.c. will be understood better. Therefore the guidance given recommendation seems to be important.

But lots of mock-ups do not display the route of administration, at least not satisfactorily. Furthermore especially for tablets it is not mentioned on the package, that they have to be administered orally.

Relatively good examples have been seen on Mock-up No. 01, Mock-up No. 02, Mock-up No. 05, Mock-up No. 06, Mock-up No. 14 and Mock-up No. 15, where the route of administration is stated on the outer packaging and appears in the same field of vision as the rest of the critical information. Mock-up No. 10 displayed the information only on the font flap and on Mock-up No. 11 and Mock-up No. 12 the space between the lines is much too big, especially between the route of administration and the rest of the critical information. Therefore they do not really appear in the same field of view. On Mock-up No. 13 the statement regarding the route of administration is missing at all in the context of the critical information it just appears in between the other information.

4.2.4.4 Active substance

If medicinal products are injectable, topical or eye preparations all excipients have to be declared on the labeling regarding Article 54c of Directive 2001/83/EC. If excipients have a recognized action or effect and are included in the guidelines published by the Commission pursuant to Article 65, they also have to be declared on the labeling regarding Article 54(1)(c) of Directive 2001/83/EC. The relevant guideline “Excipients in the label and package leaflet” gives precise advice.

This recommendation was not followed on Mock-up No. 07 and not that good on Mockup No. 08 and Mock-up No. 09. On all the other mock-ups it was followed.

4.2.5 Braille

The recommendations given in the “Readability Guideline” are almost exactly the same as in the “Guidance concerning the Braille requirements for labeling and the package leaflet” from 2005, so the Guideline gives no new references [21]. They are very important for blind or partially-sighted people because otherwise these persons had no chance to differentiate between medicinal products.

On Mock-up No. 03, Mock-up No. 06, Mock-up No 07, Mock-up No. 09, Mock-up No. 10, Mock-up No. 16 the name of the medicinal product is not stated at all in Braille. On Mock-up No. 05 No. 06 it is only stated as comment beside the picture of the mock-up that the placement of “Braille” is on the front but no illustration can be found.

4.3 Further considerations after evaluating the mock-ups

After completing the decision matrix for a mock-up it would be useful to provide additionally an overall assessment with comments for each mock-up because with the help of the decision matrix not all aspects can be captured.

For example for Mock-up No. 07 bad colors were used and on Mock-up No. 10 lots of information was given several times and the reason is not clear. On Mock-up No. 11 the strength is written in yellow, a different color than the name of the medicine is chosen, but the contrast to the white background is not good enough. Or on Mock-up No. 16, very few information's are given and summarizing all aspects under evaluation it is a real bad example: the dimensions of the package are not given and the font is not clear because the other information is written in a font like Times New Roman and it is not clear, if it will be the definite font.

On Mock-up No. 18 a Company Logo can be found, hard to interpret, but no name of the MAH. Only the MAHs address is stated on the front panel and not on a side panel what is not recommended. On Mock-up No. 19 no colors are given and no dimensions, only the critical information is written in green. It also is a bad example for the design of a mock-up and respectively folding box.

4.4 Recommendations for Marketing Authorization Holders for mock-ups that can be easier reviewed

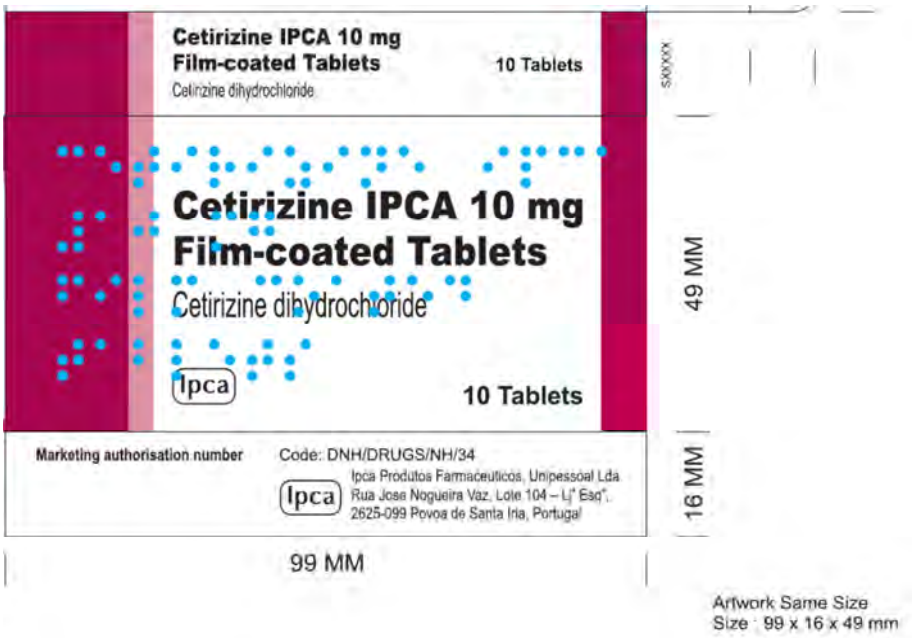
In the following is listed, which details should be displayed on a mock-up, easy to review by the Competent Authorities. The most important information was "highlighted".

4.4.1 Overall layout and design

4.4.1.1 Type size and font

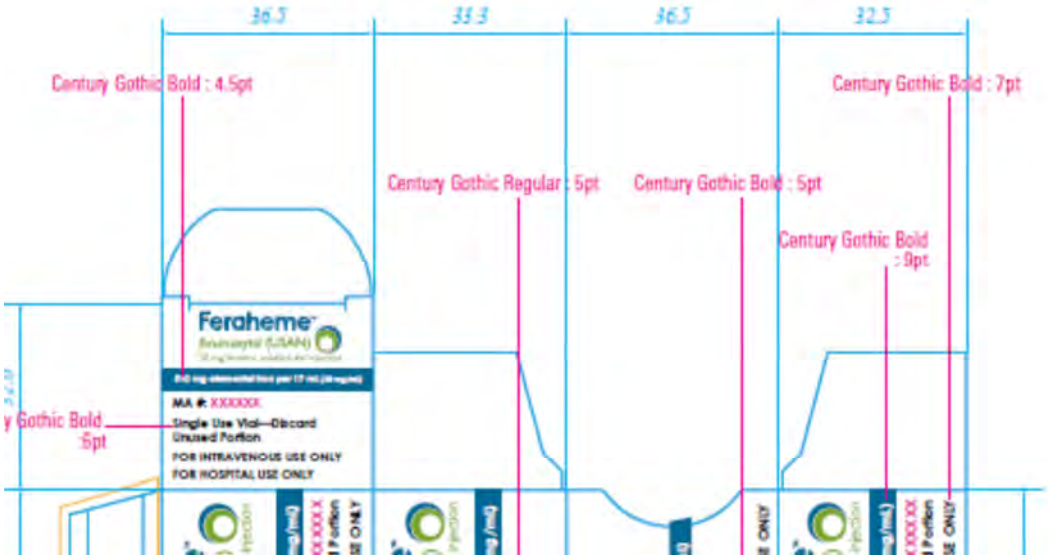
The dimensions of the format of the later package must be given on the mock-up with the correct measuring unit and when possible and useful in the order "(L x W x D)" (see Figure 6). In some cases it may not be not possible to define Length, Widths and Depts because the size of the flaps is equal or it cannot be clearly defined what is what.

Figure 6 Mock-up No. 13 with given dimensions / sizes of the format of the package but in the order L X D X W and not in the order "L x W x D"



The type size in points and the font which is used (especially which individual font, if it is a serif or sanserif font and if it is condensed or not) should be presented in the mock-up like for example in Mock-up No. 09 MAA (see Figure 7).

Figure 7 Mock-up No. 09 MAA with given fonts and type sizes and dimension of the package in detail



4.4.1.2 Design and layout of information

For the "design and layout information" no recommendations can be given regarding the presentation of the mock-ups. Only, that the mock-ups should be presented in color to evaluate the contrast between the text and the background and those should contain the information's about the colors and that they are designed like the later folding box.

4.4.1.3 Text positioning and boxing

It must be clear where the Company details can be found on the mock-up (see Figure 8 and Figure 9).

Figure 8 Mock-up No. 04 with good information on company details; additionally in box with the technical data: Telephone, Fax and e-mail; information on dates when mock-up was created or approved, on dimensions and on colors

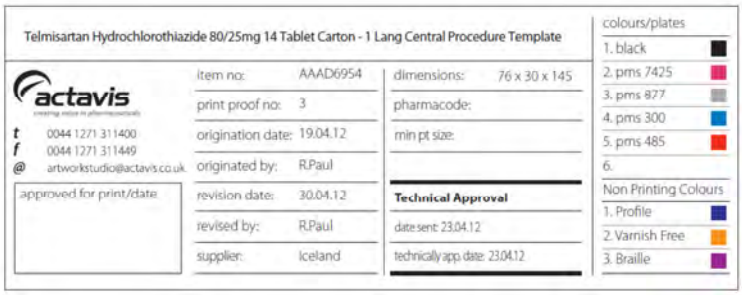


Figure 9 Mock-up No. 04 with good information on company details on the side flap, big enough but the amount of space used was not too big

It must be clear, if the package is a multi-lingual one.

The space for the “dispensing label” or the “blue-box” which must be included must be clearly marked on the mock-up. Therefore there must appear a boxed area (in the best case with a surrounding maybe colored line) on the mock-up with a text in it, for example: “Please affix dispensary label here” like on Mock-up No. 15 (see Figure 10 for a “dispensary label” and figure 11 and figure 12 for a “blue-box”).

Figure 10 Mock-up No. 15 with boxed area for space for "dispensary label"

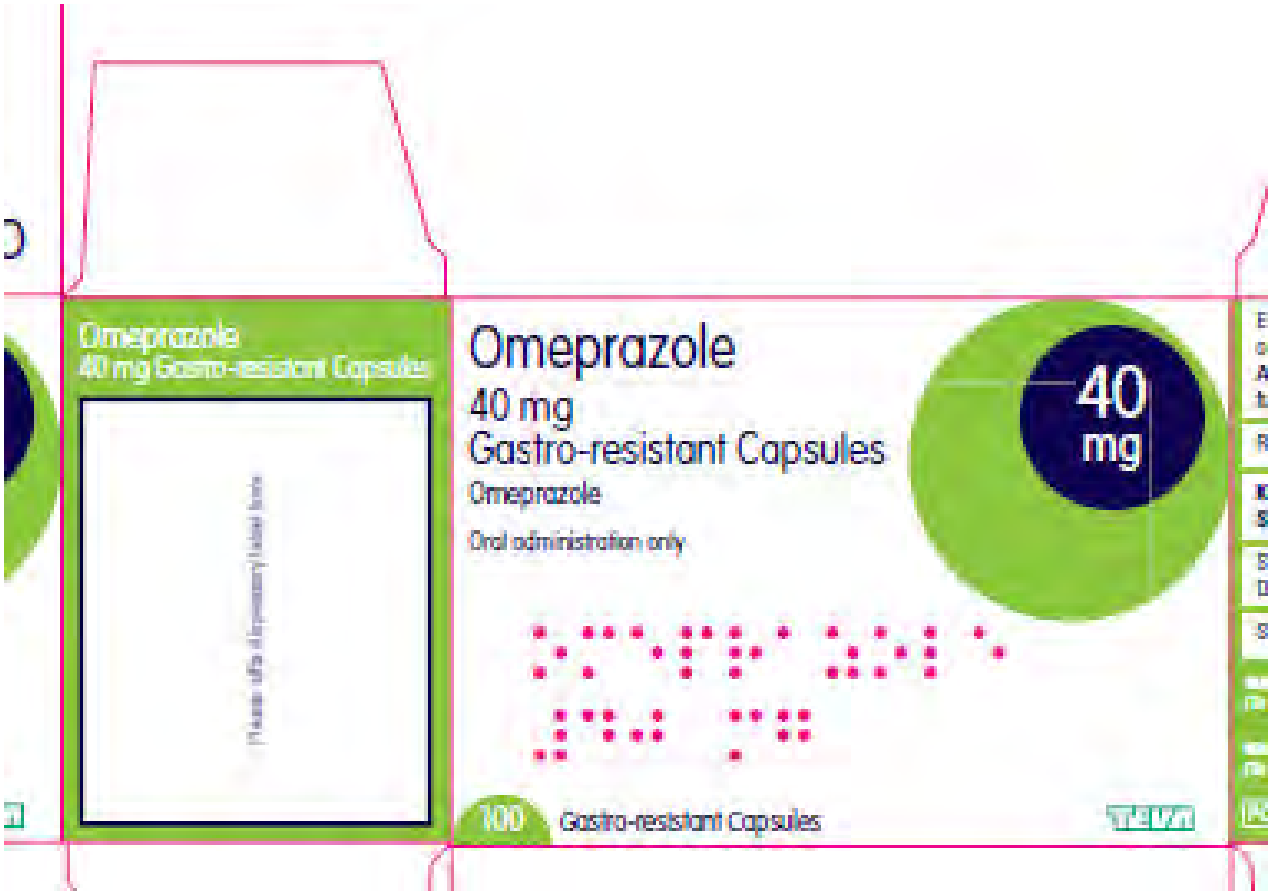
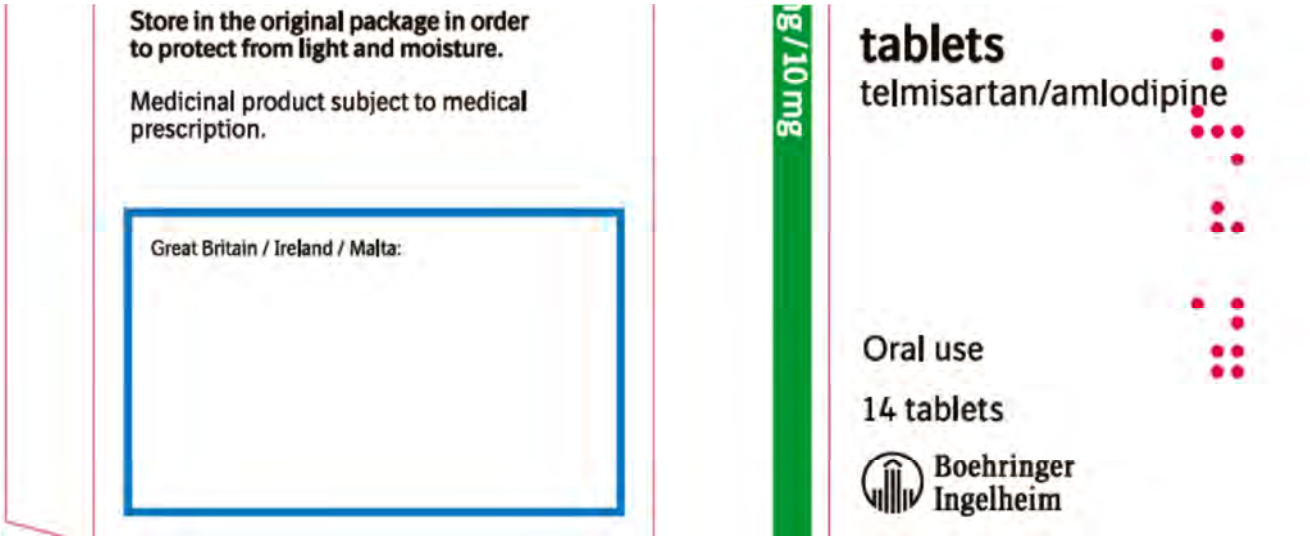


Figure 11 Mock-up No. 01 with a clearly boxed area for the "blue-box" and text in it

Figure 12 Mock-up No. 12 with a clearly boxed area for the "blue-box" and text in it



4.4.2 Use of colors and pictograms

4.4.2.1 Print color

Mock-ups should be presented in color to evaluate for example, if good colors are used and if the contrast between background and text is good or not.

4.4.2.2 Paper

For mock-ups which are submitted generally electronically and can only be displayed on monitors or printed on normal paper it cannot be evaluated, if uncoated carton was used or highly glossy, metallic or reflecting packaging material was avoided. This would only be possible for specimen.

4.4.2.3 Use of symbols and pictograms

Mock-ups should be submitted in a size in which symbols and pictograms are presented in the original size respectively they should be presented separately (on a separate document) in the original size so the evaluation, if they are useful or not, or if they are of promotional nature, or not, would be possible.

4.4.3 Other important information for non-prescription medicines

For the other information no recommendations can be given regarding the presentation on the mock-ups only that this information should appear on the package and that it should be possible to recognize, what kind of information it is.

4.4.4 Presentation and positioning of critical labeling information for safe use of medicines – Differentiation between strength

For “Presentation and positioning of critical labeling information for safe use of medicines – differentiation between strength” - no recommendations can be given regarding the presentation on the mock-ups.

4.4.5 Braille

It must be able to easily recognize (for example also with a different color) on a mock-up were the Braille-Format can be found. Even the best is to give same more precise information about the kind of the Braille-Format (see Figure 13 and Figure 14 and Figure 15).

Figure 13 Mock-up No. 04 with clear information regarding Braille

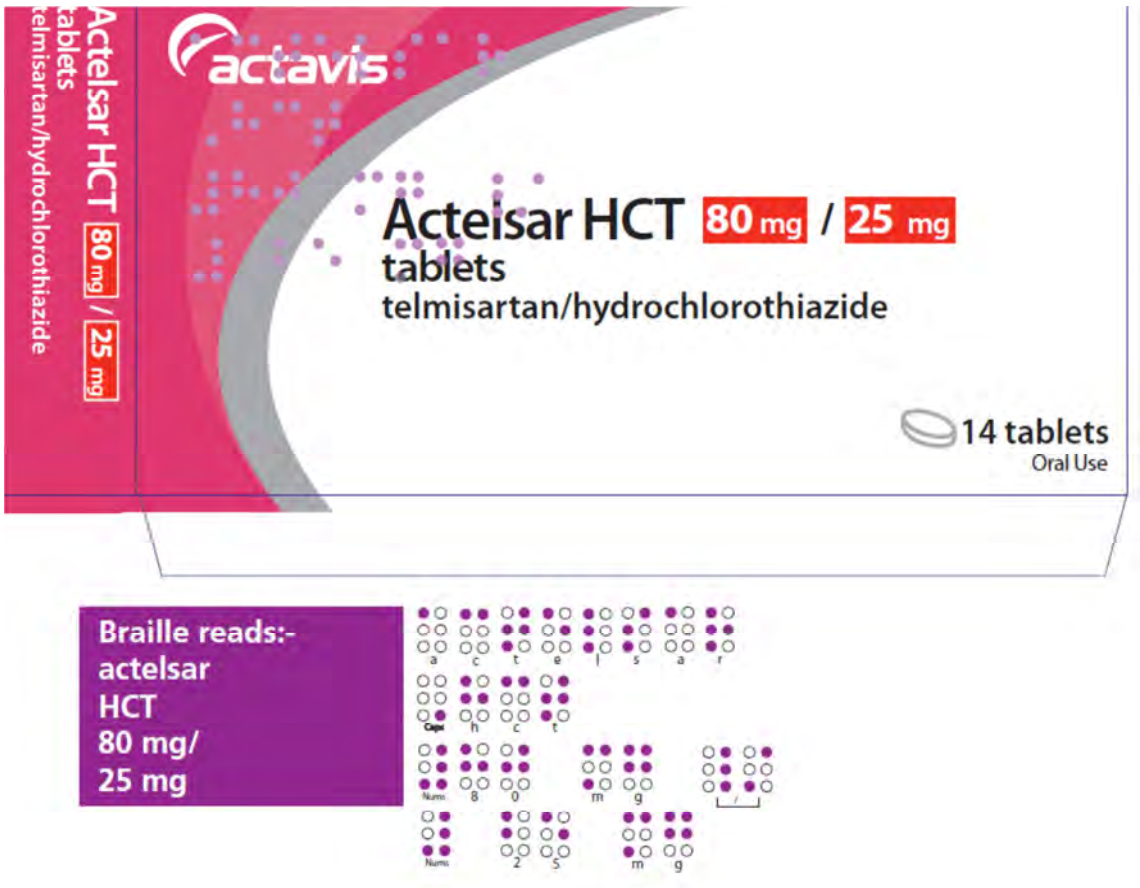
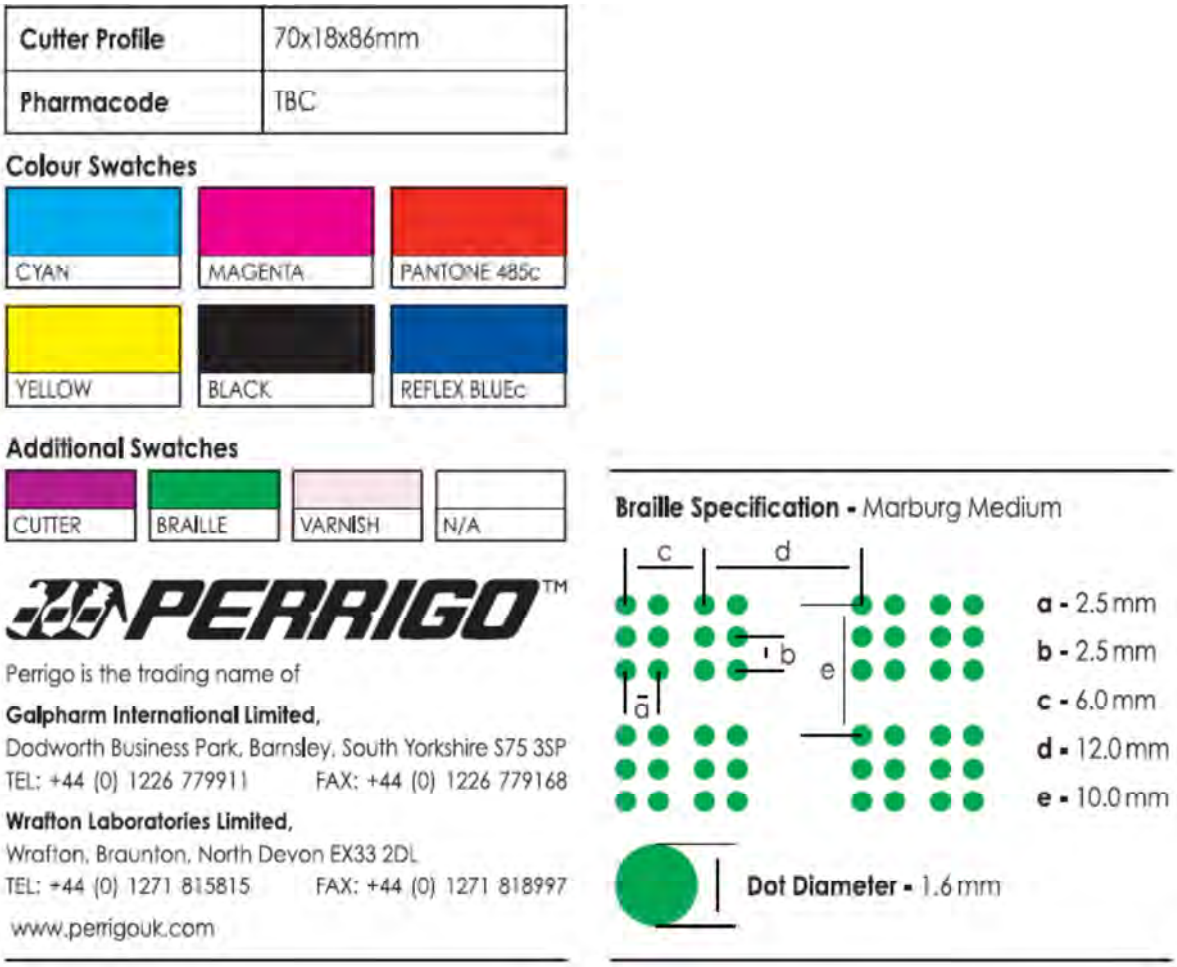


