Assessment of the quality of pharmaceutical packaging in the light of the requirements of the European Pharmacopoeia

Ocena jakości opakowań farmaceutycznych w świetle wymagań Farmakopei Europejskiej

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Abstrakt

W artykule przedstawiono wyniki analizy zawartości metali w wybranych wyrobach z tworzyw sztucznych, stosowanych do produkcji pojemników - poliolefin, do których zalicza się m. in. polietylen, polipropylen, poli(tereftalan etylenu). W pracy uwzględniono etap przygotowania i badania próbek metodą atomowej spektrometrii emisyjnej z plazmą wzbudzoną indukcyjnie ICP-OES oraz spektroskopii podczerwieni FT-IR (ALPHA II). Wszystkie badane opakowania spełniły wymagania określone w Farmakopei Europejskiej (Ph. Eur.)–w kontekście zawartości metali ciężkich i analizy tożsamości A. Widma badanych tworzyw wykazują maksima przy wymienionych w Ph. Eur. liczbach falowych dla danej próbki i są identyczne z widmem otrzymanym dla tworzywa wybranego na próbkę standardową. Badania wykazały, że opakowania do produktów leczniczych mogą zostać dopuszczone do zastosowania ich na terenie Unii Europejskiej.

Abstract

The article presents the results of the analysis of metal contents in selected plastic products used for the production of containers which are divided into polyolefins, polyethylene, polypropylene, poly(ethylene terephthalate). This work includes the sample preparation and testing by inductively coupled plasma atomic emission spectrometry (ICP-OES) and FT-IR spectroscopy (ALPHA II). All tested packaging met the requirements of the European Pharmacopoeia (Ph. Eur.) in the context of heavy metals content. The spectra of the tested materials showed peaks at those mentioned in Ph. Eur. wavenumber for a given sample. The spectrum obtained is identical to that obtained with the material selected for the type sample. This study showed that packaging for medicinal products can be approved for use in the European Union.

Słowa kluczowe: opakowania, pojemniki, metale ciężkie, Farmakopea Europejska, spektroskopia podczerwieni, FT-IR

Keywords: packaging, containers, heavy metals, European Pharmacopoeia, spectroscopy FT-IR

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1. Introduction

In Poland the basic legal act regulating the pharmaceutical packaging market is the pharmaceutical law [1]. The information about packaging requirements are included in the European Pharmacopoeia [2] and the Polish Pharmacopoeia [3]. If the European Pharmacopoeia does not contain relevant monographs, the relevant regulations are applied [4, 5, 6]. In practice, there are also used documents such as: Regulation (WE) No 1935/2004 of 27 October 2004) [7] on plastic immediate packaging, Commission Regulation (WE) No 10/2011 of 14 January 2011 on materials and plastic products intended to come into contact with food [8]. The above-mentioned Commission Regulation (WE) No 10/2011 is the most important document concerning plastic materials and articles for contact with food. In Annexes I and II, the Commission Regulation lists the substances allowed for use in the production of plastics. The acceptable concentration limits for metals are listed in Tab. 1. The main difference in the requirements for food and cosmetic packaging is that tests are carried out on the extract of shredded plastic, and not the migration from the complete packaging. Innovative packaging solutions for medicinal products continue to appear on the market, which should be subjected to detailed tests [9, 10]. Packaging from the pharmaceutical industry is to ensure the safety of the product during storage, and thus the health of the patient [11, 12]. Packaging is made of one material or (complex packaging) from a combination of two or more different materials. Several basic materials such as: LDPE (Low Density Polietthylene), LLDPE (Linear Low-Density Polyethylene), HDPE (High Density Polyethylene), PP (Polypropylene), PVC (Polyvinyl Chloride), PET (Poliethylene Terephthalate), PS (Polystyrene) and others are used for the production of packaging. This article includes the basic requirements for plastic packaging, taking into account the compatibility of the packaging with its content. The problem of health safety of packaging is still growing and it is caused by

concern for the health of consumers and the development of analytical techniques enabling the testing of substances that pose a risk to human health or life and lower levels of quantification [13-16]. The aim of this study was to investigate the leaching of heavy metals.

Tab. 1. Permissible values of metals [ppm] present in packages (in accordance with the Ph. Eur.)

