Differences in the information about procedures after cold chain disruption provided by pharmaceutical industry to hospital and community pharmacies

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/ejhp-2015-000723>).

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Received 22 May 2015

Revised 3 August 2015

Accepted 7 September 2015

Published Online First

30 September 2015

ABSTRACT

Purpose To compare the response of the pharmaceutical industry to information requests from a hospital pharmacy and a community pharmacy regarding the inadvertent exposure of refrigerated medicines (2–8°C) to out-of-range temperatures.

Methods A complete list of all authorised medicines labelled for refrigeration was obtained from the Portuguese Medicines Agency. A standard information request regarding cold chain disruption for refrigerated medicines was sent to pharmaceutical companies from a hospital and a community pharmacy in Portugal. For companies who did not provide a response within the first 45 days, a second request was sent and an additional 45 days were allowed before completing data collection. To compare information received from the drug industry with that contained in the official European labelling, the Summaries of Product Characteristics (SmPCs) were retrieved from the regulatory agencies' databases. Response rate, response time and information appropriateness were assessed.

Results A total of 792 medicines marketed by 70 different pharmaceutical companies were included. The hospital pharmacy received 560 (70.7%) responses, with a mean response time of 6.5 days (SD=5.3) for the first request. The community pharmacy obtained a response for 411 (51.9%), with a mean response time of 15.5 days (SD=4.8). More appropriate information was provided to hospital pharmacy requests. SmPCs did not contain complete information regarding the inadvertent exposure of medicines to unrefrigerated conditions.

Conclusions When enquired about a specific piece of information, the pharmaceutical industry provided quicker, higher quality and more frequent responses to a hospital pharmacy compared with a community pharmacy.

involvement in providing drug information is controversial. Opponents argue that pharmaceutical companies' promotional activities could lead to inappropriate prescribing practices, induce premature and excessive adoption of expensive new molecules, create false expectations with regards to the safety and efficacy of medicines, and lead to society medicalisation.^{5–11} In turn, supporters defend that the provision of information by pharmaceutical companies would lead to better informed individuals who are then able to actively participate in the decision-making process, to encourage the appropriate use of medicines, to promote adherence to prescribed therapies and to reduce governments' health expenditures.^{6–12}

Despite this controversy, pharmaceutical companies provide information actively through the development of product monographs and drug labelling, which are further reviewed by regulatory agencies,^{13 14} and also passively by responding to specific information requests through their medical affairs departments.¹⁵ Several studies have assessed the response of the pharmaceutical industry to specific information requests from hospital pharmacy and community pharmacy including: the adequate storing conditions of a drug that was removed from its original container,¹⁶ the room temperature storage of drug products labelled for refrigeration^{17 18} or the stability of cytotoxic drug preparations.¹⁹ The results of these studies showed that a satisfactory response from the pharmaceutical industry was only provided for approximately 10% of the information requests;¹⁸ almost 20% manufacturers were unable to provide information about the stability of medications labelled for refrigeration that were inadvertently exposed to room temperature;¹⁷ and 30% manufacturers were unable to provide stability data for compounded anticancer drugs.¹⁹

In addition to the lack of data available from manufacturers, studies demonstrated a different behaviour of the pharmaceutical industry depending on the health professional requesting the information, with a significantly higher response rate being found for requests placed by specialist physicians comparing with general practitioners.²⁰ To date, no study has assessed whether this differentiation also occurs for information requests from a hospital pharmacy versus a community pharmacy. Medications used in a hospital setting and a community setting present different characteristics,

INTRODUCTION

Access to unbiased, complete and useful drug information is determinant to ensure that the most effective, safe and economically viable medicine is prescribed¹ and that medication errors are minimised.² Among the several drug information sources available, the pharmaceutical industry possesses a large amount of information about their products. For this reason, it should be a pharmaceutical industry's responsibility to provide impartial and objective information about their medicines to healthcare professionals. This was emphasised at WHO's Nairobi Conference in 1985.^{3 4} However, the pharmaceutical industry's

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To cite: Morais EM, Salgado TM, Vazquez Gomez I, et al. *Eur J Hosp Pharm* 2016;23:96–99.

namely prices, level of toxicity or therapeutic indexes, which could result in different perceptions and therefore different behaviour of the pharmaceutical industry when providing drug information to pharmacists practising in the hospital or in the community. The aim of this study was to compare the pharmaceutical industry's responses to a drug information request from a hospital pharmacy and a community pharmacy. The information request was performed with the ultimate goal of creating a standardised procedure for the inadvertent exposure of refrigerated medicines (2–8°C) to out-of-range temperatures.