Figure 14 Mock-up No. 18 with clear information regarding Braille and the used colors in the box with technical details

Figure 15 Mock-up No. 18 with clear information regarding Braille and the used colors in the box with technical details (in a bigger sight to demonstrate the details in a better way



5 Discussion

The main actors involved in the assessment of the product information and therefore also the labeling are the QRD-Group, the EMA and other Competent Authorities. The pharmaceutical industry, especially the MAH, takes the responsibility. Patients and consumers and health care professionals as well as all people involved in the supply chain are considered as the users of that information. The overall aim is to provide legible, clear, correct and easy to use information on medicinal products. In the case of labeling this means, support for identification, basic instruction for use and by these means reduction of medication errors.

The guidelines and recommendations on labeling should support these intentions, but they are generally low level and non-specific and mostly fail to give evidence-based guidance. The contents of the “Readability Guideline” for example can be rated as not concise and little target-oriented. The recommendations are general, extensive and interpretable and give advice for exemptions. Therefore, they cannot be regarded as clear instructions for implementation. Due to additional nationally different recommendations the option to create labeling items fulfilling all criteria becomes even worse.

For all these reasons there is a need to consider study data to specify the recommendations given in the guidelines and to avoid unrealistic guidance. Beside the guidelines like the “Readability Guideline”[6] there exit several documents with “QRD recommendations” [7] and it would be better to concentrate the recommendations on a fewer number of guidance documents. The different documents overlap more or less and furthermore cause discussions which recommendation should be followed. It would be better to shorten the guidelines and recommendations. The content should be more precise and contain only the essential information. They should also be better understandable, clearer, and more practical at last more harmonized.

So it can be assumed that there is a need for optimization especially because of the importance of pack design and labeling particularly with “over-the-counter-medicines” which can be used without prescription. For them the impact on safety and appropriate use is in relation to prescription medicines for human use extraordinary high. Additionally there is a need to simplify the labeling.

Drugs marketed in poorly designed packages can expose patients to be in a risk of serious adverse events. To reduce the risk of medication errors the design of the essential information on the labeling and packaging must be clear and unambiguous. The use of colors is frequently inappropriate. Often irrelevant information is highlighted unnecessarily while on the other hand important information is barely visible. Appropriate use of colors for dose differentiation would be very important.

Color in design is generally very subjective and colors can evoke different reactions in different persons. This can be due to personal preferences or due to cultural background [33].

Generally warm colors like red, orange, yellow and variations of those colors are energizing, passionate and positive. They stimulate the viewer while cool colors calm down and relax. How colors behave in relation to each other is a complex area of color theory.

Regarding the cultural background red for example has outside the “Western World” different associations. In China it is the color of prosperity and happiness and in other eastern cultures it is worn by brides on their wedding days. In South Africa it is the color of the morning. Red is also associated with communism and with AIDS.

Orange is very vibrant and energetic and can be associated with earth and autumn. Often it is also associated with health and vitality.

Yellow is often considered the most energizing of the warm colors and associated with happiness and sunshine but for example also with danger. Yellow stands in Egypt for mourning, in Japan for courage and in India it is a color for merchants.

Green, blue and purple are cool colors and are the colors of water, of night, of nature. They are usually calming and relaxing. Blue is often used to represent calmness and responsibility, is sometimes associated with peace and has a spiritual and religious connotation in many cultures and traditions.

Purple was long associated with royalty and also with creativity and imagination. In Thailand it is the color of mourning for widows.

Neutral colors often serve as backdrop in design and commonly combined with brighter accent colors to surround them. Black is the strongest one and commonly associated with power, elegance and formality and on the negative side with evil, death and formality. It is a traditional color of mourning in many western countries and in some cultures associated with rebellion or Halloween and the occult.

White is at the opposite end of the spectrum form black and can be combined with other colors. In the western world it is commonly worn by brides on their wedding day and also associated with the health care industry.

So using colors is a very complex matter and companies have to consider lots of aspects when choosing the colors for their packaging materials. Corporate design also plays almost at any time a role.

Beside the colors another important aspect especially for the secure use of medicinal products is their dosage. Many devices for oral administration create a risk of misuse because they are not graduated in units or weight. They are graduated in milliliters and therefore patients have to use conversion charts potentially resulting in dosing errors. The same can happen with devices graduated in kg bodyweight.

The labeling of some injectable drugs is barely legible. This can also cause big problems for patients.

In the context of the problem of medication errors beside the labeling the naming and packaging of pharmaceuticals is also important. “Sound-alike” and “look-alike” names and packages can lead pharmacists and nurses to unintended interchanges of drugs. Patient can get injured or in the worst case die.

Pictograms included on folding boxes are often difficult to interpret. They must be clear and appropriate.

So it can be assumed that poorly designed drug packaging causes risks for patients. Therefore, companies should invest time to analyze and discuss drug packaging and labeling. They should develop Packaging Material Systems regarding the state of the art and in consideration of the regulatory requirements. In this context it is especially important to create safe medicinal products for human use which can be quickly approved and placed on the market without problems. This would be also important to efficiently implement changes regarding the product-lifecycle. But also the Drug Regulatory Authorities should help to ensure that drugs are sold in safe packaging. Nowadays packaging materials have a great significance for many medicinal products.

For example French Regulatory Agency worked on labeling of injectable drugs and the European Directive 2004/27/EC on medicines for human use provides for improvements in labeling (for example Braille) and PILs.

6 Conclusion and outlook

After creating the decision matrix and using it to evaluate the example mock-ups the overall conclusion is, that it is a valuable tool to support Regulatory Affairs staff.

The most important aspects regarding the evaluation of packaging design were listed in the decision matrix and it was useful to formulate the single points of the different categories in form of questions to allow a clear assessment with “yes” or “no”.

It can be discussed, whether there is a need to use a level of compliance but with this level of compliance it was easier to evaluate if one specific recommendation was implemented completely and to full satisfaction or not. To use an assessment “not applicable” was also helpfully because not always all aspects are relevant for all mock-ups. For example, if the mock-up refers to a multi-lingual package or not.

Maybe different points under one category or subcategory could be summarized to one point like under the category “Presentation and positioning of critical labeling information for safe use of medicine” on Page 3 of the decision matrix. Especially under the subcategory “Strength and (where relevant) total content of this category”. There was no mock-up under the evaluated mock-ups where trailing zeros appeared or where different strength of the same medicinal product where not expressed in the same manner (250 mg, 1000 mg not 1 g).

The most relevant point under this subcategory was the point: “Were micrograms spelt out in full and not abbreviated for safety reason”. In all evaluated mock-ups this recommendation was not realized, what means that microgram was always abbreviated what is not recommended.

Sometimes there are two or more questions in one point for example under “Use of colors and pictograms”: Is color chosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colors used? Are not too many colors used? When asking more than one questions in one point in the decision matrix it can be discussed, if it would be easier to understand to ask each question in a different point. But this would make the decision matrix more complicated and more voluminous. Furthermore in terms of saving time it should be taken into consideration to put various points in one question.

And it could even be considered, if even more points of the decision matrix could be eliminated and the decision matrix condensed.

Completing the decision matrix did not cost a lot of time, just about 15 minutes for each mock-up. If the mock-ups would be presented in a better way in the future the evaluation would be even easier and faster.

After filling in the decision matrix it would be helpful to give an overall assessment and recommendations for each mock-up. In this evaluation some points could be adhered to those which were not captured by the decision matrix or to make some more detailed remarks.

So it can be summarized that the decision matrix is a valuable tool to support Regulatory Affairs whether a given design will match with regulatory requirements.

It could be shown in this thesis that lots of recommendations were not followed and there was no mock-up where all of them were implemented. Furthermore, the presentation of the mock-ups was loss-making and could be improved a lot in most of the cases.

As stated in the discussion, there is a need to improve the guidelines and recommendations by shortening them and making them more precise focusing on only the essential information. They should be better understandable, clearer and more practical. It would be also very helpful to bring together all the national recommendations that exist apart from the European recommendations like for example in Germany, UK and France. It could be shown in the thesis that some of this information is really helpul and should be considered when revising the recommendations. As a preliminary action it would be most important to provide advice to pharmaceutical companies to improve their design of packaging material.

To facilitate the assessment on Agency' side the MAH must be given additional advice presenting their mock-ups in a better way as described under "4.4 Recommendations for MAHs for mock-ups that can be easier reviewed". This will include as a minimum the declaration of all dimensions of the planned package.

This would help to improve the usability of outer and immediate packaging of medicinal products for human use and help to improve their quality, safety and efficacy as required by Community law.

7 Summary

Human medicinal products must be used safely and appropriate and medication errors must be avoided because they will cause a substantial threat to patient's safety. Therefore the design of the immediate and outer packaging of medicines is very important and must guarantee a clear and unambiguous identification. Especially the critical information, like…., must be legible and easily accessible for the users so that they can understand and act according to this information. For non-prescription medicines this is particularly important as there is often no pharmacist´s advice reachable.

For this reason detailed legal requirements for labeling and European recommendations for the design process exist.

The objective of this thesis is to evaluate a number of different exemplary mock-ups with the help of above mentioned recommendations. They were read and assessed in terms of packaging design. A decision matrix was created containing just the points relevant for the overall layout and design of the folding boxes.

In total 19 mock-ups for different products were selected at random. The set could not be judged as representative one, but included prescription only and OTC products as well. The assessment demonstrated that lots of recommendations were not followed. Further on it could be identified that especially the presentation of the mock-ups was not satisfying. Therefore, proposals for the improvement of presentation of mock-ups were drawn up to support an easier review; arguments have been evaluated whether the decision matrix is a valuable tool to support Regulatory Affairs to assess compliance with regulatory requirements. Based on the practical experience it could be ascertained that it is a useful tool for Authorities to evaluate mock-ups.

In addition, MAHs must be given better advice how to present their mock-ups through improved guidelines and recommendations. These documents must be shortened, become more precise and should contain only the essential information. Furthermore, they should be better understandable, clearer and more practical. It would be also very helpful to harmonize and bring all the national recommendations together that exist apart from the European recommendations.

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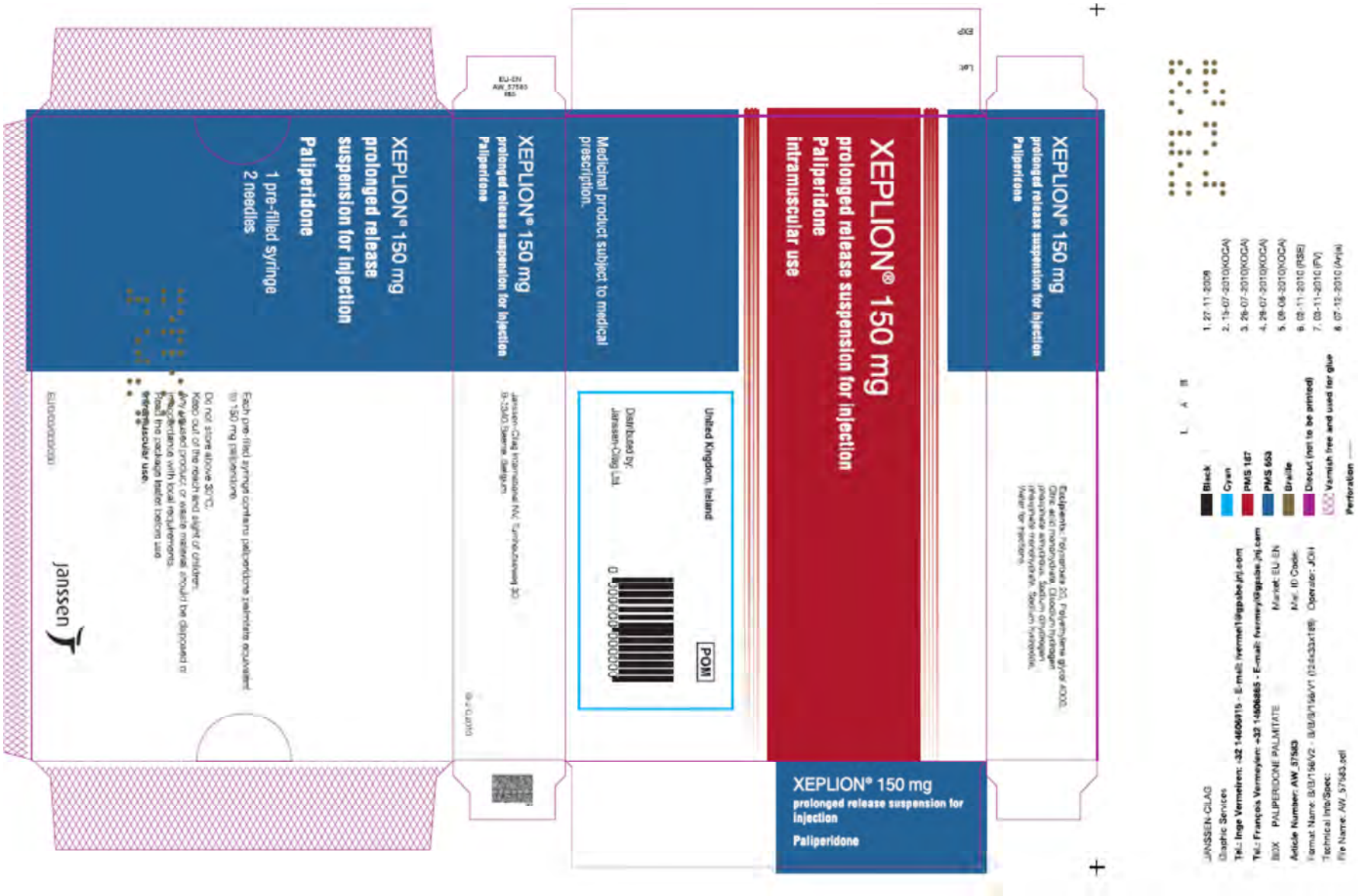
Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Annex 1 = Mock-up No. 01



Decision matrix Mock-up No. 01 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 01 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = 0; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes**	**5**
	• Type size as large as possible used?	**no**	**0**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**5**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no (bold)**	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**no**	**0**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**5**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**5**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**yes**	**5**

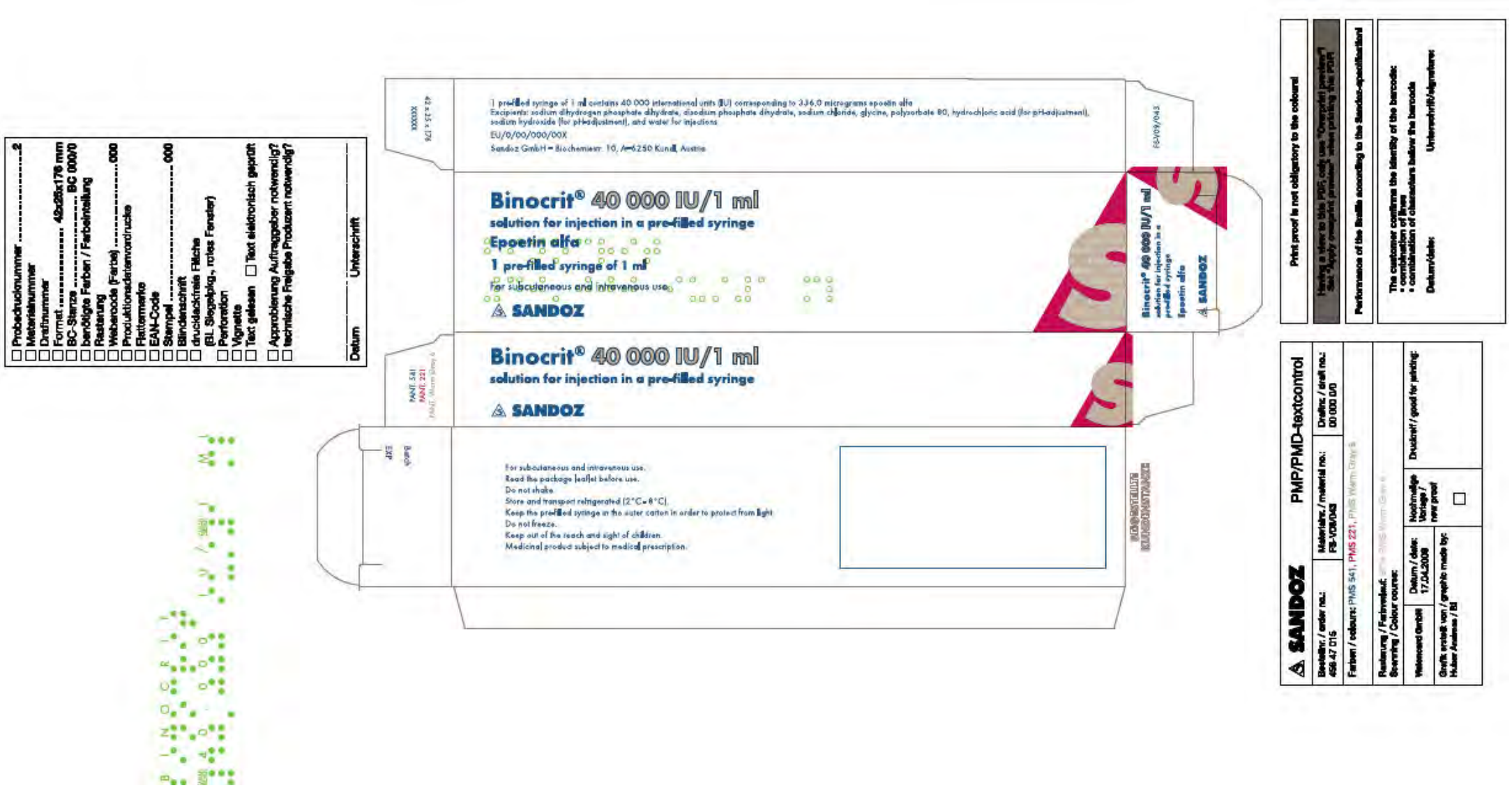
Decision matrix Mock-up No. 01 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 01 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = 0; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**5**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**no**	**0**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**3**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**na** (no symbols used)	**-**
	• Are no elements of promotional nature used?	**na** (no symbols used)	**-**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**na** (no symbols used)	**-**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