The point of Ph. Eur.	Permissible metal content										
	Al	**Ba**	**Co**	**Cr**	**Mn**	**Sb**	**Ge**	**Ti**	**V**	**Zn**	**Zr**
3.1.3	<1	-	-	-	-	-	-	<1	-	<1	-
3.1.4	-	-	-	-	-	-	-	-	-	-	-
3.1.5	<1	-	-	<0,05	-	-	-	<1	<0,1	<1	<0,1
3.1.6	<1	-	-	<0,05	-	-	-	<1	<0,1	<1	<0,1
3.1.15	<1	<1	<1	-	<1	<1	<1	<1	-	<1	-

2. Materials and methods

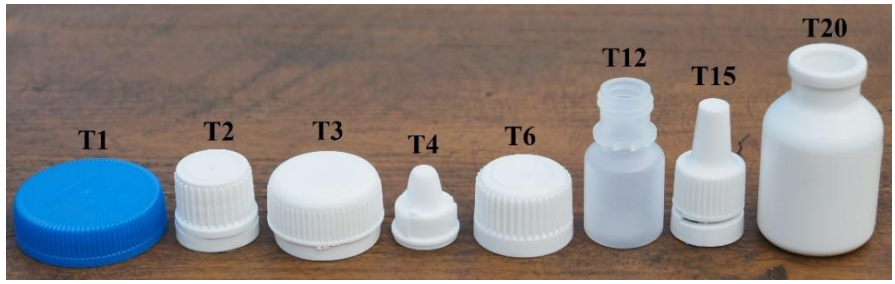
2. Materials

Tests were performed for the presence and content of the mentioned metals in 22 plastic samples. Plastic samples in the form of pharmaceutical containers were:
a) polyolefins (Ph. Eur. point. 3.1.3),
b) polyethylene without additives for containers and parenteral preparations and for eye preparations (Ph. Eur. point 3.1.4),
c) polyethylene with additives for containers for parenteral preparations and for eye preparations (Ph. Eur. point 3.1.5),
d) polypropylene for containers and closures for parenteral preparations and for eye preparations (Ph. Eur. point 3.1.6),
e) poly(ethylene terephthalate) for containers and for preparations not intended for parenteral administration (Ph. Eur. point 3.1.15).
The container samples are characterized in Tab. 2 and presented in Fig. 1.

Tab. 2. Characteristics of the studied plastics

Sample name	**Sample type**	**Sample color**	**Type of material declared by the manufacturer**
T1	cap	blue	HDPE
T2	cap	white	HDPE
T3	cap	white	HDPE
T4	cap	white	HDPE
T5	cap	blue	PS
T6	cap	white	HDPE
T7	bottle	white	PE
T8	liner	white	PE
T9	bottle adapter	colorless	PET
T10	bottle	white	LDPE
T11	jar	white	PP
T12	bottle	colorless	HDPE
T13	dropper	colorless	LDPE
T14	bottle	white	LDPE
T15	cap	white	LDPE
T16	bottle	blue	LDPE
T17	bottle	white	LDPE
T18	cap	white	PP
T19	cap	white	PP
T20	bottle	white	HDPE
T21	bottle	brown	PET
T22	bottle	brown	PET
T23	bottle	colorless	PET
T24	bottle	white	PET

a)



b)

c)

d)

e)

f)

Fig. 1. The materials described in Table 2: a) HDPE, b) LDPE, c) PS, d) PE, e) PE, f) PP

Fig. 2. Marking of tested plastics on packaging

2.1. Preparation of samples for testing

Packaging samples used in the pharmaceutical industry were tested. Represented samples were selected for the tests. The method of preparing samples for analysis depends metals and the technique used. The samples were ground and homogenized to obtain an average sample. The material was cut into pieces with a maximum side dimension of no more than 1 cm. The sample for testing are prepared in accordance with point 3.1.3, 3.1.5, 3.1.6 Ph. Eur. (S3 solution) and 100 g of ground material was placed in a ground-glass borosilicate conical flask. Then, 250 ml of 0,1 M hydrochloric acid (HCl analytical grade, Chempur) was added to each sample. The mixture was refluxed for 1 h, with constant stirring. Next, 20 g of ground material was placed in a ground-glass borosilicate conical flask in accordance with point 3.1.15 Ph. Eur. (S3 solution). To each sample 50 ml of 0,1 M hydrochloric acid (HCl analytical grade, Chempur) was added and then. Heated for 5 h at 50°C. In the next step 20 g of ground material was placed in a ground-glass borosilicate conical flask in accordance with point 3.1.15 Ph. Eur. (S4 solution). Subseuently, to each sample 50 ml of 0.01 M sodium hydroxide (NaOH analytical grade, Chempur) was added and heated for 5 h at 50°C. The prepared solutions were allowed to cool, decanted and used for determinations within 4 hours of their preparation. It should be emphasized that the preparation of the S3 solution for various Ph.Eur. it is different in terms of weight, temperature and heating time. Blanks were prepared in the same way. To determine the identity of A, tests were