METHODS

A complete list of all authorised medicines labelled to be stored at 2–8°C was requested to the Portuguese Authority for Medicines and Health Products (INFARMED) in February 2010. Drugs whose marketing authorisation holders or legal representatives lacked an address in Portugal were excluded.

A standard information request to pharmaceutical companies was created including the following queries: (1) maximum number of hours that the medicine could be kept at a temperature of (i) +10°C, (ii) +15°C, (iii) +20°C and (iv) +25°C before being refrigerated again; (2) maximum number of hours that the medicine could be kept at room temperature (maximum 25°C); and (3) whether the medicinal product could be frozen. Five specific temperature intervals were included in this request given that the ultimate goal was to design an implementable standard operating procedure (SOP) on cold chain disruption. A table including all the information requested was attached to the letter and the companies were asked to fill out the blank cells when providing a response (see online supplementary appendix 1). All requests were sent to each of the pharmaceutical companies by registered postal mail, first on behalf of an independent community pharmacy (October 2010) and then on behalf of a 230-bed private hospital pharmacy (February 2011), both located in Portugal. In both cases, a first request was sent to pharmaceutical companies and if no response was received after 45 days, a second request was sent. An additional 45 days were allowed for companies to provide a written response to this second request. Any responses received after the 90 days' time frame were not included in the study.

In order to identify the information contained in the official European drug labelling the Summaries of Product Characteristics (SmPCs) of all the medicines included in the study were retrieved either from the website of the Portuguese Medicines Agency (INFARMED), for nationally approved medicines, or the European Medicines Agency (EMA), for centrally approved medicines (pan-European authorisation). SmPCs were appraised to retrieve information pertaining to specific actions to undertake as a result of an inadvertent exposure of refrigerated medicines to out-of-range temperatures.

Response rate, time elapsed until the receipt of a response and the appropriateness of the information provided by pharmaceutical companies to create the SOP were assessed. When companies did not explicitly respond to the request or when the information provided was inadequate for the SOP, the authors considered it as missing information. Descriptive statistical analyses were performed, with absolute values and relative frequencies reported for categorical variables and means and SDs being reported for continuous variables. Bivariate analysis was conducted by applying the Pearson's χ^2 test and the χ^2 test to estimate the association between categorical variables. All statistical analyses were performed using SPSS for Windows, V.20.0. Chicago, USA. All tests were two-tailed and statistical significance defined as $p < 0.05$.

RESULTS

The complete list of medicines available in Portugal and labelled to be stored at 2–8°C included 941 medicines, which were marketed by 123 pharmaceutical companies. A total of 135 (14.3%) medicines were excluded because their marketing authorisation holders or legal representatives lacked a postal address in Portugal and another 14 (1.5%) medicines because the letter was undelivered. The medicines excluded from the study were marketed by 57 different marketing authorisation holders or legal representatives. Ultimately, a total of 792 medicines corresponding to 70 different pharmaceutical companies were included in the study.

Of the 792 SmPCs retrieved, 67.4% were centrally approved ($n=534$) and 32.6% were nationally approved ($n=258$). All SmPCs contained information regarding the minimum and maximum storing temperatures of the medicine, but none contained a complete procedure in the event of an unintended exposure of the drug to unrefrigerated conditions. Information on the maximum storing temperature and maximum storing time outside the refrigerator was presented in 15.7% ($n=124$) of the SmPCs and 5.1% ($n=40$) presented the maximum number of hours that the medicine could be kept at room temperature (maximum 25°C). Information regarding the possibility of freezing the product was provided in 74.6% ($n=591$) SmPCs, and 2.5% (15/591) of these also contained the procedure to adopt in case the product had been frozen. A statistically significant difference was identified in favour of centrally approved SmPCs versus nationally approved SmPCs with regards to the presence of the following information: maximum storing temperature outside the refrigerator (17.8% vs 11.2%, Pearson's χ^2 test, $p=0.017$); maximum storing time outside the refrigerator (17.8% vs 11.2%, Pearson's χ^2 test, $p=0.017$); and possibility of freezing the product (84.8% vs 53.5%, Pearson's χ^2 test, $p<0.001$). No statistical difference was found for information regarding the reintroduction of medicines in the refrigerator after the cold chain had been disrupted (Pearson's χ^2 test, $p=0.482$). Likewise, no statistically significant differences were found in the median time since approval of centrally approved and nationally approved SmPCs (2008 vs 2007, two-sample median test, $p=0.141$).