Decision matrix Mock-up No. 01 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 01 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = 0; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**no**	**0**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no differnt strenght)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**no**	**0**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**no**	**0**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**3**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**yes**	**3**

Annex 2 = Mock-up No. 02



Decision matrix Mock-up No. 02 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 02 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na) -** Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**3**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**no**	**0**
	• Type size as large as possible used?	**yes**	**3**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**3**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no (bold)**	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**no**	**0**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**3**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**3**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**yes**	**5**

Decision matrix Mock-up No. 02 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 02 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable (na) - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**3**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**yes**	**3**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**3**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**na** (no symbols used)	**-**
	• Are no elements of promotional nature used?	**na** (no symbols used)	**-**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**na** (no symbols used)	**-**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes** (but type size not big enough)	**3**

Decision matrix Mock-up No. 02 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 02 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**3**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**yes**	**5**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**3**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no differnt strenght)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**3**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**3**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**no**	**0**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**5**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**yes**	**5**

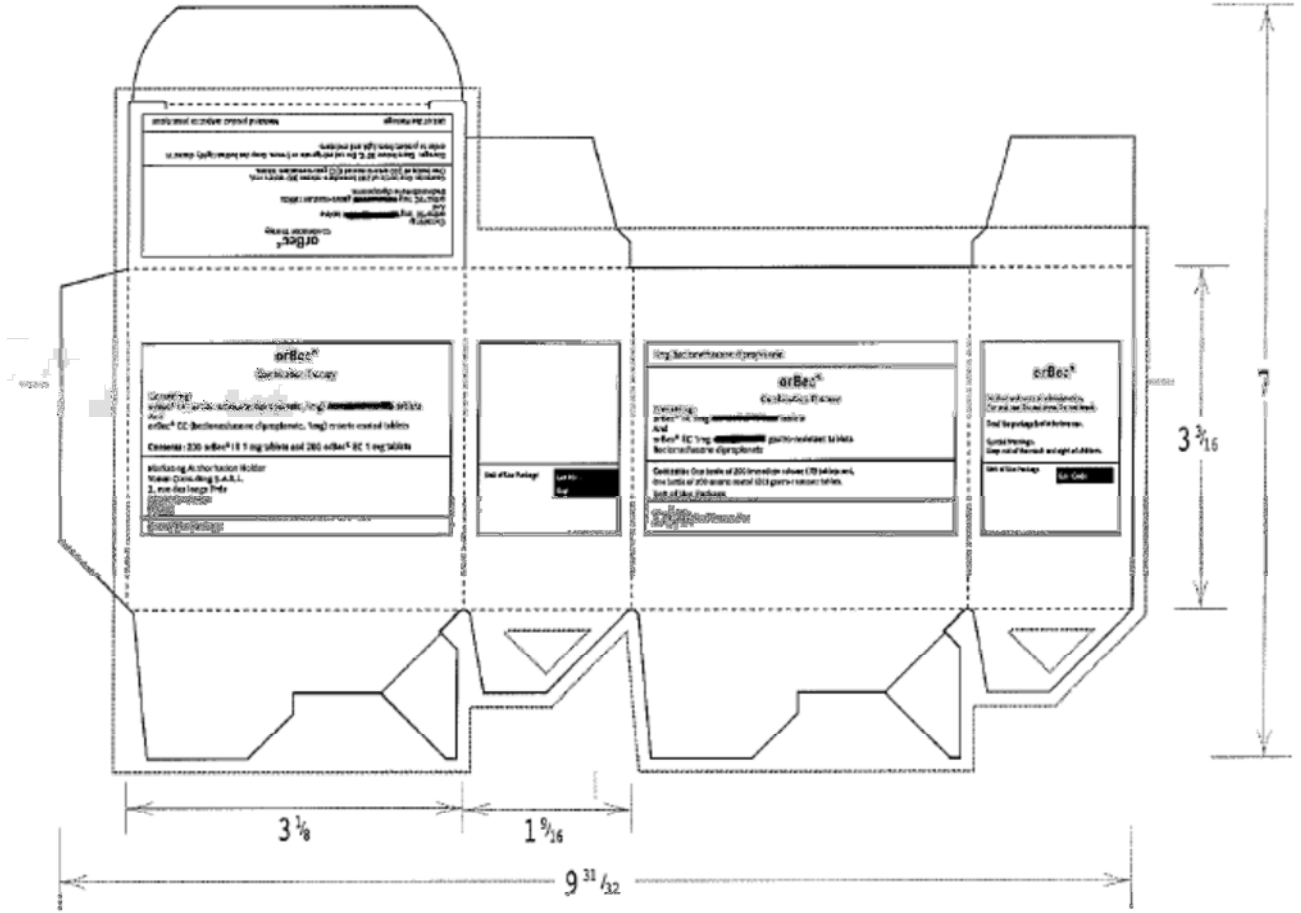
Annex 3 = Mock-up No. 03 – Page 1

CUSTOMER: BioPharma
PRODUCT:
SAMPLE #: 6114C
DATE: 03/17/06

SIZE: 3 7/8 x 1 7/16 x 9/10
STYLE: TUCK TOP - AUTO BOTTOM
CALIPER: 0.016
SUBSTATE: SBS
VIEW: PRINTED SIDE

GRAIN

= GRAPHICS BLEED BOUNDARY



Mock-up No. 03 – Page 2

QUALITY • INTEGRITY • SERVICE MGI Mini Graphics, Inc. SPECIALIZING IN PHARMACEUTICAL PACKAGE INSERTS AND ROLL LABELS 45 St. John's Place Freeport, NY 11520 Tel.: 516-223-6464 Fax: 516-223-6486	CUSTOMER: DOR PLATE #: 20885-1 JOB #: 20885 P.O. #: MISC. CODE #: ATTN: ALLISON BAWDEN PROOF #: 1	LABEL SIZE: 1.625" X 4.75" DATE PROOF OUT: 10/26/06 PREPARED BY: Danielle UPC CODE SPECIFICATIONS SCALE (%): 80 PRINTER DPI: 2400 B.W.R.: 2 Narrow Bar Width: .01"	☐ SUBMIT ADDITIONAL PROOFS ☐ O.K. TO PRINT AUTHORIZED BY: _____ _____ DATE: _____ Production delivery 2-3 weeks from receipt of O.K. TO PRINT.

PROOF ENTIRE LABEL NOTES: _____	PLATES REQUIRED 4	COLOR CHECK	☐ APPROVED	☐ RESUBMIT
	Pantone 273 Purple	Pantone 131 Gold		
	Pantone Black			Spot Varnish

Decision matrix Mock-up No. 03 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 03 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**3**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes**	**1**
	• Type size as large as possible used?	**yes**	**3**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**3**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**yes** (but different fonts)	**3**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**no**	**0**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**5**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**5**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**3**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**no**	**0**

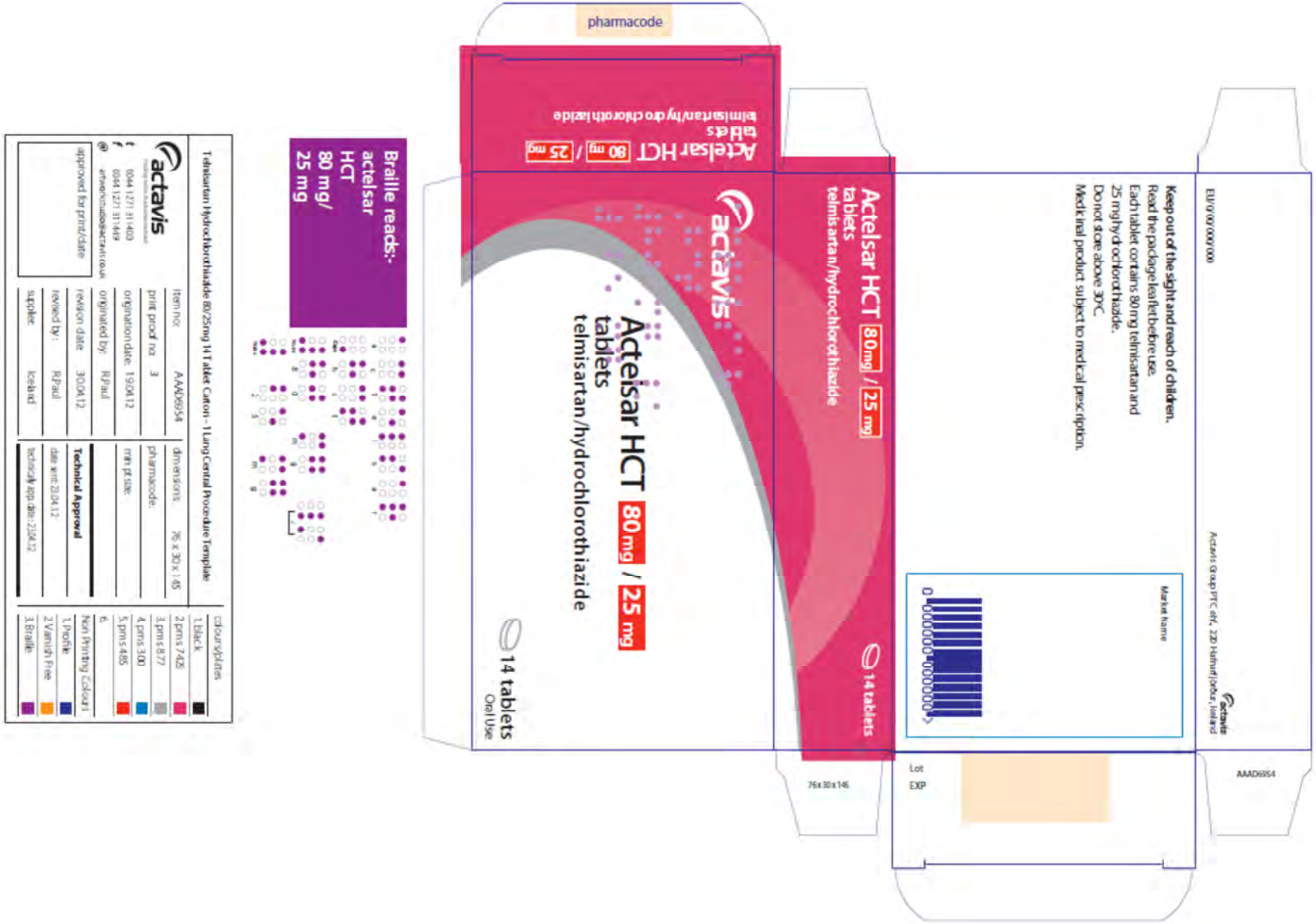
Decision matrix Mock-up No. 03 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 03 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable (na) - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**5**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**no**	**0**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**3**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**na** (no symbols used)	**-**
	• Are no elements of promotional nature used?	**na** (no symbols used)	**-**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**na** (no symbols used)	**-**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

Decision matrix Mock-up No. 03 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 03 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**3**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**3**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**3**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** **(less than 3 active ingredients)**	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**na**	**-**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**3**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** **(no differnt strenght)**	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**5**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**no**	**0**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**na** **(tablets)**	**-**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**3**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**1**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**3**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**no**	**0**

Annex 4 = Mock-up No. 04



Decision matrix Mock-up No. 04 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 04 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0;** Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes** (except company information)	**3**
	• Type size as large as possible used?	**yes**	**3**
	• Is space between lines at least 3 mm?	**yes**	**5**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**5**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no (bold)**	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**yes**	**5**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**5**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**5**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**yes**	**5**

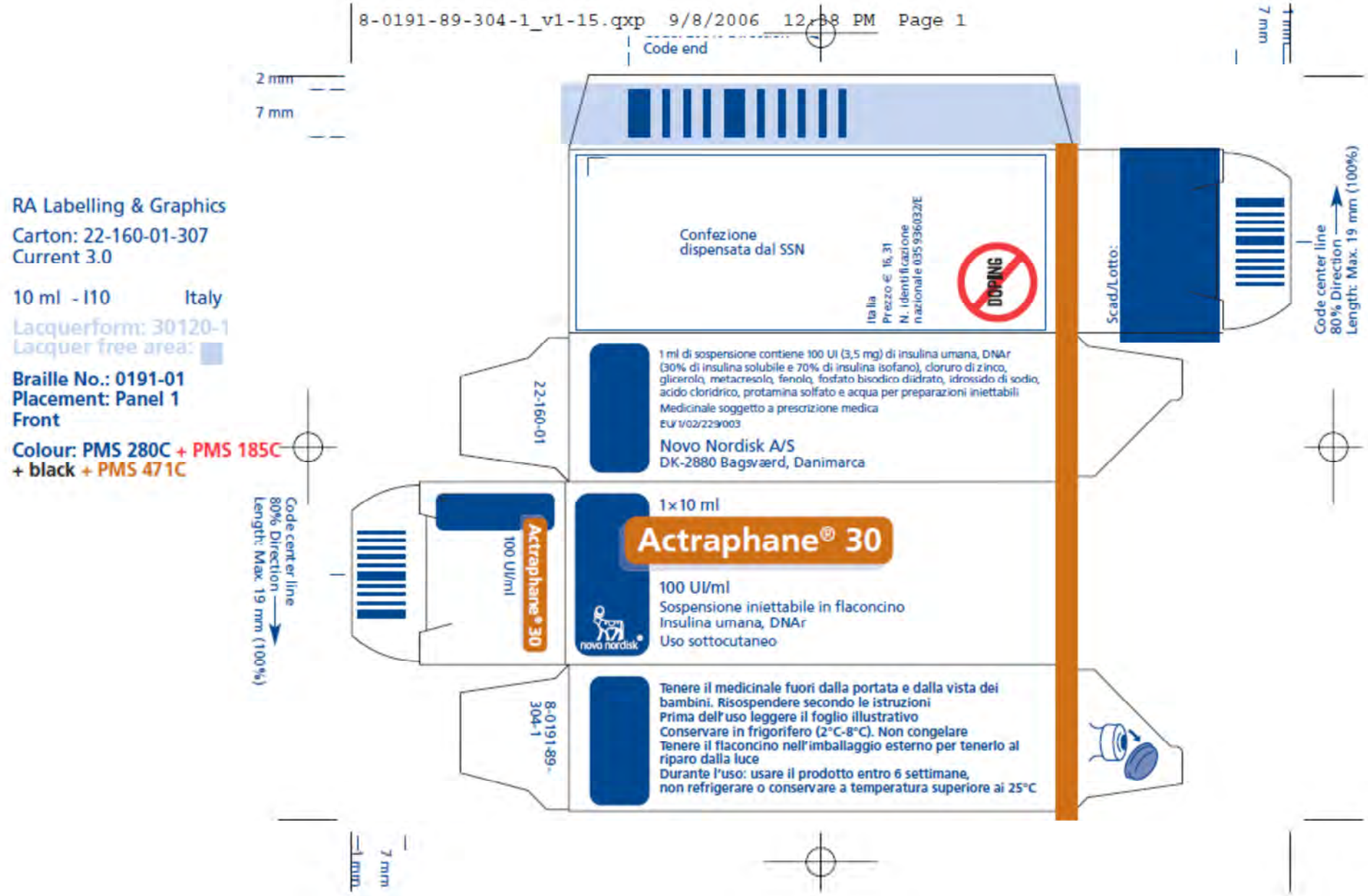
Decision matrix Mock-up No. 04 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 04 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**5**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**yes**	**5**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**5**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**yes**	**5**
	• Are no elements of promotional nature used?	**yes**	**5**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**yes**	**3**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

Decision matrix Mock-up No. 04 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 04 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**na**	**-**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no different strength)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**no**	**0**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**1**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**na (tablets)**	**-**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**3**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**yes**	**3**

Annex 5 = Mock-up No. 05



Decision matrix Mock-up No. 05 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 05 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0;** Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**no**	**0**
	• Type size as large as possible used?	**yes**	**5**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**1**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no** (bold)	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**yes**	**3**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**5**
	• Is related information standing together?	**yes**	**3**
	• Is there enough contrast between text and background?	**yes**	**5**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**yes**	**5**

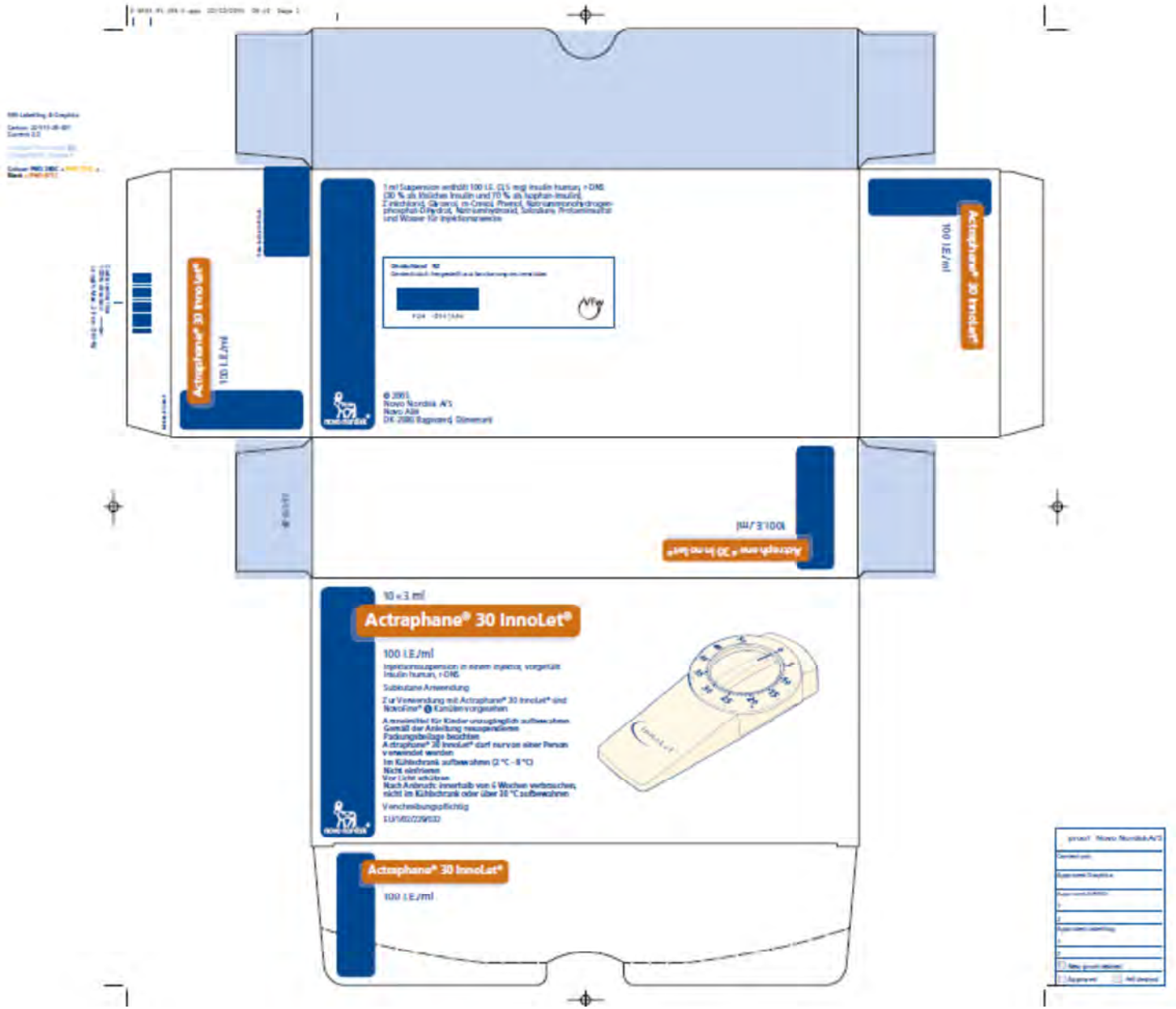
Decision matrix Mock-up No. 05 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 05 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**5**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**no**	**3**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**3**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**yes**	**5**
	• Are no elements of promotional nature used?	**yes**	**5**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**yes**	**5**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