performed directly on a cut piece of the appropriate size.

2.2. Apparatus

For the determination of metals, the inductively coupled plasma atomic emission spectrometry technique (spectrometer ICP-OES 5110, Agilent) [17-18] to measure the radiation emitted by excited element atoms was used. The sample was atomized and excited in an argon plasma. Measurements were made in the dual-view optical configuration (positions in which the camera sees the sample). In order to obtain maximum efficiency in a given analytical system, a number of optimization activities were performed, e.g. sample preparation and selection of the concentration of reagents, their appropriate flow, analytical lines and the optimal mode of operation [19]. To determine the concentration of elements, a linear calibration curve fit was used. Samples were analyzed in duplicate. Calibration was performed with the use of a series of chemical standards (reference materials) and different levels of the test component tested content. The values were read from the standard curves of the prepared standards of individual metals (1000 µg/ml Al, Ba, Co, Cr, Ge, Mn, Sb, Ti, V, Zn, Zr in 5% HNO_3 v/v solution) by appropriate dilution of standards. To measure the identity of the materials, the technique of infrared spectrometry was performed on a FT-IR spectrometer (ALHA II, Bruker) with an ATR attachment equipped with a monolithic diamond crystal.

3. Research results and their discussion

As part of the work, tests for the presence and content of the mentioned metals were performed (Tab. 3).

Tab. 3. Metal content in the tested plastic samples, ND - below the detection limit (standard deviation in brackets), the identity of A.

Sample name	Ph. Eur. point	Al	Ba	Co	Cr	Mn	Sb	Ge	Ti	V	Zn	Zr	The identity of A
T1	3.1.3	0,185 ±0,020	-	-	-	-	-	-	ND	-	0,075 ±0,002	-	PE
T2	3.1.3	0,101 ±0,008	-	-	-	-	-	-	ND	-	0,051 ±0,002	-	PE
T3	3.1.3	0,012 ±0,002	-	-	-	-	-	-	ND	-	0,029 ±0,001	-	PE
T4	3.1.3	0,010 ±0,001	-	-	-	-	-	-	ND	-	0,010 ±0,001	-	PE
T5	3.1.3	0,020 ±0,002	-	-	-	-	-	-	ND	-	0,021 ±0,002	-	PS
T6	3.1.3	0,145 ±0,006	-	-	-	-	-	-	ND	-	0,050 ±0,003	-	PE
T7	3.1.3	0,139 ±0,003	-	-	-	-	-	-	ND	-	0,575 ±0,0020	-	PE
T8	3.1.3	ND	-	-	-	-	-	-	ND	-	0,084 ±0,006	-	PE
T9	3.1.3	ND	-	-	-	-	-	-	ND	-	0,849 ±0,010	-	PET
T10	3.1.3	0,173 ±0,009	-	-	-	-	-	-	ND	-	0,076 ±0,002	-	LDPE
T11	3.1.3	ND	-	-	-	-	-	-	ND	-	0,194 ±0,008	-	PP
T12	3.1.4	-	-	-	-	-	-	-	-	-	-	-	PE
T13	3.3.4	-	-	-	-	-	-	-	-	-	-	-	LDPE
T14	3.1.5	0,050 ±0,003	-	-	ND	-	-	-	ND	ND	0,102 ±0,002	ND	LDPE
T15	3.1.5	ND	-	-	ND	-	-	-	ND	ND	0,115 ±0,003	ND	PE
T16	3.1.5	ND	-	-	ND	-	-	-	ND	ND	0,030 ±0,002	ND	LDPE
T17	3.1.5	0,027 ±0,002	-	-	ND	-	-	-	ND	ND	0,045 ±0,002	ND	LDPE
T18	3.1.6	0,034 ±0,002	-	-	ND	-	-	-	ND	ND	0,054 ±0,003	ND	PP