Response rate and response time

Of the 792 medicines included in the study, the hospital pharmacy received a response from the pharmaceutical industry to 560 (70.7%) information requests. The community pharmacy obtained a response for 411 (51.9%) information requests. As presented in table 1, significant differences in the response rate of pharmaceutical companies for information requests sent by the hospital and the community pharmacy were found (Pearson's χ^2 $p<0.001$). Of the 560 (=402+158) information request responses provided by pharmaceutical companies to the hospital pharmacy, 33.6% (188=80+108) were not provided to the community pharmacy, whereas for the 411 (=216+195) information request responses sent out to the community pharmacy, only 9.5% (39=35+4) were not sent to the hospital pharmacy as well.

After the 90 day-period allowed for the receipt of information request responses, the community pharmacy still received information for 14 medicines (marketed by three companies), while the hospital pharmacy received a response for only one medicinal product. A total of 193 (24.4%) information requests were not provided by pharmaceutical companies neither to the hospital pharmacy nor to the community pharmacy.

The mean response time to the first request from the hospital pharmacy was 6.5 days (SD=5.3) whereas it was 15.5 days (SD=4.8) for the community pharmacy. After sending the second information request, the mean response time of pharmaceutical companies was 16.8 days (SD=10.6) for the hospital pharmacy and 24.6 days (SD=18.7) for the community pharmacy.

Response content

Pharmaceutical companies completed the table attached to the information request letter in 141 (25.2%) of their responses to the hospital pharmacy and 55 (13.4%) to the community pharmacy. This corresponds to 17.8% of the total 792 information requests sent by the hospital and to 6.9% of the community pharmacy requests. For 79 (14.1%) and 82 (20.0%) of the responses provided to the hospital and the community pharmacy, respectively, the information was included in the body of the response letter instead of the table provided. The appropriateness of the information conveyed by pharmaceutical companies to each of the specific information requests sent from the hospital pharmacy and the community pharmacy is presented in table 2.

For 340 (60.7%) of the hospital pharmacy and 274 (66.7%) of the community pharmacy requests, pharmaceutical companies responded without providing any information, regardless of whether it was relevant or not.

DISCUSSION

Within the context of a quality management system implementation, it is critical to design SOPs that enable the organisation to identify, measure, control and improve the various core processes that will ultimately lead to improved performance.²¹ In the healthcare setting, assuring the safe storage of medications is an essential process that serves as a foundation for any pharmacy safety programme, and this obviously includes ensuring adequate storing conditions for refrigerated items.²²

Although the European drug labelling has a specific section for information regarding 'special precautions for storage' (Section 6.4), over 80% of the SmPCs lacked all the required information to create a standardised procedure to address the disruption of the ideal storing conditions of refrigerated medicines. Although SmPCs are the official drug information sources for healthcare professionals in the European Union, these sources have been criticised for presenting several information insufficiencies.²³ Additionally, differences found in the information content of SmPCs retrieved from the EMA and the Portuguese Medicines Agency (INFARMED) were not related with the time since SmPCs' approval which suggests that other possible reasons, such as different rigorousness in SmPCs'

Table 2 Appropriateness of information provided by pharmaceutical companies to each of the specific information requests whether they were sent from the hospital pharmacy or the community pharmacy

Number (%) of relevant responses from pharmaceutical companies	Hospital pharmacy	Community pharmacy
Maximum number of hours at X°C before being refrigerated again		
+10°C	105 (18.8)	48 (11.7)
+15°C	105 (18.8)	48 (11.7)
+20°C	105 (18.8)	48 (11.7)
+25°C	102 (18.2)	46 (11.2)
Maximum number of hours at room temperature (max 25°C)	105 (77.8)	182 (82.7)
Medicinal product can be frozen?	105 (78.4)	195 (88.6)

approval criteria of both regulatory bodies or different complexity of the medicines approved by each agency, might be underpinning this finding. However, this would need further research.