Decision matrix Mock-up N0. 05 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 05 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0;** Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**3**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**1**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**3**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**no** (only on two sides)	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**yes**	**3**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**3**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no different strength)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**no**	**0**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**1**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**no**	**0**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**3**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**1**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**no**	**0**

Annex 6 = Mock-up No. 06



Decision matrix Mock-up No. 06 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 06 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**no**	**0**
	• Type size as large as possible used?	**yes**	**3**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**1**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no** (bold)	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**no**	**0**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**3**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**5**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**yes**	**5**

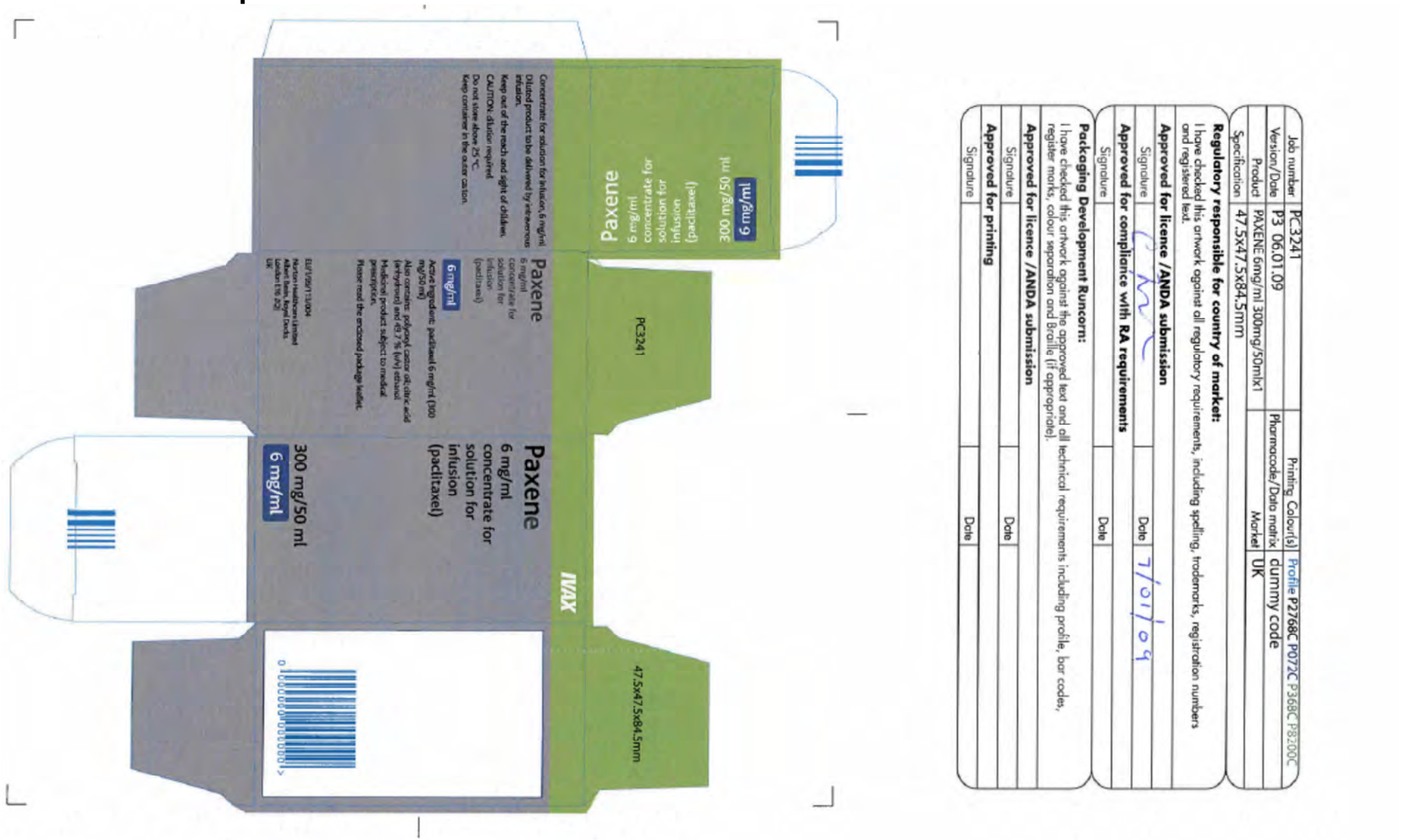
Decision matrix Mock-up No. 06 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 06 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**5**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**no**	**0**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**3**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**yes**	**5**
	• Are no elements of promotional nature used?	**yes**	**5**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**yes**	**1**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

Decision matrix Mock-up No. 06 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 06 - Page 3			
Category / Requirement	**Criteria** **yes:** strong correlation = Level of Compliance = **5** / moderate correlation - Level of Compliance = **3** / weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**3**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**1**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**3**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** **(less than 3 active ingredients)**	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**yes**	**5**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** **(no different strength)**	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**5**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**no**	**0**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**5**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**no**	**0**

Annex 7 = Mock-up No. 07



Decision matrix Mock-up No. 07 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 07 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**no**	**0**
	• Type size as large as possible used?	**no**	**0**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**1**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no (bold)**	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**yes**	**3**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**3**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**1**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**3**
	• Is dark print on light background considered where small type sizes have been used?	**no**	**0**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**yes**	**5**

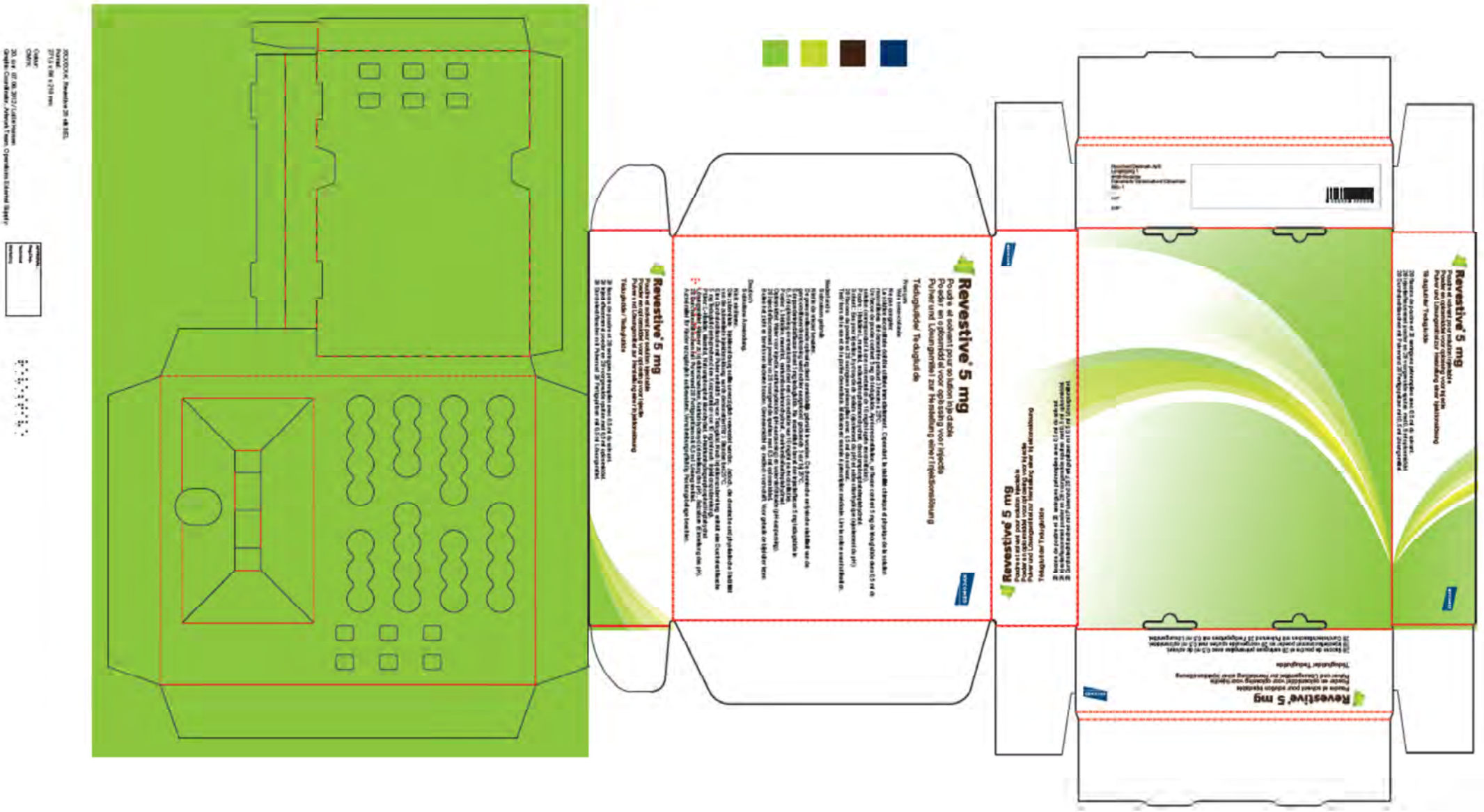
Decision matrix Mock-up No. 07 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 07 - Page 2			
Category / Requirement	**Criteria** **yes**: Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**no**	**0**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**no**	**0**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**no**	**0**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**na** (no symbols used)	**-**
	• Are no elements of promotional nature used?	**na** (no symbols	**-**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**na** (no symbols used)	**-**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**3**

Decision matrix Mock-up No. 07 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 07 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**3**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**3**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**yes**	**5**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**1**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no different strength)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**5**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**no**	**0**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**no**	**0**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**5**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**no**	**0**

Annex 8 = Mock-up No. 08



Decision matrix Mock-up No. 08 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 08 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes**	**5**
	• Type size as large as possible used?	**yes**	**5**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**3**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no** (bold)	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**no**	**0**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**3**
	• Is related information standing together?	**yes**	**1**
	• Is there enough contrast between text and background?	**yes**	**5**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**yes**	**5**
	- Is clear demarcation between different languages infixed where space permits?	**yes**	**1**
	- Is information per language grouped when feasible?	**yes**	**1**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**no** (all information is displayed on one panel)	**0**
	- Is content of all languages versions identical?	**yes**	**5**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**yes (but to small)**	**1**

Decision matrix Mock-up No. 08 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 08 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**5**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**no**	**0**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**5**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**yes**	**5**
	• Are no elements of promotional nature used?	**yes**	**5**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**yes**	**1**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

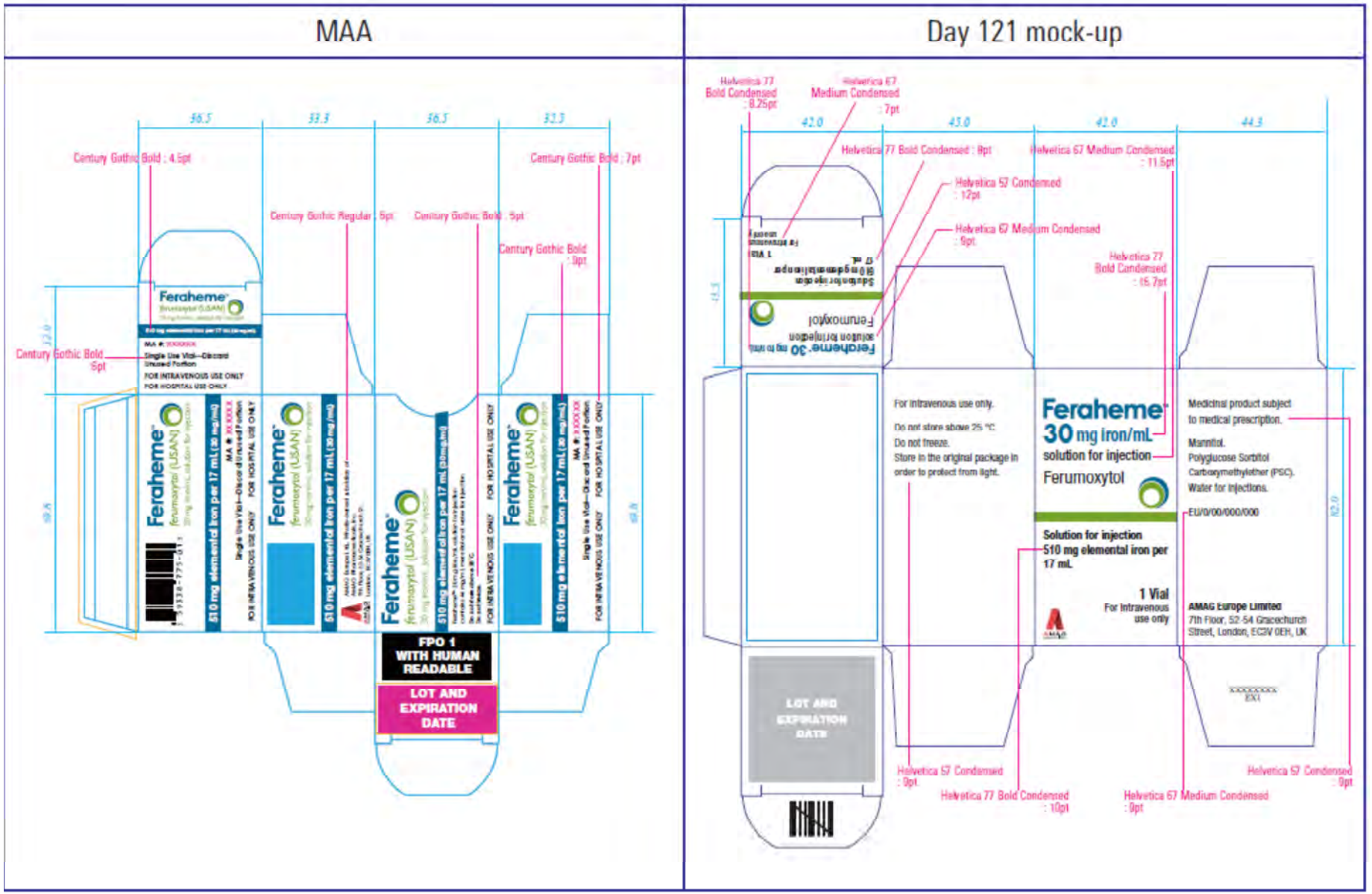
Decision matrix Mock-up No. 08 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 08 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**no**	**0**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no different strength)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**5**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**yes**	**5**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**3**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**3**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**yes**	**1**

Annex 9 = Mock-up No. 09 – Page 1

No.1_Ferumoxytol 1V Carton MAA mock-up ： Day 121 mock-up comparison table(English)

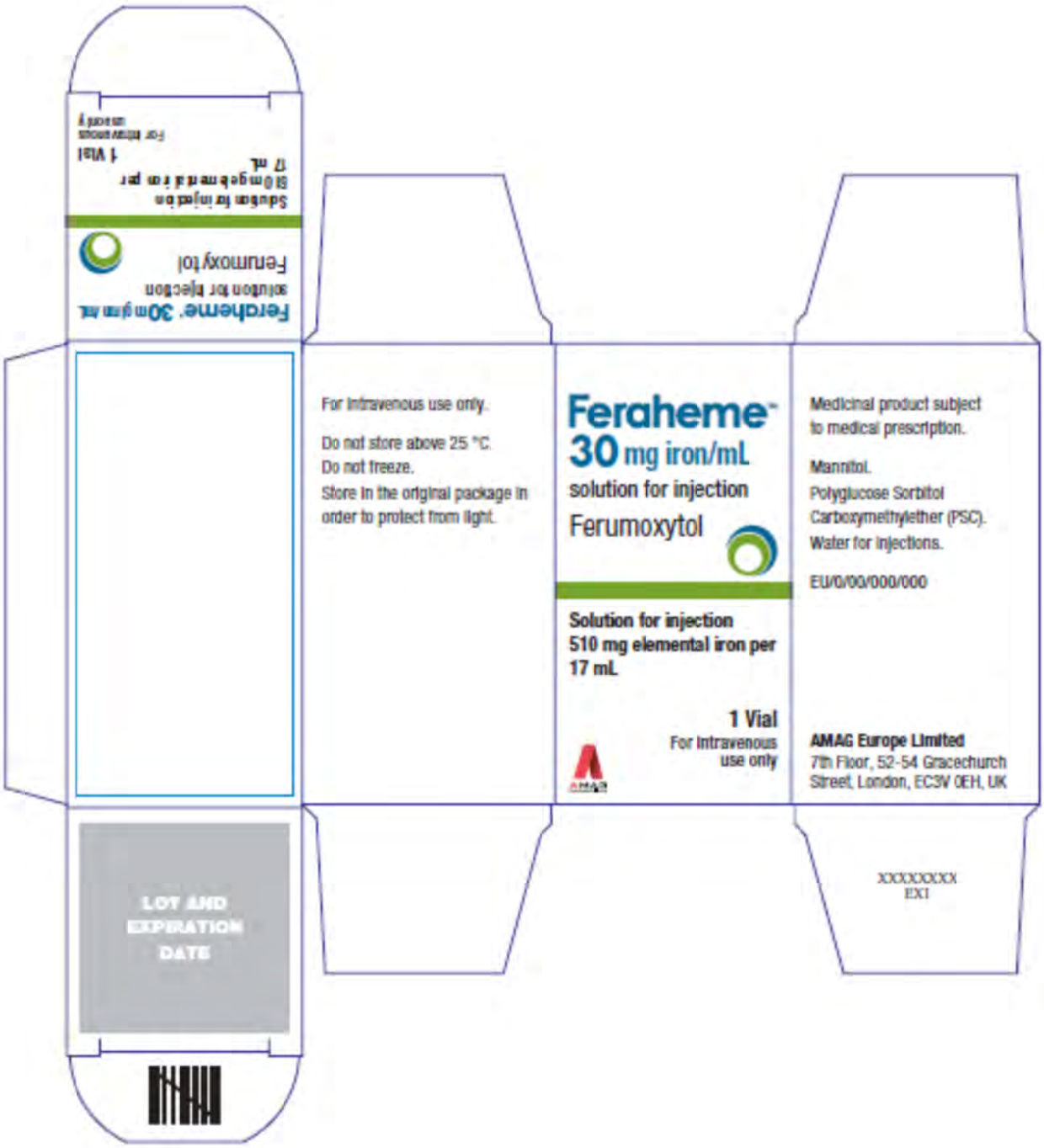
scale : 70%



Mock-up No. 09 – Page 2

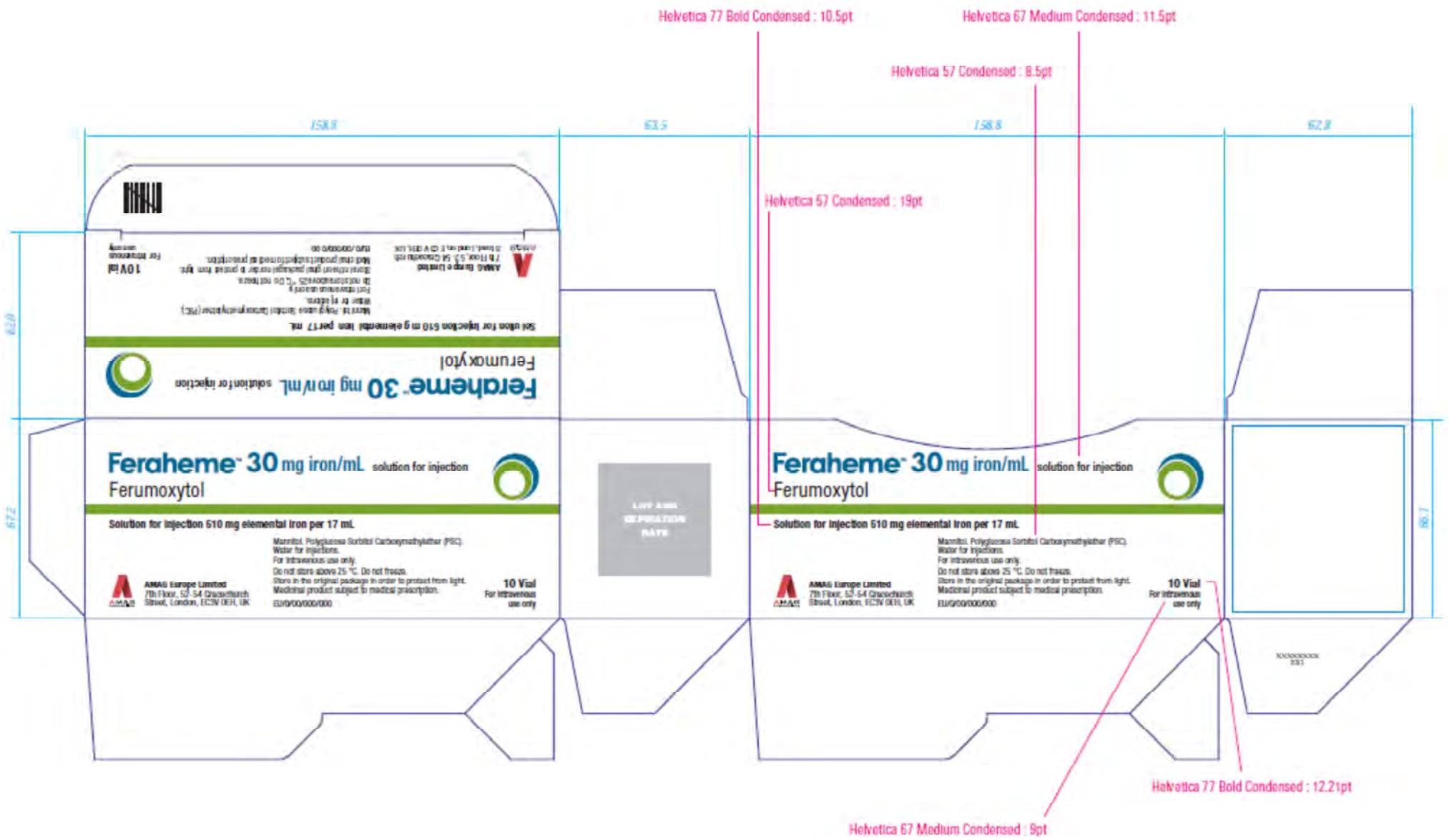
EX_Ferumoxytol 30mg_1V Carton 2011.04.05

scale : **100%**



Mock-up No. 09 – Page 3

No.9_Ferumoxytol 10V Carton Day 121 mock-up(English)



