The role of labelling and packaging information in medication adherence

Fernando Fernandez-Llimos
University of Lisboa
Conflict of interests

• I have no conflict of interest related with this lecture.

• These slides contain pictures of medicines marketed in EU, and they should be considered just as examples supporting the information.

• Neither me or my institutions at any time received payment or services for any aspect of this lecture.

• The views and opinions expressed in this lecture do not necessarily reflect the official policy or position of any if the institutions that I’m involved.
The role of labelling and packaging information in medication adherence

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Labeling vs. Labelling

The single-l spelling is well established in American English. American writers adopted the newer forms around 1900, and labelled and labelling are now scarcely seen in American publications. This Ngram renders the story visually, graphing the use of labeled and labelled in a large number of American books, magazines, and journals published from 1800 to 2000:

http://grammarist.com/spelling/label/
Google Books Ngram viewer

Graph these comma-separated phrases: labeled, labelled


https://books.google.com/ngrams/graph?content=labeled%2Clabelled&year_start=1800&year_end=2000&corpus=0&smoothing=3&direct_url=t1%3B%2Clabeled%3B%2Cc0%3B.t1%3B%2Clabelled%3B%2Cc0
Labeling vs. Labelling

Summary

Is it labeled or labelled? *Labeling* and *labelling* are alternate spellings of the same verb.

- Labeled and labeling are the accepted forms in American English.
- Labelling and labelling are the accepted forms in British English.

You can remember to reserve *labelled* for writing designed for a predominantly British audience by thinking about the II. The British towns Collumpton, Ellesmere, and Ferryhill also feature a double l, so it shouldn’t be difficult to remember that labelling, like these three towns, is British.

http://writingexplained.org/labeled-vs-labelled-difference
Labeling vs. Labelling

Summary

Is it labeled or labelled? *Labeling* and *labelling* are alternate spellings of the same verb.

http://writingexplained.org/labeled-vs-labelled-difference
U.S. drug labeling

- A prescription drug product’s FDA approved labeling (also known as “professional labeling,” “package insert”, “direction circular”, or “package circular”) is a compilation of information about the product, approved by FDA, based on the agency’s thorough analysis of the new drug application (NDA) or biologics license application (BLA) submitted by the applicant.

- This labeling contains information necessary for safe and effective use. It is written for the health care practitioner audience, because prescription drugs require “professional supervision of a practitioner licensed by law to administer such drug” (section 503(b) of the act (21 U.S.C. 353(b))).
U.S. drug labeling

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ASTHMA-RELATED DEATH

1 INDICATIONS AND USAGE
   1.1 Treatment of Asthma
   1.2 Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD)

2 DOSAGE AND ADMINISTRATION
   2.1 Asthma
   2.2 Chronic Obstructive Pulmonary Disease (COPD)

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
   5.1 Asthma-Related Death
   5.2 Deterioration of Disease and Acute Episodes
   5.3 Excessive Use of SYMBICORT and Use with Other Long-Acting Beta2-Agonists
   5.4 Local Effects
   5.5 Pneumonia and Other Lower Respiratory Tract Infections
   5.6 Immunosuppression
   5.7 Transferring Patients From Systemic Corticosteroid Therapy
   5.8 Hypercorticism and Adrenal Suppression
   5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
   5.10 Paradoxical Bronchospasm and Upper Airway Symptoms
   5.11 Immediate Hypersensitivity Reactions
   5.12 Cardiovascular and Central Nervous System Effects
   5.13 Reduction in Bone Mineral Density
   5.14 Effect on Growth
   5.15 Glaucoma and Cataracts
   5.16 Eosinophilic Conditions and Churg-Strauss Syndrome
   5.17 Coexisting Conditions
   5.18 Hypokalemia and Hyperglycemia

6 ADVERSE REACTIONS
   6.1 Clinical Trials Experience in Asthma Patients 12 years and older
   6.2 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease
   6.3 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
   8.1 Pregnancy
   8.2 Labor and Delivery
   8.3 Nursing Mothers
   8.4 Pediatric Use
   8.5 Geriatric Use
   8.6 Hepatic Impairment
   8.7 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action
   12.2 Pharmacodynamics
   12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
   13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
   13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
   14.1 Asthma
   14.2 Chronic Obstructive Pulmonary Disease (COPD)