This study compared pharmaceutical companies' responses to the same drug information request sent from a hospital pharmacy and a community pharmacy regarding the inadvertent exposure of thermolabile medications to out-of-range temperatures. Our study highlights a higher response rate and appropriateness of information provided by the pharmaceutical industry to a request from a hospital pharmacy compared with one from a community pharmacy. This dual conduct was justified by companies with the fact that several of the medicines for which information was being requested were to be used exclusively in the hospital setting and not in community pharmacies. A previous study also showed a different behaviour of the pharmaceutical industry when providing drug information depending on whether the request was placed by a specialist physician or a general practitioner.²⁰

In general, the response rates of pharmaceutical companies obtained in our study were similar to other studies.^{18 24} With regards to response time, the hospital experienced approximately half the time to obtain a response from the companies than the community pharmacy. Comparing with previous studies for which the response time was around 30 days,^{18 20} the response time in the present study was slightly shorter. However, if the request involves decision-making in the everyday life of a busy hospital or community pharmacy, companies would be considered slow information providers as also concluded by previous authors.^{18 20}

As practical implications of this study, we highlight the need for regulatory agencies to demand the inclusion of medicines stability information at different temperatures in drug labelling, that

Table 1 A cross tab depicting the provision of medicines information by pharmaceutical companies to requests from a hospital pharmacy versus a community pharmacy

	Information provision to the hospital pharmacy			Total
	1st request n (%)	2nd request n (%)	No response n (%)	
Information provision to the community pharmacy				
1st Request n (%)	141 (17.8)	40 (5.1)	35 (4.4)	216
2nd Request n (%)	181 (22.9)	10 (1.3)	4 (0.5)	195
No response n (%)	80 (10.1)	108 (13.6)	193 (24.4)	381
Total	402	158	232	792

What this paper adds

What is already known on this subject?

- ▶ Not all information about a drug is available in the official drug labelling. Therefore, health professionals need to contact the drug industry directly to obtain the information needed for decision-making in their clinical practice.
- ▶ The drug industry has a different behaviour when providing information to physicians depending on whether they are general practitioners or specialists.

What this study adds?

- ▶ This study showed that the drug industry behaves differently when providing drug information to a hospital pharmacy and a community pharmacy.
- ▶ Even when a response was obtained from the drug industry, the information provided was not satisfactory to design a standardised procedure for the inadvertent exposure of thermolabile medicines to out-of-range temperatures, which was the aim of this study.

is, SmPCs, as well as a detailed procedure in the event of an exposure of medicines labelled for refrigeration to out-of-range temperatures. This information would eventually result in less medicines being discarded due to lack of information, therefore increasing the efficiency of the system. The lack of adequate information in the SmPC along with the absence of a response to an information request from the pharmaceutical company would lead to an unnecessary discard of medications. Previous studies have found that for many medicines labelled for refrigeration their stability was not compromised after exposure to room temperature for several hours or even days.¹⁷ The disparity between the information collected by contacting the pharmaceutical companies and the information included in the SmPCs suggests that companies are not promoting the inclusion of new information in SmPCs and thus making it available to all healthcare professionals. However, the reasons for this fact are unknown.

A limitation of our study is that the results cannot be generalised to pharmaceutical companies in other European countries. Nonetheless, given that the guidance emanates from the EMA to every member of the European Union, a large variability across countries is unlikely to exist. In addition, the fact that the community pharmacy request preceded the one from the hospital pharmacy could be considered to have influenced response rate. However a higher response rate for the hospital than community is consistent with previous works from the literature.

CONCLUSION

Significant differences in the rate, time and content appropriateness of the responses provided by the pharmaceutical industry to information requests from a hospital pharmacy and a community pharmacy were observed, with companies favouring the hospital pharmacy. Yet, from all the information requested, companies have only fully replied to 18% of the requests from the hospital and 7% from the community pharmacy.

In a nutshell, neither the information retrieved from SmPCs nor the information provided by pharmaceutical companies was

satisfactory to design a standardised procedure for the inadvertent exposure of medicines labelled for refrigeration to out-of-range temperatures. In order to reduce waste and increase the efficiency of the health system, regulatory agencies should be stricter in demanding that this information be included in SmPCs during the marketing authorisation process.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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