Mock-up No. 09 – Page 4

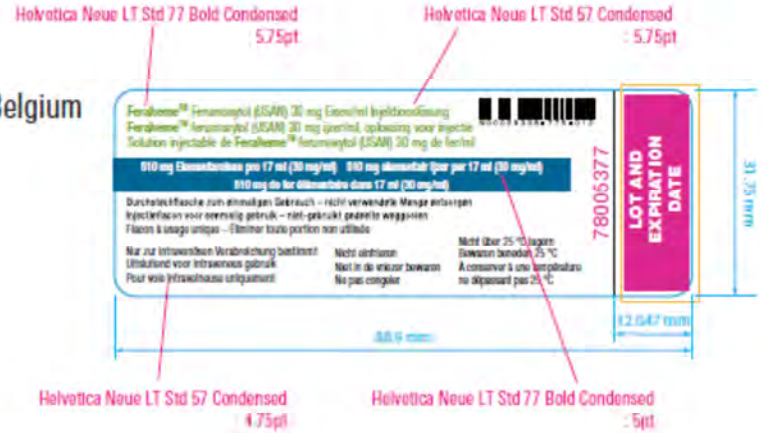
No.15_Ferumoxytol Vial Label MAA mock-up : Day 121 mock-up comparison table

scale : **100%**

MAA

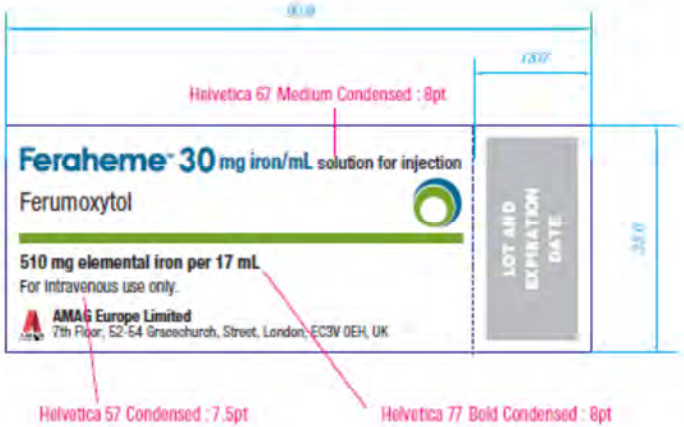
English

Belgium

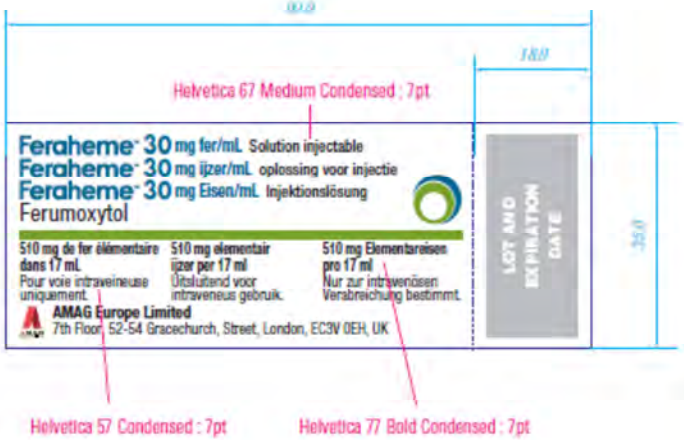


Day 121 mock-up

English



Belgium



Decision matrix Mock-up No. 09 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 09 MAA - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**no**	**0**
	• Type size as large as possible used?	**yes**	**3**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**3**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no** (bold, italics)	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**yes** (but only partially)	**3**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**5**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**5**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**1**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**yes**	**5**
	- Is clear demarcation between different languages infixed where space permits?	**no**	**0**
	- Is information per language grouped when feasible?	**yes**	**3**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**no**	**0**
	- Is content of all languages versions identical?	**yes**	**5**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**yes**	**5**

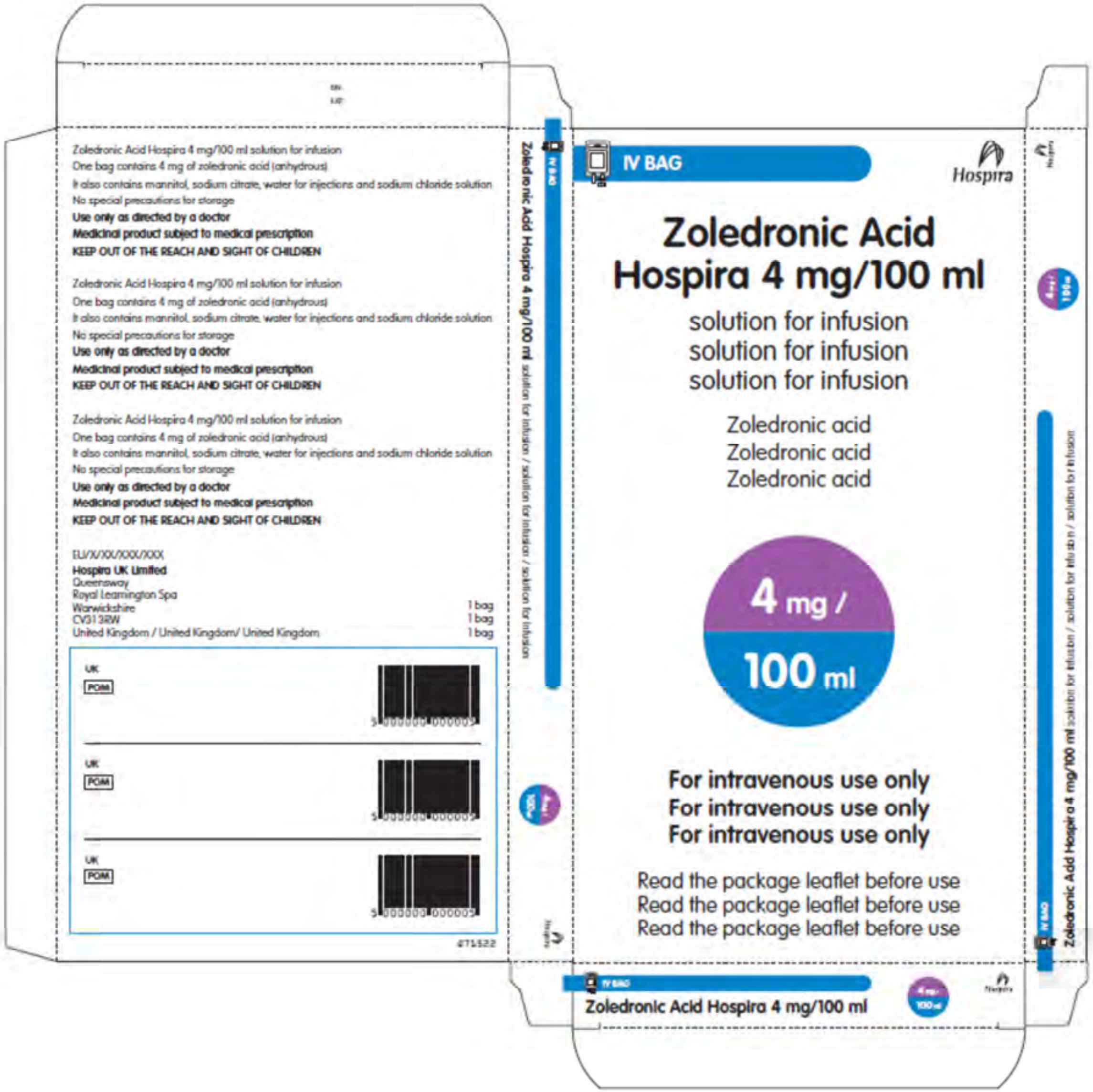
Decision matrix Mock-up No. 09 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 09 MAA - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**5**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**no**	**0**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**5**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**na** (no symbols used)	**-**
	• Are no elements of promotional nature used?	**na** (no symbols	**-**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**na** (no symbols used)	**-**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

Decision matrix Mock-up No. 09 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 09 MAA - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**no** (only on two sides)	**0**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**na**	**-**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no different strength)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**5**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**yes**	**5**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**5**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**no**	**0**

Annex 10 = Mock-up No. 10



Decision matrix Mock-up No. 10 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 10 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0;** Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes**	**5**
	• Type size as large as possible used?	**yes**	**5**
	• Is space between lines at least 3 mm?	**yes**	**3**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**5**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no** (bold)	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**no**	**0**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**5**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**5**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**yes**	**5**

Decision matrix Mock-up No. 10 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 10 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**5**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**yes**	**5**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**5**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**yes**	**5**
	• Are no elements of promotional nature used?	**yes**	**5**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**yes** (pictogram not useful)	**1**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

Decision matrix Mock-up No. 10 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 10 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**3**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** **(less than 3 active ingredients)**	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**na**	**-**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** **(no different strength)**	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**5**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**3**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**yes**	**5**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**5**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**no**	**0**

Annex 11 = Mock-up No. 11

Decision matrix Mock-up No. 11 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 11 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**3**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes**	**5**
	• Type size as large as possible used?	**yes**	**3**
	• Is space between lines at least 3 mm?	**yes**	**5**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**3**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no** (bold)	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**yes**	**5**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**5**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**3**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**yes**	**5**

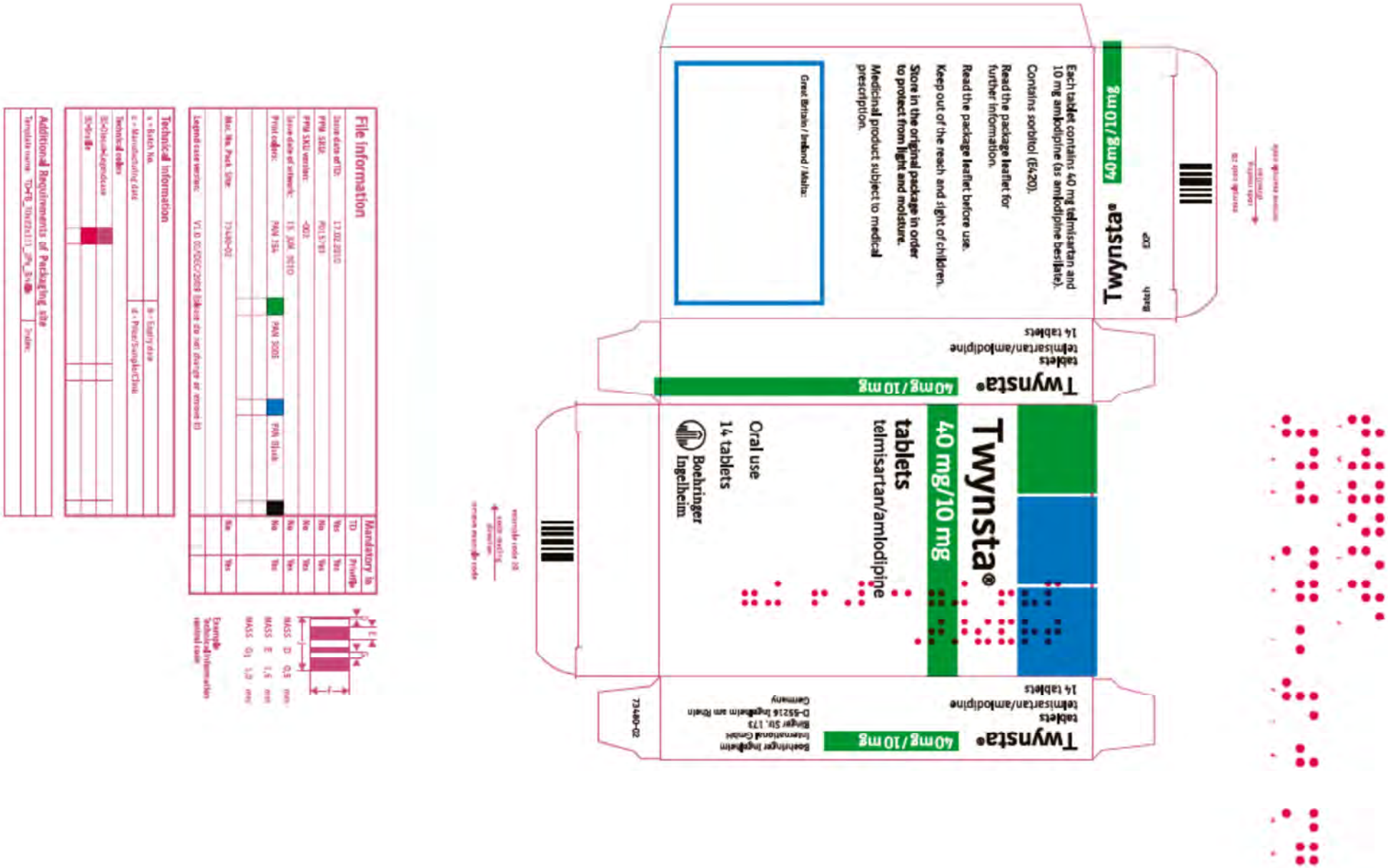
Decision matrix Mock-up No. 11 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 11 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**3**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**yes**	**3**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**5**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**yes**	**5**
	• Are no elements of promotional nature used?	**yes**	**5**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**yes**	**1**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**3**

Decision matrix Mock-up No. 11 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 11 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**na**	**-**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no different strength)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**1**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**yes**	**5**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**3**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**5**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**yes**	**5**

Annex 12 = Mock-up No. 12



Decision matrix Mock-up No. 12 Page 1

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 12 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes**	**5**
	• Type size as large as possible used?	**yes**	**3**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**3**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no** (bold)	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**yes**	**3**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**3**
	• Is related information standing together?	**yes**	**3**
	• Is there enough contrast between text and background?	**yes**	**5**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**3**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**yes**	**5**

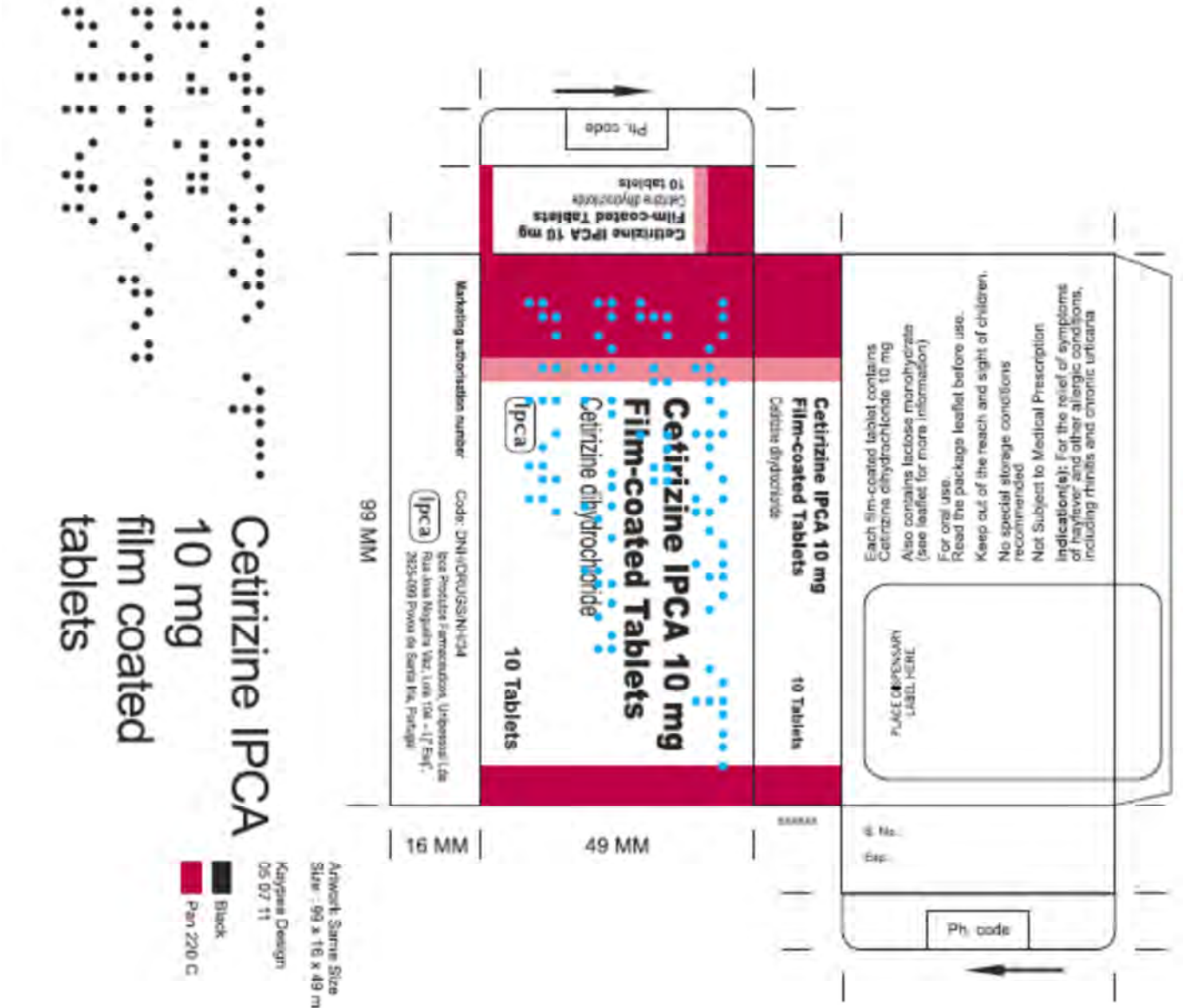
Decision matrix Mock-up .No. 12 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 12 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**5**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**yes**	**5**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**5**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**na** (no symbols used)	**-**
	• Are no elements of promotional nature used?	**na** (no symbols	**-**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**na** (no symbols used)	**-**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

Decision matrix Mock-up No. 12 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of centrally approved medicinal products - MOCK-UP No. 12 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**na**	**-**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no different strength)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**no**	**0**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**no**	**0**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**na (tablets)**	**-**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**3**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**3**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**yes**	**5**

Annex 13 = Mock-up No. 13



Decision matrix Mock-up No. 13 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 13 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes**	**5**
	• Type size as large as possible used?	**yes**	**5**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**3**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no (bold)**	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**no**	**0**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**5**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**5**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**yes** (clearly characterized)	**5**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**na (not centrally approved)**	**-**