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION
   17.1 Asthma-Related Death
   17.2 Not for Acute Symptoms
   17.3 Do Not Use Additional Long-Acting Beta2-Agonists
   17.4 Risks Associated With Corticosteroid Therapy
   17.5 Risks Associated With Beta-Agonist Therapy

* Sections or subsections omitted from the full prescribing information are not listed.
E.U. Labelling

• Article 1: For the purposes of this Directive, the following terms shall bear the following meanings:

25. Labelling:

Information on the immediate or outer packaging.

23. Immediate packaging:

The container or other form of packaging immediately in contact with the medicinal product.

24. Outer packaging:

The packaging into which is placed the immediate packaging.
The adherence project has adopted the following definition of adherence to long-term therapy, a merged version of the definitions of Haynes (2) and Rand (3):

*the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.*
Potential issues

- intention
- prescription
- dispensing
- home storage
- actual taking

Errors
Poor counselling
Poor economy
Storage conditions
Errors
Forgetting
Poor attitudes
Misunderstandings
Elements influencing adherence

• Information for professionals
  – FDA labeling
  – EU SmPCs
• Information for patients (and caregivers)
• Outer packaging (secondary packaging)
• Immediate packaging (primary packaging)
• Administration aids
Product monographs supplied by drug manufacturers to community pharmacists in Spain

A checklist with 54 aspects grouped in five areas was designed: desired effects (i.e., mechanism of action, efficacy with respect to analogs, efficacy with respect to placebo, sites of absorption, excretion routes), undesirable effects (i.e., adverse drug reactions, acute intoxication symptoms, chronic toxicity symptoms, teratogenicity, carcinogenicity), treatment compatibility (i.e., drug–drug interactions, drug–food interactions, other pathologies, precautions), advice to be given to the patient, and other relevant aspects (i.e., maximum concentration, time to reach maximum concentration, AUC, protein binding). Analysis of content involved rating of coverage (rated as coverage, no coverage, or not applicable) of the 54 aspects. In addition, the text relating to each applicable aspect was evaluated regarding literature citations (refereed, nonrefereed, and their Science Citation Index [SCI] impact factor).

Table 1. Coverage Provided by Product Monographs of Specific Aspects from the Checklist

<table>
<thead>
<tr>
<th>Area</th>
<th>Coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total coverage</td>
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<tr>
<td>Desired effects</td>
<td>45.1</td>
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<tr>
<td>Undesired effects</td>
<td>35.8</td>
</tr>
<tr>
<td>Compatibility</td>
<td>35.8</td>
</tr>
<tr>
<td>Advice to patients</td>
<td>12.5</td>
</tr>
</tbody>
</table>
FDA labeling (Symbicort)

14 CLINICAL STUDIES
  14.1 Asthma
  14.2 Chronic Obstructive Pulmonary Disease (COPD)

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION
  17.1 Asthma-Related Death
  17.2 Not for Acute Symptoms
  17.3 Do Not Use Additional Long-Acting Beta_2-Agonists
EU SmPCs (Symbicort)

1. Name of the medicinal product
2. Qualitative and quantitative composition
3. Pharmaceutical form
4. Clinical particulars
   4.1 Therapeutic indications
   4.2 Posology and method of administration
   4.3 Contraindications
   4.4 Special warnings and precautions for use
   4.5 Interaction with other medicinal products and other forms of interaction
   4.6 Pregnancy and lactation
   4.7 Effects on ability to drive and use machines
   4.8 Undesirable effects
   4.9 Overdose

5. Pharmacological properties
   5.1 Pharmacodynamic properties
   5.2 Pharmacokinetic properties
   5.3 Preclinical safety data

6. Pharmaceutical particulars
   6.1 List of excipients
   6.2 Incompatibilities
   6.3 Shelf life
   6.4 Special precautions for storage
   6.5 Nature and contents of container
   6.6 Special precautions for disposal and other handling

