Article title: Evaluation of the type and structure of the imprints used on the surface of medicines

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Abstract

Background: Drug imprints on the surfaces of medicines could be used as accessible and economic anti-counterfeiting measures. **Aims:** to identify and study the structure of different types of imprints, and discuss potential problems related to their structure/format. **Method:** 531 Portuguese package leaflets (PLs) were manually inspected to confirm and collect the description of the imprints. The number of letters, symbols or mixtures of both was quantified in each imprint. An electronic tool was used to evaluate the linguistic characteristics. **Results:** Only 7.9% of 531 PLs described imprints. 55 imprints were identified: 23 (41.8%) only formed by letters and 32 (58.2%) formed by letters, numbers or symbols. It was possible to identify 171 words. **Conclusion:** It seems, that the imprints were not systematically used as anti-counterfeiting measures. Experimental studies and the updating of the pharmaceutical regulation on the suitability and specificities of these imprints are recommended.

Keywords: Consumer Product Safety; Legislation as Topic; Quality Improvement; Production of Products; Counterfeit Drugs

INTRODUCTION

The graphical systems used as product identifiers (e.g. holograms or imprints on the surface of medicines) are serialization procedures to more accurately identify the medicines, thus working as anti-counterfeiting measures.^{1,2} However, there are reports from health authorities supporting that the medicines' visual aspect may not be enough to confirm the authenticity of the medicine (e.g. laboratorial tests may be required).^{2,3} According to the pharmaceutical regulations, it is advisable to include in the package leaflets (PLs) information on the physical nature of the medicines (e.g. shape) to fully describe the aspect of the medicines.⁴

Furthermore, patient safety issues, including accidental deaths associated with the improper labelling of medicines or the incorrect use of symbols and abbreviations in health documents are widely documented in literature reports.^{5,6}

Computational linguistics is a recent discipline, which aim is, among other things, the automatic the automatic evaluation of phrases/texts through the use of informatics tools. These automatic tools are prepared to retrieve linguistic metrics of a certain language (e.g. number of orthographic words/syllables).⁷ The informatics tool FreP (Frequency Patterns of Phonological Objects in Portuguese) was specifically developed to automatically determine specific metrics in European Portuguese.^{8,9}

In this context, the main aims were to a) identify different types of imprints used on the surface of medicines, b) evaluate the structural characteristics of these imprints (e.g. linguistic or graphic), and c) discuss potential problems related to their structure/format.

METHODS

531 Portuguese PLs were manually inspected to check the presence of imprints. All the PLs were previously randomized from all the branded medicines mentioned in the Portuguese Prescribing Guide.¹⁰ The medicines of the PLs with the description of the imprints were characterized in relation to their therapeutic group, pharmaceutical presentation and administration route.

There was a brief evaluation of the linguistic characteristics of the imprints, i.e. the number of orthographic words, segments (consonants, vowels and glides) and syllables, syllables and occurrence of abbreviations (i.e. shortened words or phrases) or acronyms (formed by the initial letters of the words that compose a larger expression).¹¹ This evaluation was performed through the use of the informatics tool FreP.⁹ It was needed to write all the identified imprints according the way they are orally read (e.g. the imprint “51B” was wrote as “cinquenta e um bê” in Portuguese, “fifty-one bee” in English), before they were evaluated/processed by this automatic tool. All the retrieved results were re-evaluated by a linguist, because of quality reasons. The presence of symbols, abbreviations and acronyms in the imprints were also manually checked.

RESULTS

Number and type of PLs with imprints

Only 42 (7.9%) out of 531 PLs described imprints. The medicines mentioned in these 42 PLs were from the following a) routes of administration: 40 (95.2%) oral and two (4.8%) parenteral, and b) pharmaceutical presentations: tablets 35 (83.3%), capsules five (11.9%) and injectable forms (solution and suspension) two (4.8%). Moreover, these 42 PLs were from

medicines of diverse therapeutic groups: antibacterial (five) (e.g. ciprofloxacin); central nervous system (nine) (e.g. sertraline), cardiovascular system (four) (e.g. amlodipine), blood (four) (e.g. acenocoumarol), respiratory system (one) (bromexin), digestive system (three) (e.g. esomeprazole), genitourinary (five) (e.g. finasteride), hormones (three) (e.g. cabergoline), locomotor system (four) (e.g. diclofenac), antiallergic (one) (e.g. cetirizine), electrolytes (one) (sodium) and antitumour (two) (e.g. imatinib).

Number and type of imprints: some graphic and linguistic features

55 different imprints were identified, with six imprints being abbreviations (e.g. SER) (Table 1). These imprints were formed by 474 segments (nine segments per imprint in average) and 171 orthographic words with only one syllable in the majority of cases (111; 64.9%) (Table 2).

Insert Table 1 here.