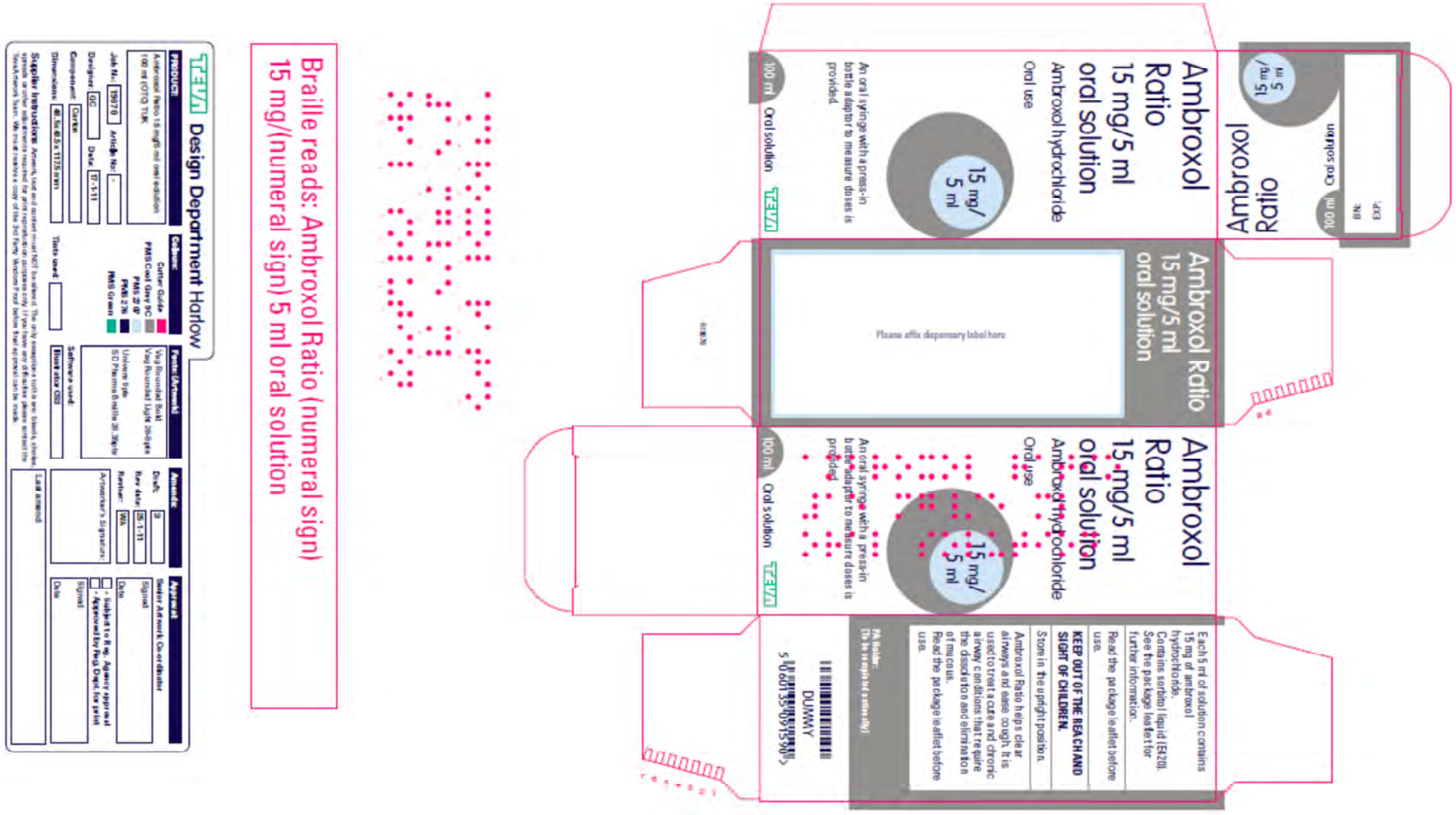
Decision matrix Mock-up 13 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 13 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**5**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**no**	**0**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**3**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**na** (no symbols used)	**-**
	• Are no elements of promotional nature used?	**na** (no symbols used)	**-**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**na** (no symbols used)	**-**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

Decision matrix Mock-up No. 13 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 13 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**na**	**-**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**no** (pharmaceutical form to big)	**0**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no different strength)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**3**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**no** (only under other info)	**0**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**na (tablets)**	**-**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**5**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**yes**	**5**

Annex 14 = Mock-up No. 14 – Page 1



Mock- up No. 14 – Page 2

THIS IS A REPRESENTATION OF AN ELECTRONIC RECORD THAT WAS SIGNED ELECTRONICALLY AND THIS PAGE IS THE MANIFESTATION OF THE ELECTRONIC SIGNATURE

Teva Pharmaceuticals Europe B.V

1.3.2 15mgper5ml-mockup-outer duplicate 1

APPROVALS

Signed by	Meaning of Signature	Server Date
Afrodita Bijelic	Regulatory Affairs Approval	26-Jan-2011 11:03:54 AM

Decision matrix Mock-up No. 14 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 14 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**3**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes**	**3**
	• Type size as large as possible used?	**yes**	**5**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**3**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no** (bold)	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**yes**	**1**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**1**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**3**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**yes**	**5**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**na (not centrally approved)**	**-**

Decision matrix Mock-up No. 14 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 14 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**3**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**no**	**0**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**3**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**na** (no symbols used)	**-**
	• Are no elements of promotional nature used?	**na** (no symbols	**-**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**na** (no symbols used)	**-**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

Decision matrix Mock-up No. 14 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 14 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** **(less than 3 active ingredients)**	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**na**	**-**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** **(no different strength)**	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**no**	**0**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**1**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**yes**	**5**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**3**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**yes**	**5**

Annex 15 = Mock-up No. 15 – Page 1

Mock-up No. 15 – Page 2

THIS IS A REPRESENTATION OF AN ELECTRONIC RECORD THAT WAS SIGNED ELECTRONICALLY AND THIS PAGE IS THE MANIFESTATION OF THE ELECTRONIC SIGNATURE

Teva Pharmaceuticals Europe B.V

1.3.2 mockupouteruk

APPROVALS

Signed by	Meaning of Signature	Server Date
Steve Smith	Regulatory Affairs Approval	25-May-2011 10:46:09 AM

Decision matrix Mock-up No. 15 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 15 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes**	**5**
	• Type size as large as possible used?	**yes**	**5**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**3**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no (bold)**	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**no**	**0**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**3**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**5**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**yes**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**na (not centrally approved)**	**-**

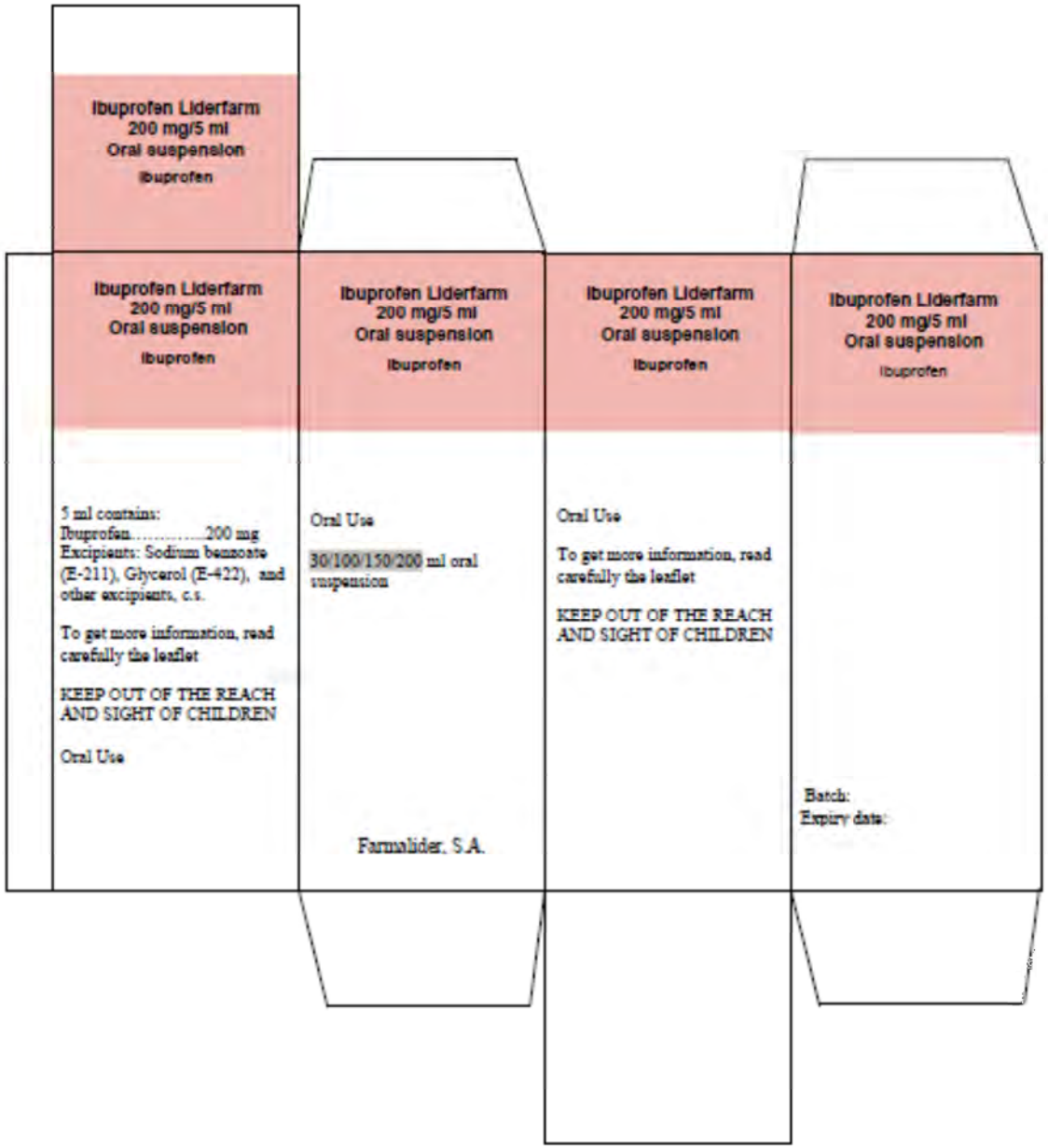
Decision matrix Mock-up No. 15 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 15 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**5**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**yes**	**3**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**1**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**na** (no symbols used)	**-**
	• Are no elements of promotional nature used?	**na** (no symbols	**-**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**na** (no symbols used)	**-**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

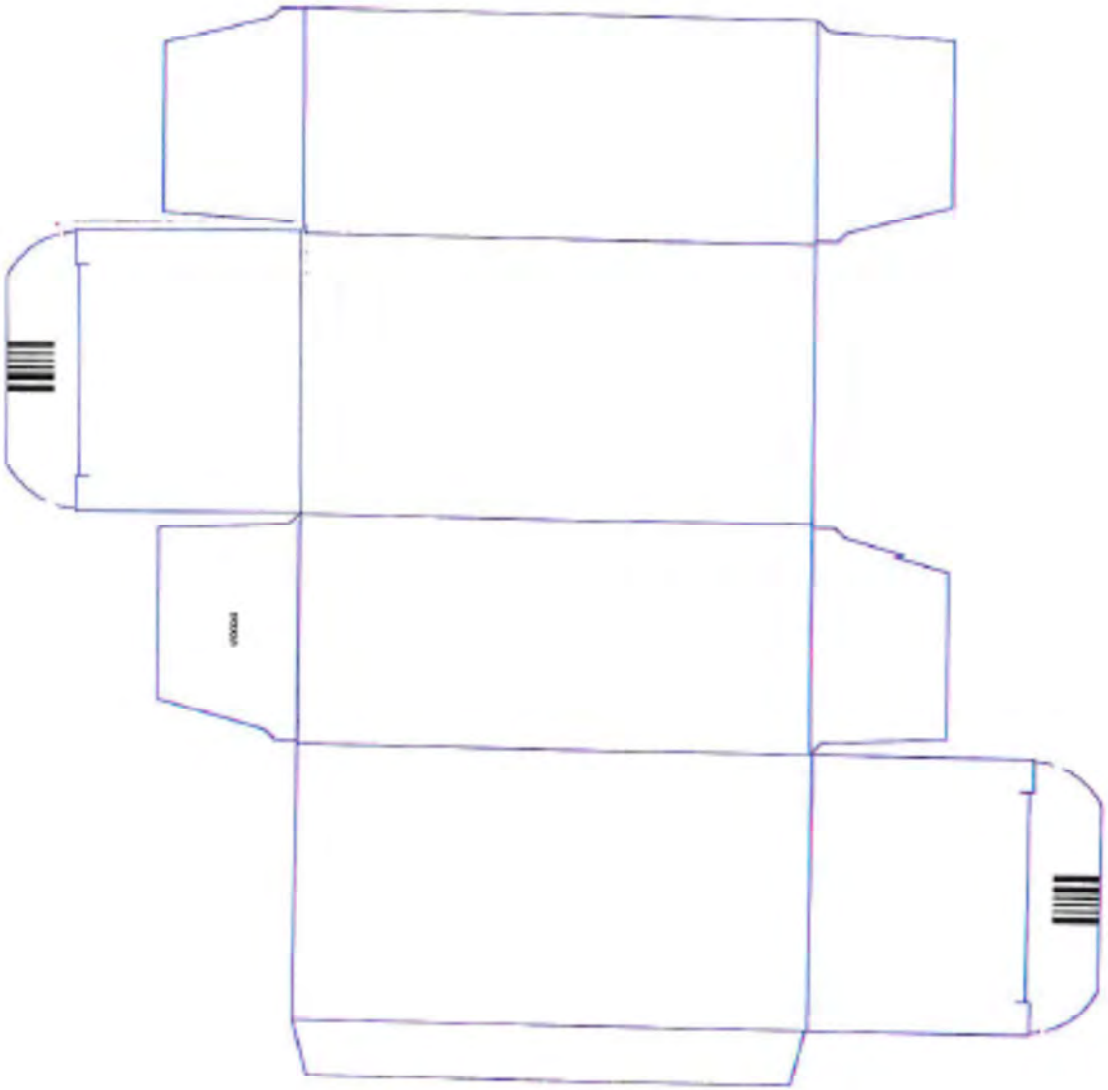
Decision matrix Mock-up No. 15 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 15 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**3**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**na**	**-**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no different strength)	**5**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**5**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**na (capsules)**	**-**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**5**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**yes**	**5**