7. Marketing authorisation holder
8. Marketing authorisation number(s)
9. Date of first authorisation/renewal of the authorisation
10. Date of revision of the text

https://www.medicines.org.uk/emc/medicine/4821
EU patient leaflet (Symbicort)

Acceso de los profesionales a los prospectos de los medicamentos
Sr. Director: Aunque en la Unión Europea las falsificaciones de medicamentos no son un problema prioritario, ya se han denunciado algunos casos y la OMS considera este problema como uno de los que se de-

Al igual que hay una base menes de características prospectos para los medicamentos, la Agencia Española de Medicamentos y Productos Sanitarios ha tenido que hacer disponibles los prospectos aprobados.

EU patient leaflet (Symbicort)

https://www.aemps.gob.es/cima/fichasTecnicas.do?metodo=detalleForm
EU SmPCs


In conclusion, important information on the use of medicines during pregnancy and breastfeeding is missing in European SmPCs, and the time elapsed since a SmPC’s marketing authorization was issued was not associated with an increased information quality. Post-authorization data on the use of medicines during pregnancy and breastfeeding is missing in European SmPCs, and the time elapsed since a SmPC’s marketing authorization was issued was not associated with an increased information quality. Post-authorization data on the use of medicines during pregnancy and breastfeeding is missing in European SmPCs, and the time elapsed since a SmPC’s marketing authorization was issued was not associated with an increased information quality. Post-authorization data on the use of medicines during pregnancy and breastfeeding is missing in European SmPCs, and the time elapsed since a SmPC’s marketing authorization was issued was not associated with an increased information quality. 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Post-authorization data on the use of medicines during pregnancy and breastfeeding is missing in European SmPCs, and the time elapsed since a SmPC’s marketing authorization was issued was not associated with an increased information quality.


In conclusion, current versions of SmPCs are characterised by several information deficits, as well as by containing recommendations that are not relevant for clinical practice in terms of dose adjustment in renal impairment. This may have implications for the decision-making process of healthcare professionals in daily clinical practice. Furthermore, current
EU SmPCs


CONCLUSION
Our analysis identified several weaknesses in the quality of pharmacogenetic information provided in EU SmPCs compared with US labels for the use of medicines in CYP polymorphic metabolizers. European sources have been revealed to be less user-friendly, complete and applicable than US labels. To prevent the occurrence of these weaknesses, it is essential that recommendations be implemented.


It seems that we are facing a global issue that should be tackled by international initiatives, like the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, in order to bring uniformity to recommendations for the classification of stages of renal impairment and, ultimately, for drug dosing recommendations in renal patients.
Should we revise the EU SmPCs?

...and include a “patient counseling information” section?
Medication regime complexity and 30-day heart failure readmissions

A. Carmine Colavecchia, David R. Putney, Michael L. Johnson, Rajender R. Aparasu

Discharge medication complexity and 30-day heart failure readmissions

Polypharmacy and medication regimen complexity as factors associated with staff informant rated quality of life in residents of aged care facilities: a cross-sectional study

Samanta Lalic, Kris M. Jansen, Barbara C. Wimmer, Edwin C.K. Tan, Sarah N. Hilmer, Leonie Robson, Tina Emery, J. Simon Bell

Medication Regimen Complexity and Number of Medications as Factors Associated With Unplanned Hospitalizations in Older People: A Population-based Cohort Study

Barbara Caecilia Wimmer, J. Simon Bell, Johan Fastbom, Michael David Wiese and Kristina Johnell

Medication regimen complexity and readmissions after hospitalization for heart failure, acute myocardial infarction, pneumonia, and chronic obstructive pulmonary disease

Nada Abou-Karam, Chad Bradford, Kajua B Lor, Mitchell Barnett, Michelle Ha and Albert Rizos
Medication regime complexity

Development and Validation of the Medication Regimen Complexity Index

Johnson George, Yee-Teng Phun, Michael J Bailey, David CM Kong, and Kay Stewart

Appendix II: Medication Regimen Complexity Index (MRCI)