T19	3.1.6	0,041 ±0,003	-	-	ND	-	-	-	ND	ND	0,064 ±0,003	ND	PP
T20	3.1.15	0,036 ±0,004	ND	ND	-	ND	ND	ND	ND	-	0,058 ±0,003	-	PE
T21	3.1.15	0,110 ±0,005	ND	ND	-	ND	ND	ND	ND	-	0,452 ±0,009	-	PET
T22	3.1.15	0,136 ±0,008	0,031 ±0,002	ND	-	ND	ND	ND	ND	-	0,261 ±0,006	-	PET
T23	3.1.15	0,081 ±0,003	ND	ND	-	ND	ND	ND	ND	-	0,208 ±0,005	-	PET
T24	3.1.15	0,331 ±0,011	ND	ND	-	ND	ND	ND	ND	-	0,682 ±0,015	-	PET

Before starting the tests, the method was optimized and approved in the laboratory in terms of planned analytical determinations. The scope of the method was determined on the basis of the limits (Tab. 3) defined in the Ph. Eur. for each points. Determined parameters of the limits of quantification for the method were lower than the acceptable limits included in the Ph. Eur., therefore the developed methodology could be successfully applied to the conducted research. The packaging assessment in accordance with the requirements of the Ph. Eur. in the field of metal determination was positive. The content of metals in all tested packages did not exceed the permissible values. The spectra of the tested materials showed the maxima suitable for individual Ph. Eur. points:

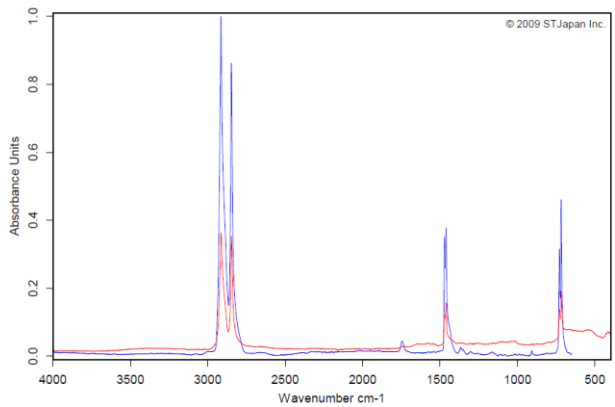
a) polyolefins (Ph. Eur. point 3.1.3). The spectrum obtained is identical to that obtained with the material selected for the type sample.
b) polyethylene without additives for containers and parenteral preparations and for eye preparations (Ph. Eur. point 3.1.4). Absorption maxima at some of the following wave numbers (tolerance: ± 5 cm^{-1}): at 2915 cm^{-1}, 2848 cm^{-1}, 1471 cm^{-1}, 1465 cm^{-1}, 729 cm^{-1} and 719 cm^{-1}.
c) polyethylene with additives for containers for parenteral preparations and for eye preparations (Ph. Eur. point 3.1.5). Absorption maxima at some of the following

wavenumbers (tolerance: ± 5 cm^{-1}): at 2915 cm^{-1}, 2848 cm^{-1}, 1471 cm^{-1}, 1465 cm^{-1}, 729 cm^{-1} and 719 cm^{-1}.

d) polypropylene for containers and closures for parenteral preparations and for eye preparations (Ph. Eur. point 3.1.6). Absorption maxima at some of the following wavenumbers (tolerance: ± 5 cm^{-1}): at 1375 cm^{-1}, 1170 cm^{-1}, 995 cm^{-1} and 973 cm^{-1}.