Annex 16 = Mock-up No. 16 – Page 1



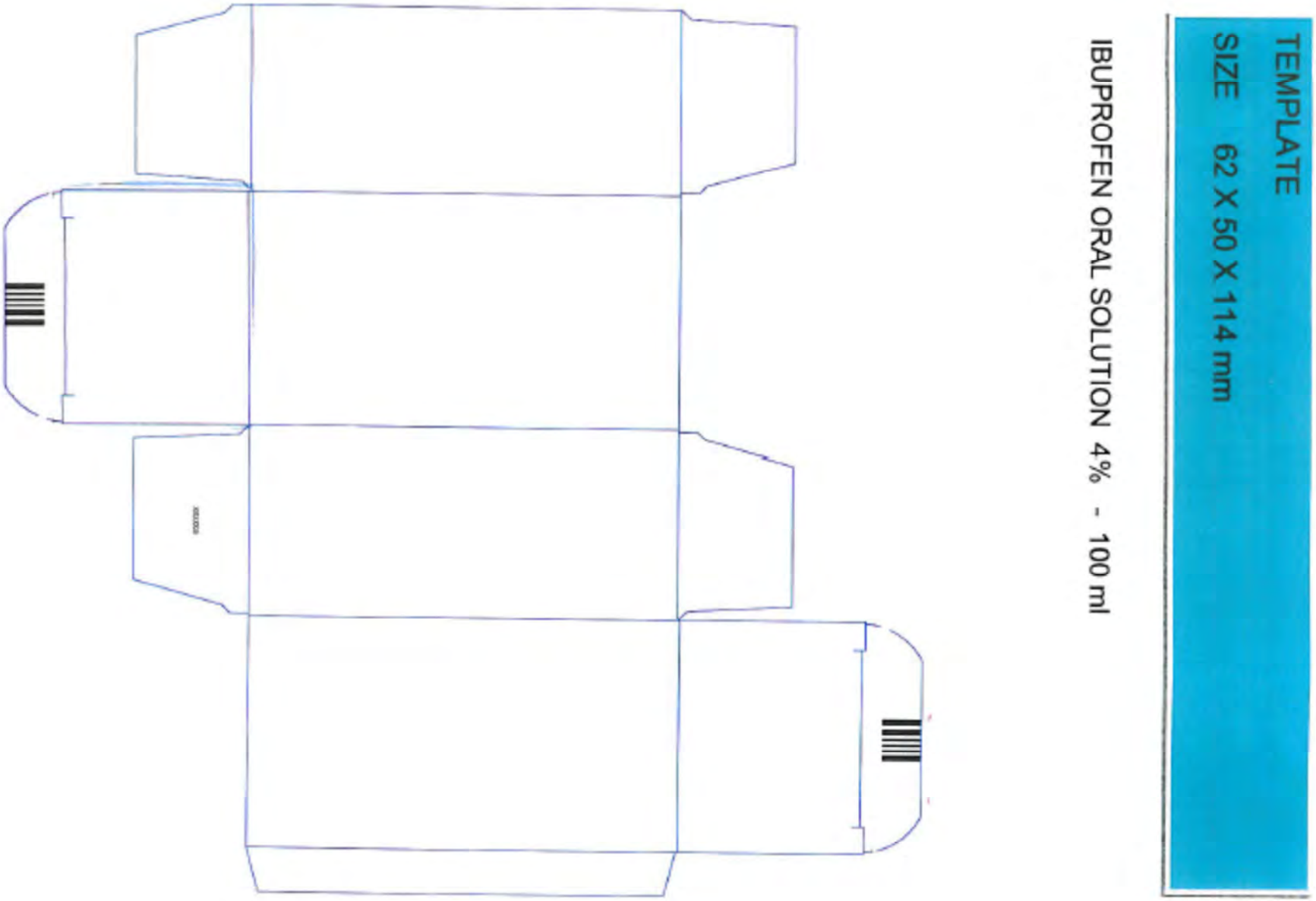
Mock-up No. 16 – Page 2



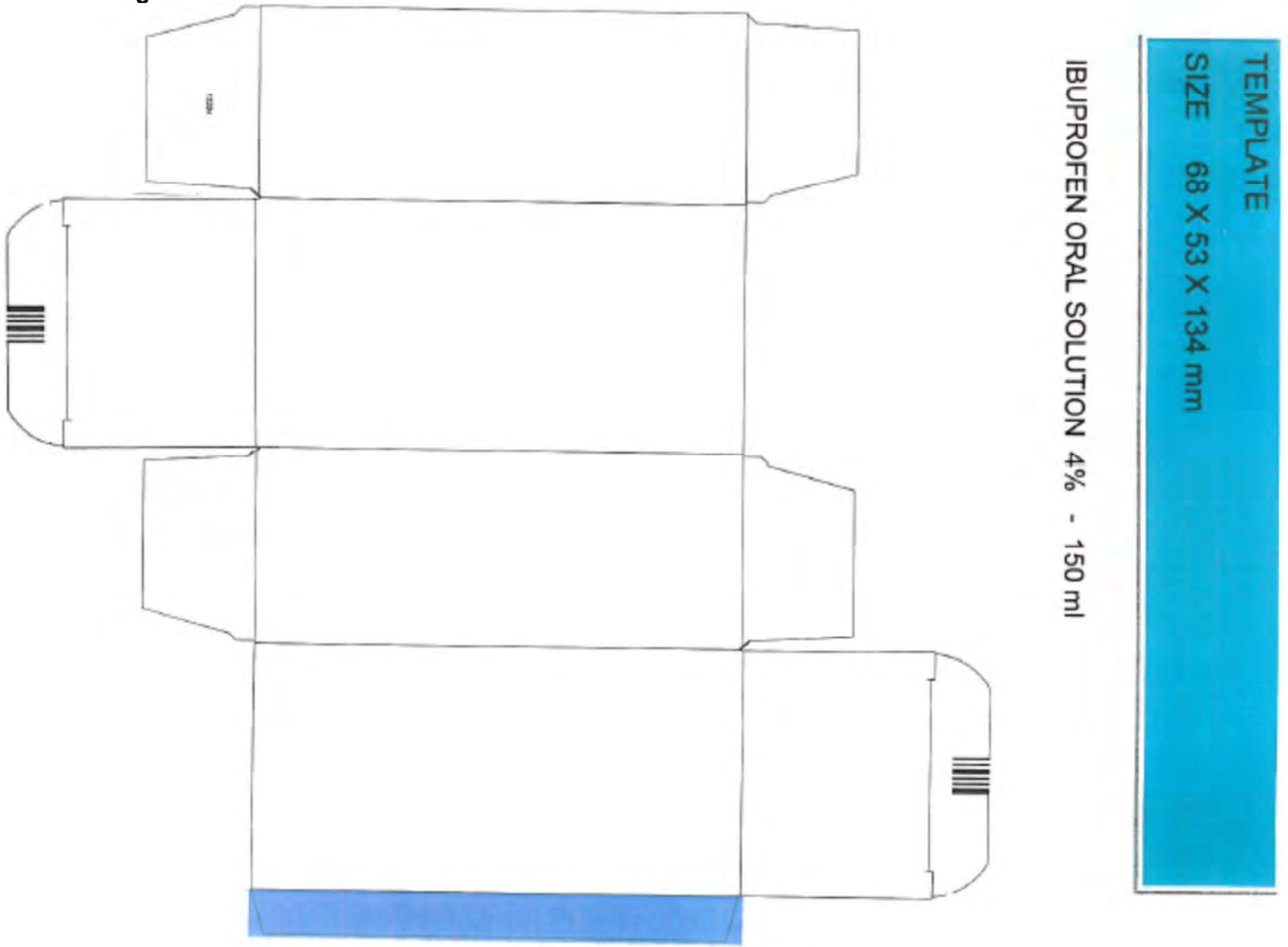
TEMPLATE
SIZE 45 X 42 X 91 mm

IBUPROFEN ORAL SOLUTION 4% - 30 ml

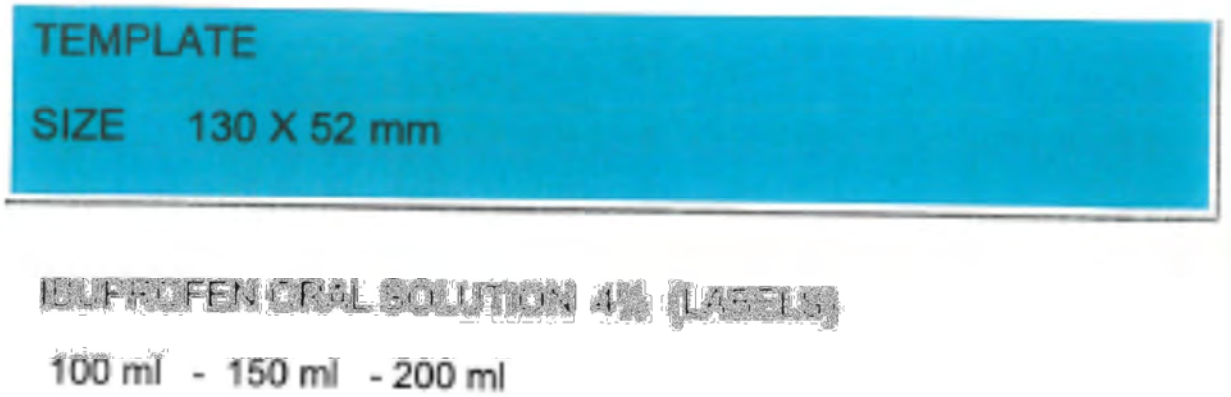
Mock-up No. 16 – Page 3



Mock-up No. 16 – Page 4



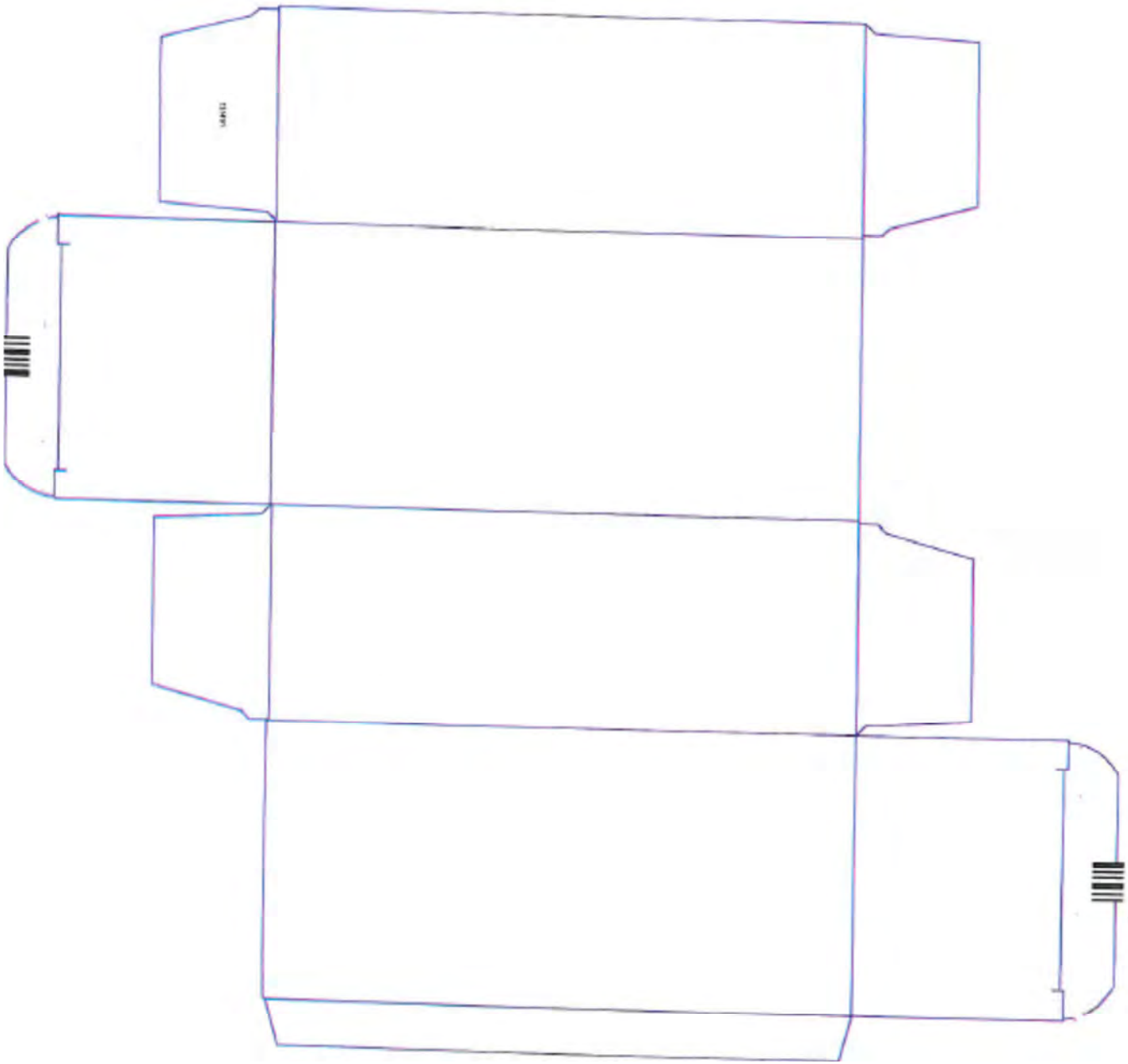
Mock-up No. 16 – Page 5



Mock-up No. 16 – Page 6

IBUPROFEN ORAL SOLUTION 4% (LABEL) - 30 ml

Mock-up No. 16 – Page 7



TEMPLATE
SIZE 73 X 56 X 153 mm

IBUPROFEN ORAL SOLUTION 4% - 200 ml

Decision matrix Mock-up No. 16 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 16 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**no** (for other information sylized font used)	**0**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes / no?** Format of package?	**?**
	• Type size as large as possible used?	**yes / no?** Format of package?	**?**
	• Is space between lines at least 3 mm?	**yes / no?** Format of package?	**?**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**no** Format of package?	**?**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no (bold)**	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**no**	**0**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**3**
	• Is related information standing together?	**yes**	**1**
	• Is there enough contrast between text and background?	**yes**	**3**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**na (not centrally approved)**	**-**

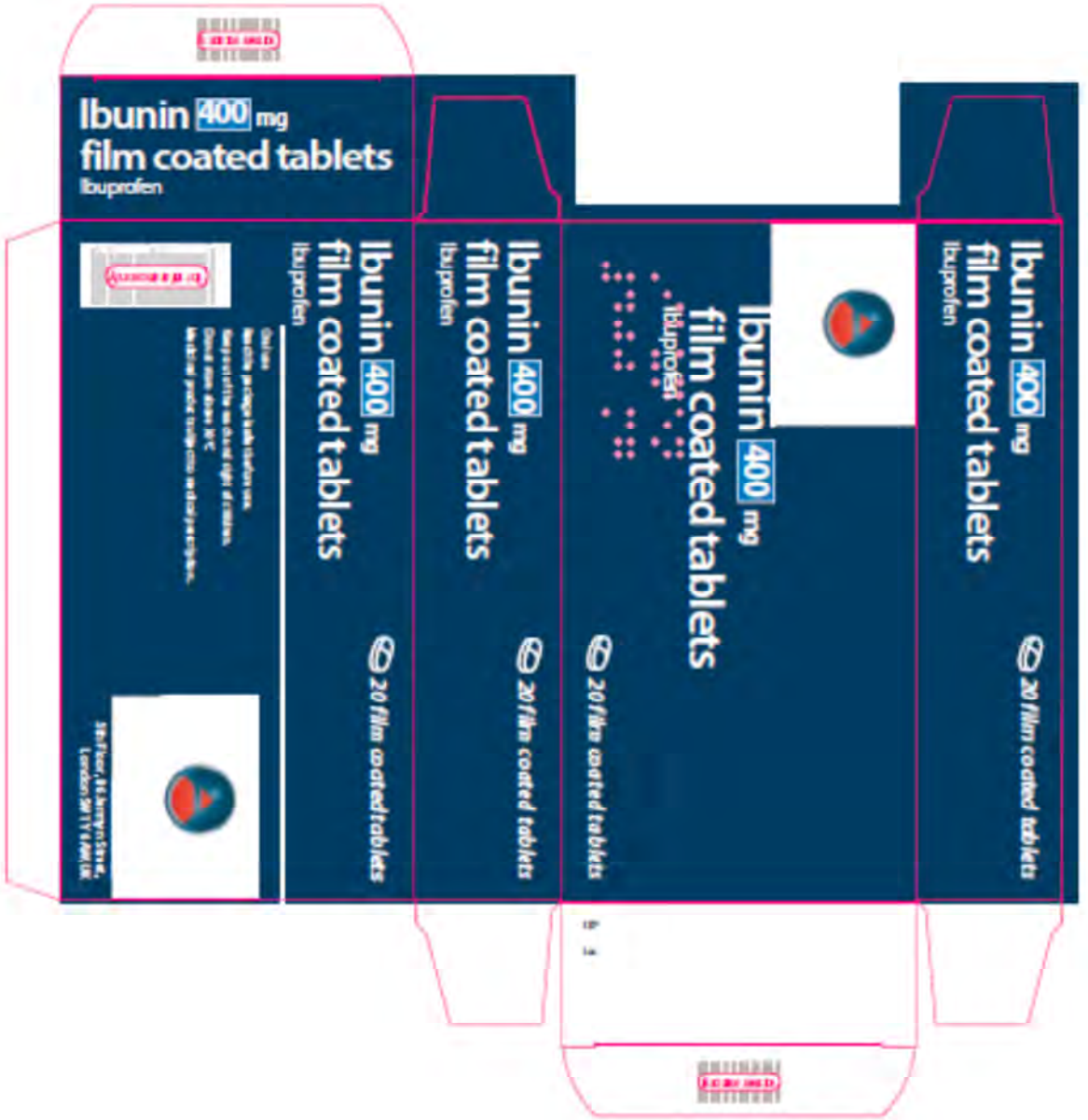
Decision matrix Mock-up No. 16 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 16 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**5**
	• Are different colours in name of product used? (Use of different colours to distinguish different strength is strongly recommended!)	**no**	**0**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**no**	**3**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? Are no background images placed behind the text?	**na** (no symbols used)	**-**
	• Are no elements of promotional nature used?	**na** (no symbols used)	**-**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**na** (no symbols used)	**-**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**1**

Decision matrix Mock-up No. 16 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 16 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labelling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**1**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• In certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**no**	**0**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**1**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**yes**	**3**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**yes**	**5**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**1**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**yes**	**1**
	• Only standard abbreviations used (i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**yes**	**5**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**3**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**5**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible.	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**no**	**0**

Annex 17 = Mock-up No. 17



Decision matrix Mock-up No. 17 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 17 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes / no?** Format of package?	**?**
	• Type size as large as possible used?	**yes / no?** Format of package?	**?**
	• Is space between lines at least 3 mm?	**yes / no?** Format of package?	**?**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**5**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no (bold)**	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**yes**	**5**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**5**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**3**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**no**	**0**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**na (not centrally approved)**	**-**

Decision matrix Mock-up No. 17 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 17 Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**1**
	• Are different colours in name of product? (Use of different colours to distinguish different strength is strongly recommended!)	**yes**	**3**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**3**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? No background images placed behind the text?	**yes**	**5**
	• Are no elements of promotional nature used?	**yes**	**5**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**yes**	**3**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**3**

Decision matrix Mock-up No. 17 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 17 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no**: Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labeling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• Place in certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**na**	**-**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no different strength)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**na**	**-**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**5**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**no**	**0**
	• Only standard abbreviations used i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**na (tablets)**	**-**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**3**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**3**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**yes**	**5**

PERRIGO

1.3 PRODUCT INFORMATION

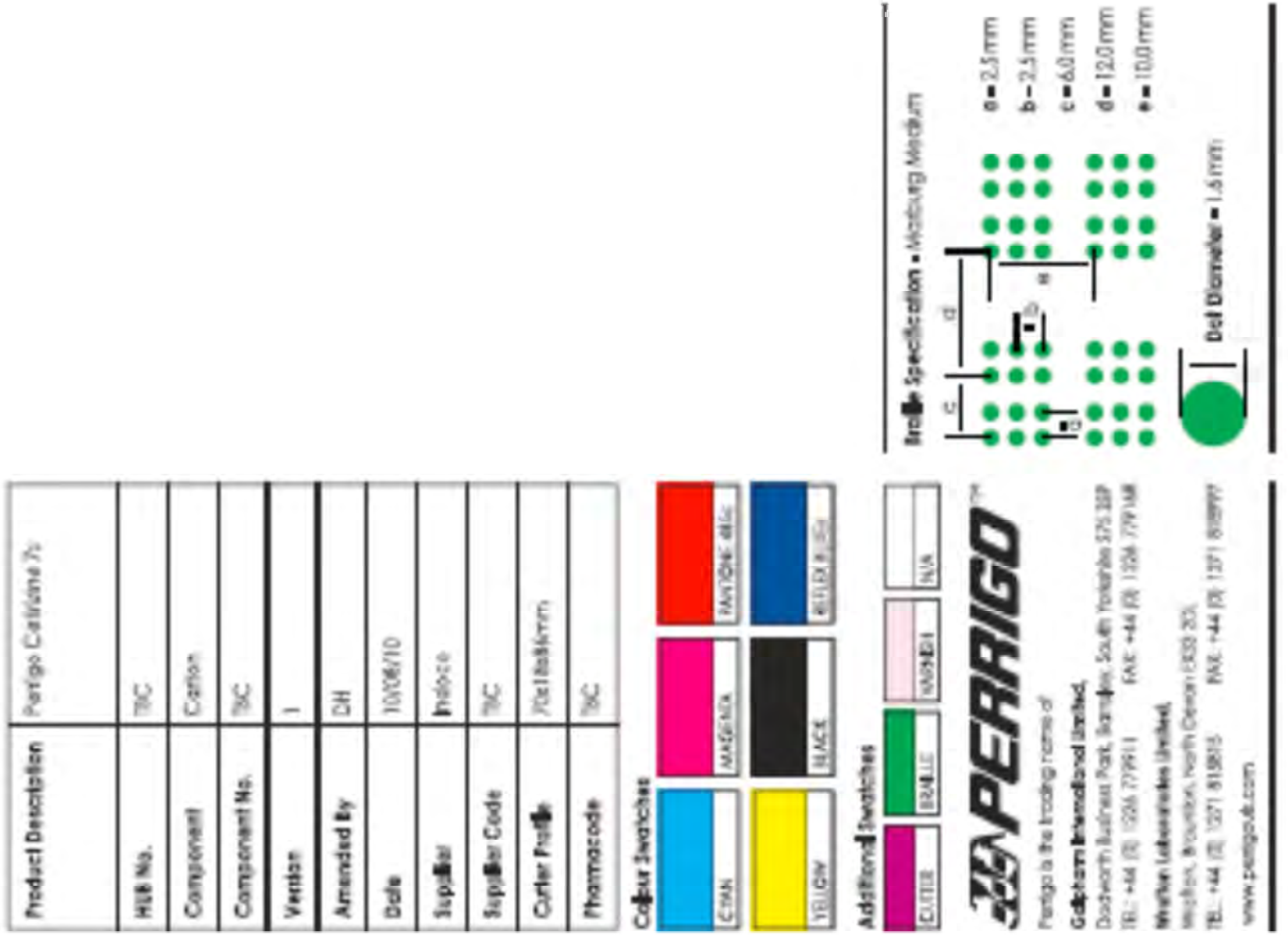
1.3.2 MOCK-UP

Labelling (carton and foil)