MEDICATION REGIMEN COMPLEXITY INDEX

[Table with columns for Patient ID, Total no of medications (including prescribed medications), and Instructions]

Instructions:
1. MRCI applies only to prescribed medications. All entries are to be made only based on information on the label or drug chart (at the time of dispensing or discharge). No assumptions are to be made based on clinical judgment.
2. There are six sections in the scale. Complete each section before proceeding to the next. At the end, add the scores for the three sections to give the MRCI.
3. If the same medication (same brand and same dosage form) is present more than once in different strengths in a regimen (e.g. Marersone 5mg, 10mg, and 15mg), it is still considered as one medication.
4. In cases where the dosage is optional, choose the dosing instruction with the smallest dose frequency (e.g. Venetol MDI 1 puff, 2 puffs: daily will get weightings for ‘metered dose inhalers’, ‘variable dose’ and ‘twice daily’, but not for ‘multiple units at one time’).
5. In cases where the dosing frequency needs to be calculated (e.g. Ramifina 1.2mg, 3.6mg twice daily).
6. It is possible that with certain ‘use as directed’ instructions, the regimen will not get a score under dosing frequency (e.g. Produtecine 5mg qds).
7. If there is more than one dose frequency, they should be scored for all the dosing frequency directions (e.g. Venetol MDI 2 puffs bid and pm, will get scores for ‘metered dose inhalers’, ‘multiple units at one time’, ‘twice daily’ as well as ‘every day’). If there is no matching option, choose the closest option (e.g. six times daily could be considered as ‘twice daily’).

A) Circle the weighting corresponding to each dosage form (ONCE ONLY) present in the regimen:

<table>
<thead>
<tr>
<th>Dosage Forms</th>
<th>Weighting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Patches</td>
<td></td>
</tr>
<tr>
<td>Sprays</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Aerosols</td>
<td></td>
</tr>
<tr>
<td>Nebulisers</td>
<td></td>
</tr>
<tr>
<td>Oxygen/Compressor</td>
<td></td>
</tr>
<tr>
<td>Nebulisers</td>
<td></td>
</tr>
<tr>
<td>Sprays</td>
<td></td>
</tr>
<tr>
<td>Total for Section A</td>
<td></td>
</tr>
</tbody>
</table>

B) For each medication in the regimen tick a box (X) corresponding to the dosing frequency. Then, add the no. of ‘X’s in each category and multiply by the assigned weighting. In cases where there is no exact option, choose the best option

<table>
<thead>
<tr>
<th>Dosing Frequency</th>
<th>Medications</th>
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<tbody>
<tr>
<td>Twice daily</td>
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<tr>
<td>Twice daily</td>
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<td>Three times daily</td>
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<td>Three times daily</td>
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<tr>
<td>Four times daily</td>
<td></td>
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<td>Four times daily</td>
<td></td>
</tr>
<tr>
<td>Five times daily</td>
<td></td>
</tr>
<tr>
<td>Total for Section C</td>
<td></td>
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</table>

C) Tick a box (X) corresponding to the additional directions, if present in the regimen. Then, add the no. of ‘X’s in each category and multiply by the assigned weighting.

<table>
<thead>
<tr>
<th>Additional Directions</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
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<tr>
<td>Total for Section E</td>
<td></td>
</tr>
</tbody>
</table>

Medication Regimen Complexity = Total (A) + Total (B) + Total (C)
Elements to consider

• Information for professionals
  – FDA labeling
  – EU SmPCs
• Information for patients (and caregivers)
• **Outer packaging (secondary packaging)**
• Immediate packaging (primary packaging)
• Administration aids
“Facial” recognition (strength)
“Facial” recognition (strength)
“Facial” recognition (strength)
“Facial” recognition (strength)
“Facial” recognition (strength)
“Facial” recognition (strength)
“Facial” recognition (strength)
“Facial” recognition (strength)
“Facial” recognition (substance)
“Facial” recognition (substance)
“Facial” recognition (substance)

identical
different
Can generics imitate the innovators?
Facilitating things

2. Pack design (logo, colour, etc.)

For practical and linguistic reasons marketing authorisation holders are likely to present the medicinal product packaging in several linguistic and/or "national" versions (i.e. with the relevant boxed areas). In such cases, the logo, format, layout, style, colour scheme and if possible also the pack dimensions must be identical for all the versions of packs of that medicinal product throughout the Community.