From the 55 imprints: 23 (41.8%) imprints were formed by letters (including 2 cases of imprints with only one letter: "A" and "T"), and 32 (58.2%) imprints were formed by an association of letters, numbers or symbols (e.g. "/"). No quality problem was detected by the linguistic expert.

Insert Table 2 here.

DISCUSSION

Counterfeiting is a growing 21st century problem representing a global market of billions of dollars and a huge problem for the safety of millions of patients.^{1,2} The use of medicine imprints may be a simple and economic anti-counterfeiting measure in comparison with other more advanced and expensive measures (e.g. holograms). Despite the advantages of using imprints on the surface of medicines as an anti-counterfeiting measure, it seems they were scarcely used in the sampled PLs.¹ As far we know, there is a lack of requirements on this issue that justifies a) a standardized use of imprints on medicines surfaces or b) an obligatory description of the imprints in the PLs. For instance in this study, there was a wide variety of PLs containing the description of imprints (e.g. PLs of medicines from different therapeutic groups). Ideally, imprints should be described in the PLs, since their presentation favor the identification of the medicine by medicines users (e.g. using a medicine illustration in the PL section).⁴

Among the linguistic features related to the use of imprints on the surface of medicines are the following: a) the imprints need to be formed by a limited number of segments/syllables, since in the majority of the cases there are limited spaces on the surfaces of medicines (e.g. tablets), which also may explain the use of abbreviations as imprints, b) the imprints formed by associations between letters and symbols may be more advantageous than the imprints formed only by letters, since it is likely that the imprints formed by a limited number of characters may be more easily confused with other imprints (e.g. the case of imprints formed by just one letter), and 3) the use of imprints formed by abbreviations (e.g. "SER" that is read as just one phonological word) may be more appropriate than the use of imprints formed by acronyms (e.g. "LTL" that is read as three phonological words, i.e. "ele" "tê" "ele" in Portuguese or "ell" "tee" "ell" in English), because the reading of acronyms is considered

more complex/difficult.¹¹ Interestingly, the number of imprints with acronyms was much higher than the number of imprints with abbreviations in this study.

Our results suggest that it would be desirable to develop a) databases with the registration of all medicine imprints to avoid the use of the same imprint in different medicines, and b) new regulatory requisites, such as: a) a more frequent use of imprints on the surface of medicines, b) the non-use of similar/equal imprints in different medicines or c) the use of the name of the medicine as an imprint in case of existing enough space on the medicine surface. These new requisites should be based on the results of additional experimental studies, such as those on a) the most appropriate format for the imprints and b) the users' satisfaction, memorization and recall on these imprints (e.g. determining how abstract/non-abstract symbols, abbreviations or acronyms are memorized and recalled by the users of medicines). For instance, studies using eye-tracking methodologies (which allow to investigate the areas of interest revealed by eye movements and amount of looking time) to evaluate how people process and read text/symbols (e.g. time to read a certain visual stimulus).¹²

Informatics tools capable of evaluating the linguistic characteristics of written texts represent a golden opportunity for the management of large amounts of information. It seems, that these tools may be useful to medicines authorities and marketing authorization holders during the process of validation and approval of health written information.

Limitations

It was not possible to check the presence of imprints through using the real packages of medicines due to logistic and economic reasons, since many blisters or other secondary

packages are opaque. This situation compromised the visual inspection of the surface of the medicines without opening the package.

Conclusions

The medicines imprints were scarcely described in the sampled PLs, which seems to support that they are not regularly used as anti-counterfeiting measures. Some typographical and linguistic features were found that may not favor the adequate legibility and readability of the identified imprints. The use of informatics linguistic tools may constitute an important step for the conception and validation of medicine imprints. Furthermore, regulation may need to be updated on this issue.

Competing interests

None declared.

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Table 1. Imprints identified in the sampled package leaflets

Medicine imprints	
20G TW	GX CE7
21G UTW	GX CF1
51B	GX CF2
77C/77C	ID
A	k200
A/EH	LTL
A/EI	MSD 72
A/FE*	N/N
ACX 30	NT
BNVA	NV
C 1000 QD	NVR
C22	p40
C24	P9
CG	PAL*
CGC	PD
DF	PU*
FF	RG
FO	RIB* 200
FXN	RVT
G12	SA*
G16	SER*
G24	T
G4	TR/5
G8	Y-Y
GS 7CZ	ZD4522
GS XJG	ZDX
GX CE2	ZLT
GX CE5	

* Abbreviations

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Table 2. Results of the linguistic evaluation

Variables	n*
Orthographic words	171
Words with 1 syllable	111
Words with 2 syllables	49
Words with 3 syllables	11
Total number of syllables	242
Consonants	222
Vowels	242
Glides	10
Segments*	474

* n: number of cases, †, Segments = Consonants + Vowels + Glides.