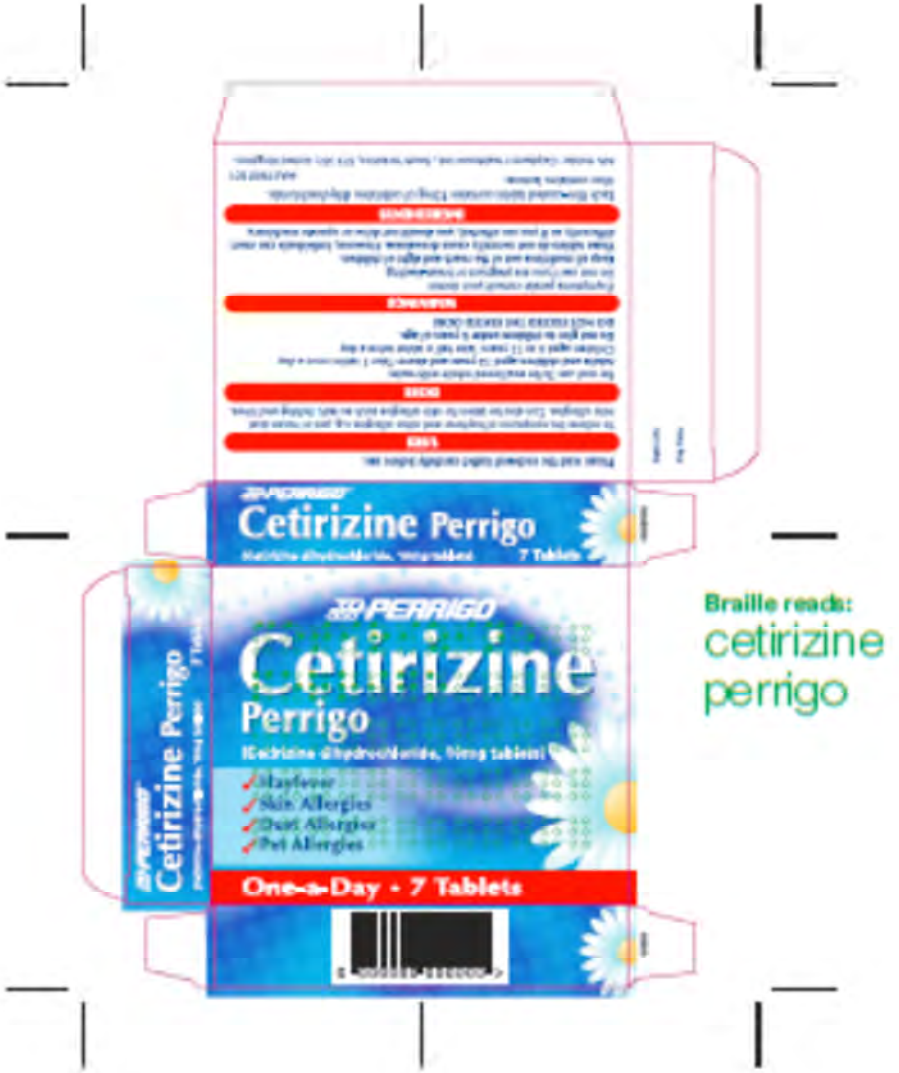
Patient Information Leaflet

Mock-up No. 18 – Page 2

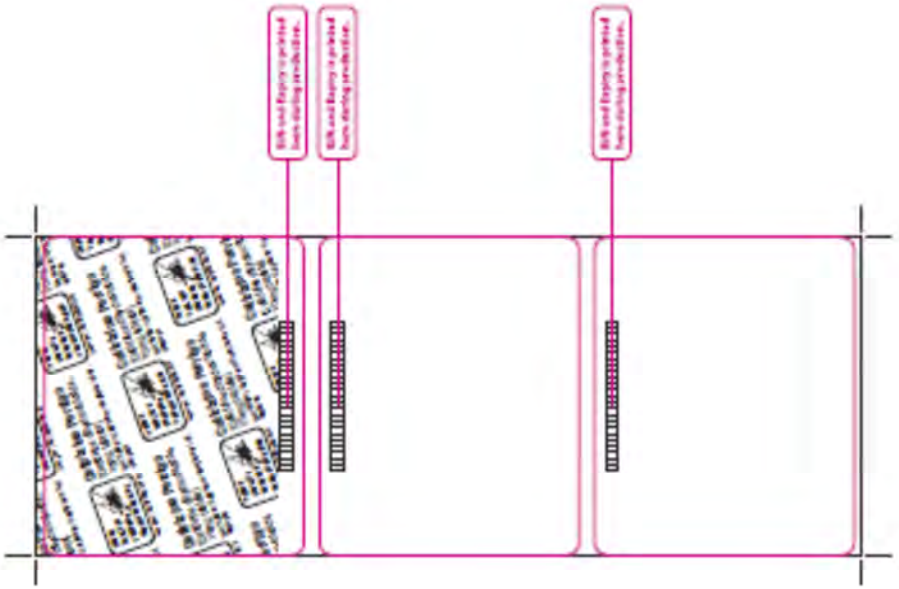
Mock-up No. 18 – Page 2 cont

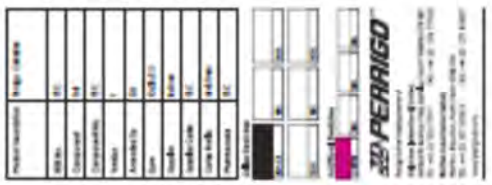


Mock-up No. 18 – Page 3

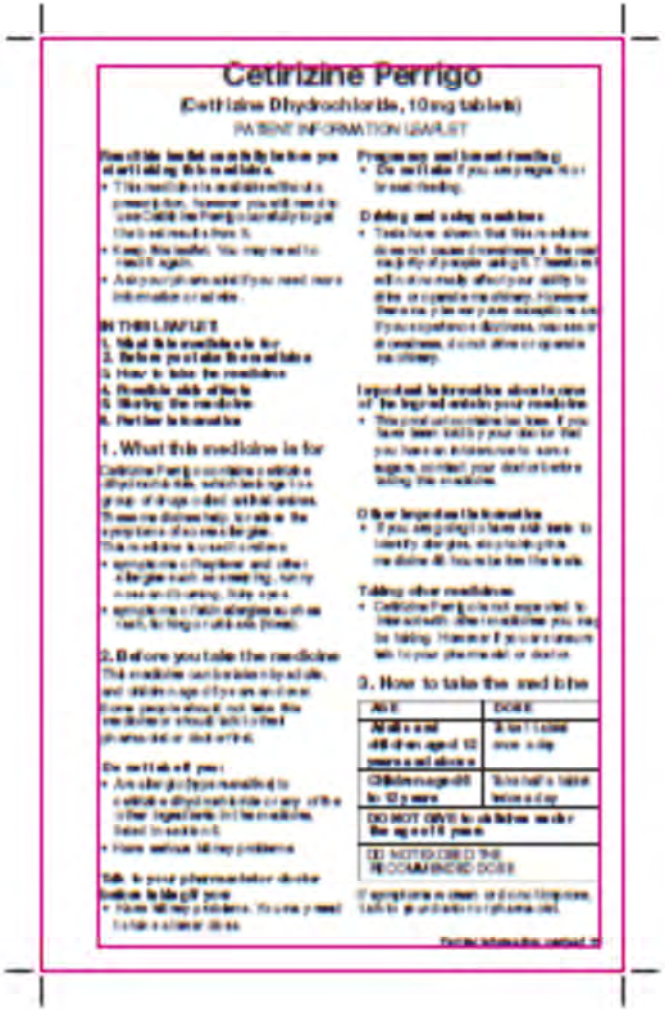


Mock-up No. 18 – Page 4





Mock-up No. 18 – Page 5



Cetirizine Perrigo

(Cetirizine Dihydrochloride, 10mg tablets)

PATIENT INFORMATION LEAFLET

1. What this medicine is for

2. Before you take the medicine

3. How to take the medicine

Decision matrix Mock-up No. 18 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 18 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes**	**5**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes**	**5**
	• Type size as large as possible used?	**yes**	**5**
	• Is space between lines at least 3 mm?	**no**	**0**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**5**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**no (bold)**	**0**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**no**	**0**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**3**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**3**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**na (not centrally approved)**	**-**

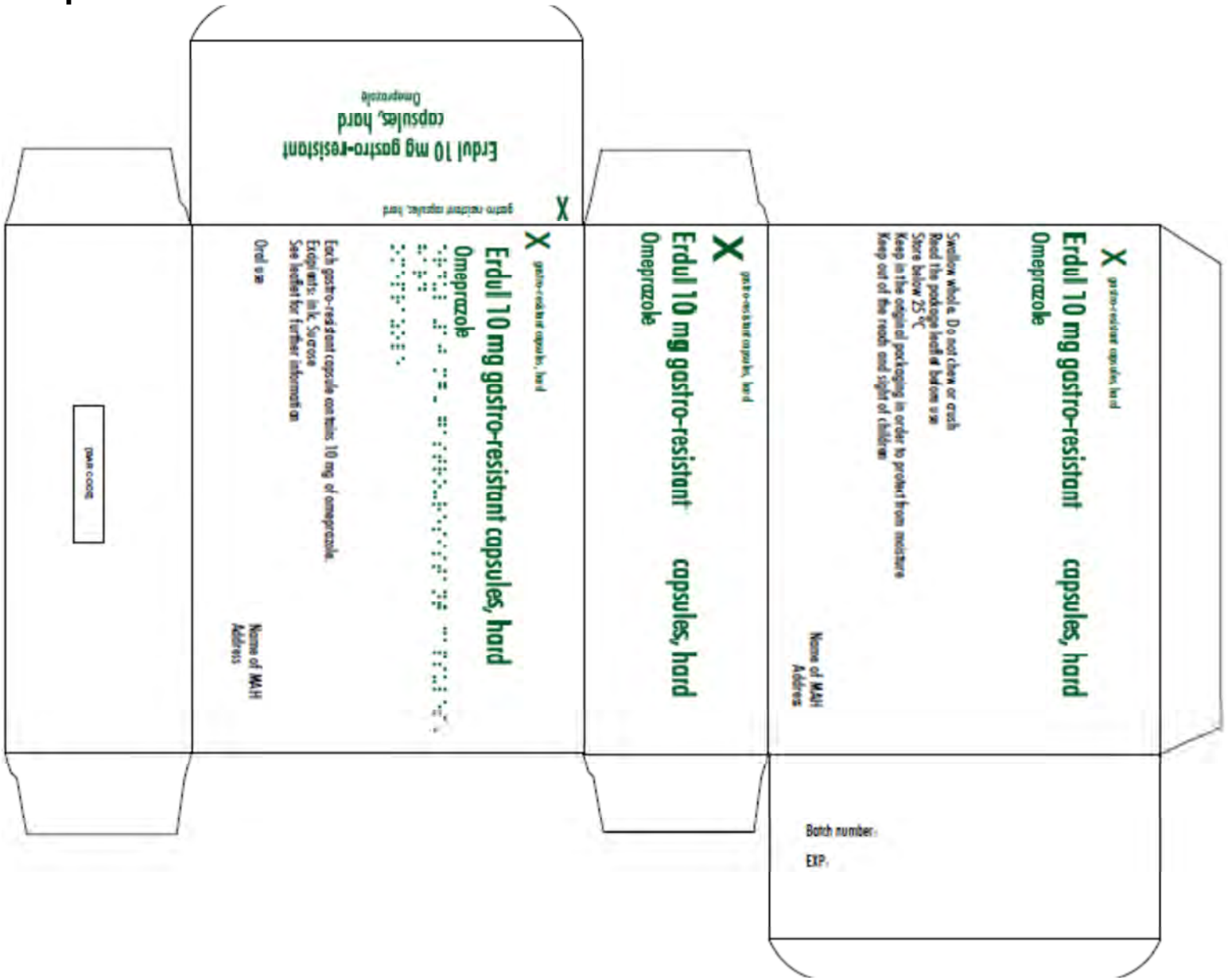
Decision matrix Mock-up No. 18 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 18 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**3**
	• Are different colours in name of product? (Use of different colours to distinguish different strength is strongly recommended!)	**no**	**0**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**3**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? No background images placed behind the text?	**na** (no symbols used)	**-**
	• Are no elements of promotional nature used?	**na** (no symbols	**-**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**na** (no symbols used)	**-**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

Decision matrix Mock-up No. 18 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 18 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labeling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**1**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**no**	**0**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• Place in certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**na**	**-**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no different strength)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**na**	**-**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**yes**	**3**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**no**	**0**
	• Only standard abbreviations used i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**na (tablets)**	**-**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**3**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**yes**	**5**

Annex 19 = Mock-up No. 19



Decision matrix Mock-up No. 19 - Page 1

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 19 - Page 1			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Overall layout and design			
TYPE SIZE AND FONT			
Best use of space available to ensure important information is clearly mentioned on prime space in sufficiently large type size.	• Font in which similar letters and numbers can be easily distinguished from each other: “i”, “l” and “1” used and no stylised font?	**yes / no?** Format of package?	**?**
	• Characters of at least 7 points (or a size where lower case “x” is at least 1.4 mm in height) used?	**yes / no?** Format of package?	**?**
	• Type size as large as possible used?	**yes / no?** Format of package?	**?**
	• Is space between lines at least 3 mm?	**yes?** Format of package?	**?**
	• Different text sizes used to enable key information to stand out (invented name, strength, pharmaceutical form, active substance, dedicated age groups)?	**yes**	**5**
	• Bold type, capitals / italics and semi-bold text as method of emphasis avoided because it is not recommended?	**yes**	**5**
DESIGN AND LAYOUT OF INFORMATION			
	• Is line space clear? (Where practical space between line and next should be at least 1.5 times the space between words on a line.)	**yes**	**5**
	• Is white space used and consideration given to line-spacing to enhance legibility of information provided?	**yes**	**5**
	• Is related information standing together?	**yes**	**5**
	• Is there enough contrast between text and background?	**yes**	**3**
TEXT POSITIONING AND BOXING			
	• Was there only little and not a too big amount of space used for company details? (Company details should be moved on to a side panel to afford a greater amount of space for rest of product information where appropriate.)	**yes**	**5**
	• Is dark print on light background considered where small type sizes have been used?	**yes**	**5**
	• Multi-lingual packaging (if relevant):	**na**	**-**
	- Is clear demarcation between different languages infixed where space permits?	**na**	**-**
	- Is information per language grouped when feasible?	**na**	**-**
	- When space does not allow display of all information in different languages on same panel is each panel per language used?	**na**	**-**
	- Is content of all languages versions identical?	**na**	**-**
	• Is space for prescribed dose included to be indicated?	**no**	**0**
	• Centrally authorised products only: Is a **”blue box”** included with a blue border? (Aimed at containing information to each Member State)	**na (not centrally approved)**	**-**

Decision matrix Mock-up No. 19 - Page 2

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 19 - Page 2			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Use of colours and pictograms			
PRINT COLOUR			
Judicious and careful use of colour on pack to reduce similarity in packaging which contributes to medication errors and to differentiate between packs! Colour on outer packaging should be carried onto primary packaging to aid identification of medicine.	• Is colour choosen that ensures good contrast between text and background (other than for small type sizes)? Are no similar colours used? Are not too many colours used?	**yes**	**3**
	• Are different colours in name of product? (Use of different colours to distinguish different strength is strongly recommended!)	**no**	**0**
	• Are characters printed in one or several colours? (Should be clearly distinguished from background) (Best: dark print on light background specially where small type sizes have to be used – for special warnings maybe use reverse type: light text on dark background). Relationship between colours is as important as colours themselves. Good colours used?	**yes**	**3**
PAPER			
	• Was uncoated carton used?	**na**	**-**
	• Was highly glossy, metallic or reflective packaging avoided?	**na**	**-**
USE OF SYMBOLS AND PICTOGRAMS			
	• Were symbols and pictograms (e.g. figures, lines) used that do not interfere with legibility of mandatory, statutory information? Does space permit symbols and pictograms? Was no actual text replaced? No background images placed behind the text?	**na** (no symbols used)	**-**
	• Are no elements of promotional nature used?	**na** (no symbols used)	**-**
	• Symbols should be useful to identify individual medicine and differentiate from other medicines and from non-medicinal products and should only clarify certain information, meaning should not be misleading or confusing. Is this true?	**na** (no symbols used)	**-**
Other important information for non-prescription medicine			
	• Is this information like e.g. therapeutic indication, dosage, warnings, instruction for use brought together in the same field of view? Is a a clear font type and a sufficiently large type size used?	**yes**	**5**

Decision matrix Mock-up 19 - Page 3

Decision matrix for Evaluation of design and layout of folding boxes of not centrally approved medicinal products - MOCK-UP No. 19 - Page 3			
Category / Requirement	**Criteria** **yes:** Strong correlation = Level of Compliance = **5** / Moderate correlation - Level of Compliance = **3** / Weak correlation - Level of Compliance = **1**; **no:** Level of Compliance = **0**; Not applicable **(na)** - Level of Compliance = **-**	**Assesment yes / no / not applicable**	**Level of Compliance**
Presentation and positioning of critical labeling information for safe use of medicine - Differentiation between strength			
Elements should be brought together in same field of view using a sufficient large size and should appear in order specified in section 1 of SmPC. **If possible invented name and strength may appear in the same line.** **For some small packs it may not be possible to put all critical information in same field of view. Then maybe use innovative technique in packaging design. Active substance is required to be indicated immediately below the full name.**	**NAME OF MEDICINE = (invented or common or scientific name + strength + pharmaceutical form)**		
	• Is full name of medicinal product with its strength and pharmaceutical form included? And if appropriate information, if intended for babies, children or adults?	**yes**	**5**
	• Invented name and strength may appear on same line (this information together with pharmaceutical form and active substance may also be presented in different lines of text as long as it appears as **cohesive unit** and is not be separated by any text or graphics).Is this true?	**yes**	**5**
	• Name of medicine should appear prominently and in sufficient large font type on prime spaces, particularly on the front panel. Is this true?	**yes**	**5**
	• If possible name of medicine should appear on at least three non-opposing sides of an outer carton (including one end panel), whenever space allows for display. Is this true?	**yes**	**5**
	• Are there up to three active ingredients? If yes, are INN/common name(s) of these active ingredient(s) stated after full name of medicine for safety reasons?	**na** (less than 3 active ingredients)	**-**
	STRENGTH and (where relevant) TOTAL CONTENT		
	• Place in certain circumstances information on both, quantity per unit volume and on total quantity per total volume (total volume e.g. for injectable products or solutions or suspensions for safety reasons). Is this true?	**na**	**-**
	• Is strength stated preferably only once on each side of package within name of medicine? If further repeated it should not be confused with pack size!	**yes**	**5**
	• Are different strength of same medicinal product expressed in same manner (250 mg, 1000 mg NOT 1 g)?	**na** (no differnt strength)	**-**
	• Do trailing zeros not appear (2.5 mg NOT 2.50 mg)?	**na**	**-**
	• Was use of decimal points (or comma) avoided (250 mg instead of 0.25 g)?	**yes**	**5**
	• Were micrograms spelt out in full and not abbreviated for safety reasons?	**no**	**0**
	• No use of the expression of strength as percentage without regard of exceptions. Is this true or are there reasons for exceptions?	**yes**	**5**
	ROUTE OF ADMINISTRATION		
	• Is route of administration displayed in same field of vision as rest of critical information?	**no**	**0**
	• Does route of administration appear in front of pack in same field of vision as name of medicine?	**no**	**0**
	• Only standard abbreviations used i.v., i.m., s.c.)? Are non-standard-routes of administration spelled out in full?	**na (capsules)**	**-**
	ACTIVE SUBSTANCE should follow after name of medicine		
	• Does active substance appear on front of pack in same field of vision as name of medicine?	**yes**	**5**
	• Are name of medicine and active substance presented in different lines of text. If it was necessary, do they appear as a cohesive unit? This is especially important where range of medicines within same umbrella brand include different active substance(s).	**yes**	**5**
	• It is not necessary to repeat names of active substances(s) on side of flaps, but where names are included, type sizes should be in same relative proportion to name of medicine as they are on front pack. Is this true?	**yes**	**5**
Braille (reading and writing system for blind and partially-sighted people)			
Underlying text must be easily legible	• Is name of medicinal product also expressed in Braille format? If multilingual packaging: is name in Braille printed in all different languages? Is underlying printed text easily legible?	**yes**	**5**

Annex 20 - History of the legal basis of labeling

Directive 65/65/EE4 [15]

COUNCIL DIRECTIVE 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products
(OJ L No 22 of 9. 2. 1965, p. 369)
(As amended by Directives 66/454/EEC, 75/319/EEC, 83/570/EEC, 87/21/EEC, 89/341/EEC, 89/342/EEC 89/343/EEC, 92/27/EEC, 92/73/EEC et 93/39/EEC)

CHAPTER IV Labelling of medicinal products; Articles 13 – 20 sets the particulars that should appear in the labelling.

These articles are repealed by Directive 92/27/EEC

Directive 92/27/EWG EUR-Lex - 31992L0027 [16]
COUNCIL DIRECTIVE 92/27/EEC of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets

CHAPTER II Labelling of medicinal products; Article 1 gives important definitions regarding labeling that can now be found in Directive 2001/83/EC.

Dir 2001/83/EC [4]
DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF NOVEMBER 2001 ON THE COMMUNITY CODE RELATING TO MEDICINAL PRODUCTS FOR HUMAN USE
Official Journal L – 311, 28/11/2004, p. 67 – 128

as amended by

Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC
Official Journal L – 33, 08/02/2003, p. 30 – 40

Directive 2004/24/EC of the European Parliament and the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use
Official Journal L – 136, 30/04/2004, p. 85 – 90

Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use

TITLE V LABELLING AND PACKAGE LEAFLET is the current legal basis for labeling:

For the safe and appropriate use of medicinal products it is required by Community law (Article 54, 55 and 59 of Directive 2001/83/EC) that medicinal products should be accompanied by labelling (outer and/or immediate packaging information) and package leaflet. This is to give the patients and health care professionals a set of comprehensible information.

Article 54 of Titel V Labelling and Package leaflet, sets which particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging. These statutory provisions refer only to the content requirements that must be made on a folding box.

The particulars that shall appear are:

(a) the name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults; where the product contains up to three active substances, the international nonproprietary name (INN) shall be included, or, if one does not exist, the common name;

(b) a statement of the active substances expressed qualitatively and quantitatively per dosage unit or according to the form of administration for a given volume or weight, using their common names;

(c) the pharmaceutical form and the contents by weight, by volume or by number of doses of the product;

(d) a list of those excipients known to have a recognized action or effect and included in the detailed guidance published pursuant to Article 65. However, if the product is injectable, or a topical or eye preparation, all excipients must be stated;

(e) the method of administration and, if necessary, the route of administration. Space shall be provided for the prescribed dose to be indicated;

(f) a special warning that the medicinal product must be stored out of the reach and sight of children;

(g) a special warning, if this is necessary for the medicinal product;

(h) the expiry date in clear terms (month/year);

(i) special storage precautions, if any;

(j) specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products, where appropriate, as well as reference to any appropriate collection system in place;

(k) the name and address of the marketing authorisation holder and, where applicable, the name of the representative appointed by the holder to represent him;

(l) the number of the authorization for placing the medicinal product on the market;

(m) the manufacturer's batch number;

(n) in the case of non-prescription medicinal products, instructions for use.

Only Article 56 of Directive 2001/83/EC gives recommendations for the design of the folding boxes. It is said that the particulars referred to in Articles 54, 55 and 62 shall be easily legible, clearly comprehensible and indelible.

Regarding Article 56 a the name of the medicinal product, must also be expressed in Braille format on the packaging.

Article 61 determines that when the marketing authorisation is requested 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.

Article 62 gives advice that 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 the product characteristics which is useful for the patient, to the exclusion of any element of a promotional nature.