In accordance with Article 61 of Directive 2001/83/EC as amended, all proposed changes to any aspect of the presentation shall be submitted to the EMEA, who will inform the Commission where relevant.
Easy labels?
Elements to consider

• Information for professionals
  – FDA labeling
  – EU SmPCs
• Information for patients (and caregivers)
• Outer packaging (secondary packaging)
• **Immediate packaging (primary packaging)**
• Administration aids
Calendar blisters
Calendar blisters
Calendar blisters
Calendar blisters
Weekly doses
Weekly doses
Weekly doses
Weekly doses
Elements to consider

• Information for professionals
  – FDA labeling
  – EU SmPCs

• Information for patients (and caregivers)

• Outer packaging (secondary packaging)

• Immediate packaging (primary packaging)

• Administration aids
Pictograms
Pictograms
Pictograms
Pictograms

Undue use may incur a fine of up to €225,000 (Law 21/2003 Air Travel Security)
Pictograms
Pictograms
Pharmaceutical forms

A
- ACE spacer
- AeroChamber Plus Flow-Vu
- Vortex
- LiteAire
- EZ-Spacer

B
- Aerolizer
- Turbuhaler
- HandiHaler
- Diskus
- Manta

C
- MicroAir NE-U22
- Aeroneb G0
- eFlow
- I-neb
- Respimat
Administration aids
Administration aids
Administration aids
Administration aids
## Splitting tablets

### CONSULTA DE ANTICOAGULAÇÃO ORAL

**IDENTIFICAÇÃO:**
NOME: 
DATA DE NASCIMENTO: __/__/__ UTENTE: 
DIAGNÓSTICO: Fibração Auricular

**INÍCIO TRATAMENTO:** __/__/__
**FINAL TRATAMENTO:** __/__/__
**TRATAMENTO:** Varfarina
**MARGEM TERAPÊUTICA:** INR 2-3

### RESUMO DAS ÚLTIMAS CONSULTAS

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<th>N</th>
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<th>Resultado</th>
<th>P Consulta</th>
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<td>44</td>
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<td>Varfarina</td>
<td>3,2</td>
<td><strong>/</strong>/__</td>
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<td><strong>/</strong></td>
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<td>42</td>
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<td>41</td>
<td><strong>/</strong></td>
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<td><strong>/</strong>/__</td>
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</table>

### CONSULTA ATUAL

**DATA**
10/__/__

**INR**
2,9

**FARMACO**
Varfarina

**PRÓXIMA CONSULTA**
09/__/__

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<td>15</td>
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</tr>
</tbody>
</table>
Splitting tablets

Sintrom 4 mg
comprimidos
acenocumarol

Vía oral
20 comprimidos
Splitting tablets

DATOS DE LA VISITA
Fecha Visita.: 31/10/2016  Hematólogo...: Médico de Primaria
Acc.Hem./Tro.:  
Test (1).....: INR  Resultado....: 2.2
Fármaco (1)...: Sintrom 4 mg. (Acenocumarina)
Dosis........: 6.50 mg/semana 1/4 dia - DOM alternos 0
Test (2).....:  
Fármaco (2)...:  
Dosis........:  
Observaciones:

DOSIFICACION

<table>
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<tr>
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<th>LUNES</th>
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<th>JUEVES</th>
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Why do patients not adhere?

It is so easy to adhere.
They just have to marry a nurse or a pharmacist
A fool’s ideas
Standardise or Standardize

• Standardize pictograms
• Package colors
  – Standardize equals
  – Differentiate different
• Tablet sizes and colors
  – Standardize equals
  – Differentiate different
• Standardize instructions
• Standardize administration aids
• Rationalize pharmaceutical forms and devices