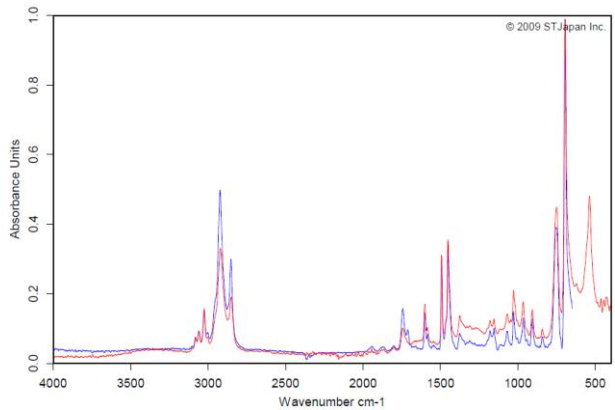
e) poly(ethylene terephthalate) for containers and for preparations not intended for parenteral administration (Ph. Eur. point 3.1.15). The spectrum of the material to be examined shows maxima in particular at 1725 cm^{-1}, 1410 cm^{-1}, 1265 cm^{-1}, 1120 cm^{-1}, 1100 cm^{-1}, 1020 cm^{-1}, 875 cm^{-1}, 725 cm^{-1}. The spectrum obtained, in addition, is identical to that of the material selected for the type sample.

Fig. 2 Shows examples of spectra for various types of materials.



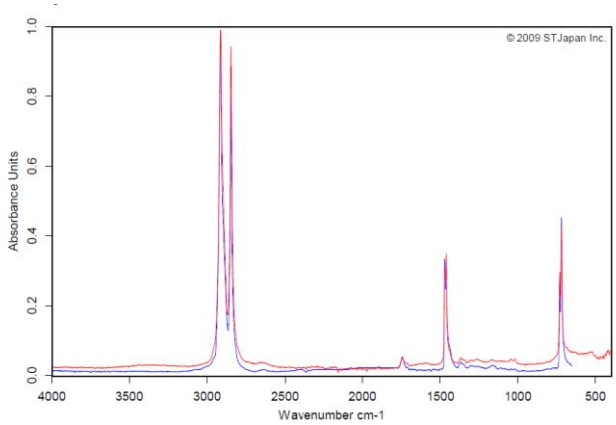
Compound Name	POLYETHYLENE, ELTEX K 52-05-159
Molecular Formula	C2H4N1
Molecular Weight	
CAS Registry Number	9002-88-4
Sample Preparation	ATR single bounce
Manufacturer	Ineos
Comment	polyethylene
Reference	304/ MP0147
Copyright	(c) 2009 Nicodom
Nr wpisu	1869

a) sample T3



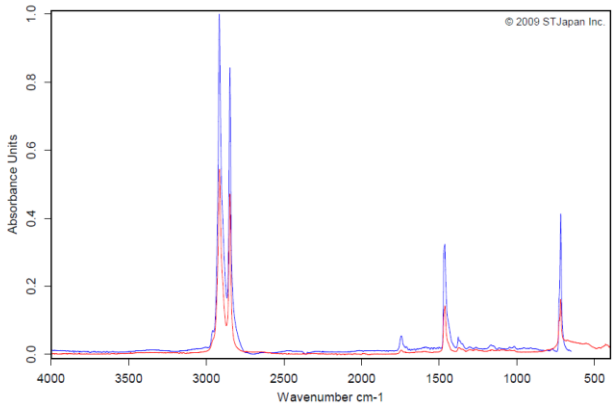
Compound Name	POLYSTYRENE HIGH IMPACT #2
Molecular Formula	C8H8N1
Molecular Weight	
CAS Registry Number	
Sample Preparation	ATR single bounce
Comment	polystyrene
Reference	652/ MP0205
Copyright	(c) 2009 Nicodom
Nr wpisu	1923
Nazwa biblioteki	ATR-LIB-COMPLETE-2-462-2.S01

b) sample T5



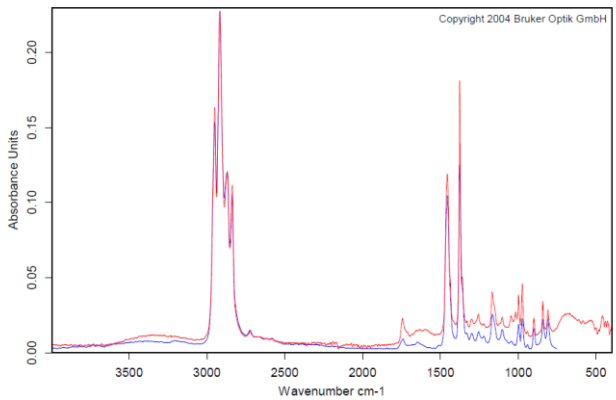
Compound Name	POLYETHYLENE, DAPLEX BF 4572
Molecular Formula	C2H4N1
Molecular Weight	
CAS Registry Number	9002-88-4
Sample Preparation	ATR single bounce
Comment	polyethylene
Reference	303/ MP0146
Copyright	(c) 2009 Nicodom
Nr wpisu	1868
Nazwa biblioteki	ATR-LIB-COMPLETE-2-462-2.S01

c) sample T7



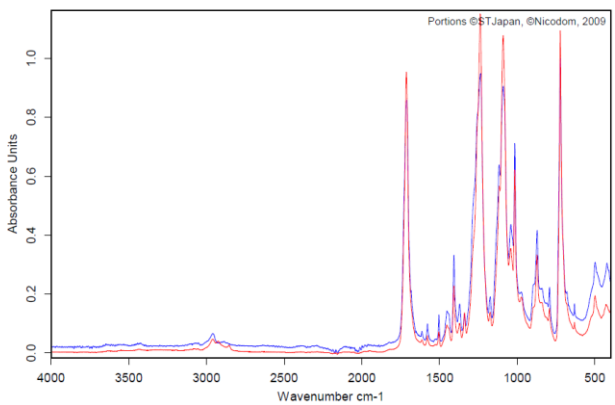
Compound Name	POLYETHYLENE LINEAR LOW DENSITY, ESCORE
Molecular Formula	C2H4N1
Molecular Weight	
CAS Registry Number	9002-88-4
Sample Preparation	ATR single bounce
Manufacturer	Exxon
Comment	polyethylene
Reference	030/ MP0002
Copyright	(c) 2009 Nicodom
Nr wpisu	1733

d) sample T16



Name	Dyed Ribbon Fiber, Polypropylene
Color	black
Company	American Mfg. Co.
Nr wpisu	180
Nazwa biblioteki	SYNTHETIC FIBERS ATR LIBRARY.S01
Opis biblioteki	A Collection of Synthetic Fibres
Prawa autorskie	Copyright 2004 Bruker Optik GmbH

e) sample T19



Compound Name	POLY(ETHYLENE TEREPHTHALATE)
Molecular Formula	(-COC6H4COOCH2CH2-)n
Molecular Weight	
CAS Registry Number	29154-49-2
Sample Preparation	ATR single bounce
Reference	J60191/ A00685
Copyright	(c) 2012 STJapan Inc.
Nr wpisu	332
Nazwa biblioteki	ATR-LIB-CHEMICALS-1-462-2.S01
Opis biblioteki	ATR-FTIR Chemicals Library, Vol. 1

f) sample T21

Fig. 2. FT-IR spectra of test and standard samples (blue line – standard, red line – sample)

Producers should also examine the packaging for metal content in the manufacture of these packaging according to applicable legal acts. Plastic packaging are used in many industries, for example, food [20], cosmetics [21-22] and pharmaceutical industries. An important advantage of plastic packaging is resistance to the penetration of substances, including metals, that is why scientists have previously undertaken research in this field [23-24]. For the production of plastic packaging, appropriate raw materials are selected, which are distinguished by both the aforementioned durability and low invasiveness to the natural environment. Some

requirements are imposed by Directive 94/62/WE on packaging and waste [25]. Due to the durability of plastic packaging, it can be used many times and then recycled. Regulation of the Minister of the Environment of 30.12.2002 [26] provides for the management of packaging waste through recycling and recovery, which also prompts the testing of plastics for the content of heavy metals [27]. Producers pay more attention to the use of plastics that can be easily processed in the recycling process [28-29]. The biodegradability is an important advantage. Therefore, it is important to test the content of metals in accordance with the requirements of the Pharmacopoeia, both in pharmaceutical packaging and in the medicinal products themselves [30-31].

4. Summary

The presence of metals in the environment is still increasing, therefore there is a need for constant monitoring of their content also in plastic samples. The conducted research was aimed at confirming the possibility of using plastics for the storage of medicinal products. The presence of some metals significantly below the standard approved by the European Pharmacopoeia allows for meeting one of the requirements with the safety of use on the pharmaceutical market of final products. In conclusion, monitoring the concentrations of metals in pharmaceutical packaging is essential in order to develop appropriate measures to reduce the risk of exposure to these elements. In addition, increasing the effectiveness of optimal production, as well as the selection of appropriate substrates in the production process, significantly reduces the metal content in packaging for storing medicinal products, which has a direct impact on human health.

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