INVESTIGATION THE DANGERS OF DRUG DISTRIBUTION AND COUNTERFEITING ON THE INTERNET

PhD Thesis

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I. Introduction

In the introduction to my thesis, I aimed to provide a comprehensive snapshot and summary of the estimated extent of pharmaceutical counterfeiting, its indirect and direct effects, and the unfortunate and sometimes fatal outcomes, using the available literature on the subject. I have compiled the methods that have been used worldwide to try to detect the damage to health caused by the consumption of counterfeit medicines. Finally, I have summarised studies showing the benefits, benefits and costs of the anti-harmonisation directive introduced in the European Union to reduce counterfeiting in the legal pharmaceutical supply chain.

The legal medicines supply chain is simple and clear, the players are known, and patient safety is ensured. Products made from raw materials of dubious origin, in factories without regulatory approval or GMP (Good Manufacturing Practice) inspection, attract the attention of customers through websites, social media or online advertising. According to the European Union Intellectual Property Office (EUIPO) 2020 report, dubious origin products are mainly (96%) received by mail order [1]. Medicines sent by letter mail can be posted by anyone, the identity of the person who sends the mail is not verified, and it is actually sent through the postal logistics system to the addressee indicated on the envelope, regardless of the name on the mailing. During the air transfer, the required transport and storage conditions are not provided. Medicines or products sold as pharmaceuticals arrive in a bulk bag containing the rest of the mail at the international mail exchange centre in the recipient's country. Here they can be checked by customs and finance officials and then turned to the postal authority of the recipient's country. This is followed by domestic postal delivery of the mailed items.

It is clear that the most appropriate sampling station for assessing the actual number of consignments containing medicines should be the place of customs control prior to delivery to the consignee. For this reason, in the course of my research entitled „Determining the real number of counterfeit or illegal medicines or products that appear to be medicines or products ordered over the internet that pose a threat to the safety of the Hungarian population”, the place of the investigation was the National Tax and Customs Administration of Hungary (NTCA) at the International Post Exchange Centre of the Hungarian Post on the site of the Airport Directorate.

In my research presented in the chapter „Questionnaire survey to find out practitioners' experiences and opinions on illegal drugs”, I focused on the opinions, professional experiences and comments of physicians actively involved in outpatient and emergency acute hospital care. Questionnaires have been carried out in many countries and among different groups

(professionals and lay people) on the issue of counterfeiting of medicines. My research team approached primary and emergency care physicians with a questionnaire to assess their knowledge of counterfeit and illegal medicines. We hypothesised that the growing number of cases of health harm from the use of unreliable, unsafe or illegal medicines or medicines that appear to be medicines, from dubious sources online, is already a problem that the patient care system is aware of and it needs to address. People consuming such products of uncertain origin should presumably be identified in the patient care system. Thus, professionals working in this area may have their own experience.

Prior to the introduction of the FMD (Falsified Medicines Directive), there was limited information available on the effectiveness and cost-benefit analysis of the system, or on studies that had looked at these in detail. At the time of conducting my research on „Costs of implementing a system to combat counterfeit medicines in the EU Member States", up-to-date information on the actual costs of the Directive was still lacking, and therefore the methodology detailed in this paper was designed to be able to collect relevant data from the domestic hospital pharmacy environment on the processes involved in the implementation of the FMD.

II. Aims

In my doctoral thesis, I investigated three key elements of the complex problem of counterfeiting of medicines: (1) The social scale of the phenomenon by determining the volume and complexity of dubious origin pharmaceutical shipments arriving in Hungary by post. (2) The experience and perception of primary care and emergency care physicians regarding the use of counterfeit and illegal medicines by consumers and patients. (3) The human and financial resource needs of domestic hospital pharmacies in the context of the launch of the Directive against counterfeiting of medicinal products ("serialisation"), which affects the legal pharmaceutical supply chain.

The first and foremost aim of my research was to develop a methodology to obtain more accurate data on the number of counterfeit and illegal health products ordered online from illegal sources that are available to the public and pose a threat to their health. By using this methodology, I hoped to provide for the first time a realistic picture, based on factual data, of the scale of the distribution of such products and the potential volume and composition of illegal pharmaceutical products in the mail order shipments of medicines arriving in our country.

My second aim was to assess the harmful effects of counterfeit or illegal medicines, or medicines that appear to be medicines, in patient care. To this end, I started to collect data from primary and emergency care physicians in order to find out their experiences and opinions on the increasing use of dubious, fake or illegal medicines or medicines that appear to be medicines. In doing so, I also sought their experience and knowledge about the recognition of adverse effects of the use of such products, the frequency of cases in the patient care system, the successful detection and identification of cases at this level and in this setting of the care system, and the attitude of professionals to the problem and their options for dealing with it.

The third objective of my work was to assess the practice, workload and financial implications of the introduction and implementation of the FMD system in Hungarian hospital pharmaceutical care during the first seven months of the stabilisation period, following its entry into force. Furthermore, we aimed to investigate the costs of implementing, operating and maintaining the serialisation system on a representative sample after consultation with the national institutional pharmacies.

III. Determining the real number of counterfeit or illegal medicines or products that appear to be medicines or products ordered over the internet that pose a threat to the safety of the Hungarian population

III.1. Methods

In this research I used a cross-sectional study design, which is one of the observational study methods.

For the organoleptic, non-destructive identification of medicines or products that appear to be medicines, and for the identification of their falsity or illegality, I developed a checklist of 9 questions requiring yes/no answers [2, 3]. I had to supplement the data from my investigation with data from the Airport Customs Directorate of the National Tax and Customs Administration (NTCA), which included the number of products that had been tested, identified and classified according to the internal procedures of the authority.

When processing the photos, I recorded the sender's country (or at least the sender's postal country code), the postcode of the recipient and the contents of the mailing, i.e. how many items were opened and how many types of product they contained (name of the product, active

ingredient, dose, packaging, quantity, whether it has a package leaflet or similar description). Knowing the active substance, I determined the ATC codes (Anatomical Therapeutic Chemical Classification System), calculated the DDD (Defined Daily Dose) of the active substance of each formulation, expressed in DDD/1000 inhabitants/day, and also determined the KEGG (Kyoto Encyclopedia of Genes and Genomes) identifier [4, 5].

III.2. Results

My research group took part in a two and a half day study in September and December 2020, wich I documenting the contents of 101 consignments with photographs. A total of 205 products was inspected, of which 95.1% were found to be counterfeit based on the checklist developed.

During the processing of the photographs I recorded the country of the consignors and the postal codes of the consignees, as well as the name, potency, unit of packaging, active ingredient, manufacturer and quantity of the products.

In 2020, I requested and received monthly breakdown of data on the total number of consignments arrived, the number of consignments selected for inspection, screened and opened from the Airport Customs Directorate of the NTCA. However, with regard to the number of consignments containing medicines or preparations that appear to be medicines, in addition to the above data, I have arrived at quantified values and conclusions based on my own and my fellow researchers' experience, observations and calculations based on data from week 45 of 2020.

Set A: *All incoming consignments*

Set B: *Consignments selected for inspection*

Set C: *Inspected consignments*

Set D: *Opened consignments*

Set E: *Consignments containing drugs of drug-like preparations*

Based on the data from week 45 in 2020, I calculated that the Set C compared with Set B was 8.92%, Set D compared with Set C was 77.52%, and Set E compared with Set D was 91.22%. The number of consignments containing a medicine or a preparation which appears to be a medicine in relation to the total number of consignments (Set E compared with Set A) was 0.26%. For the annual data, the proportion of Set C compared with Set B was 2.85% and Set D compared with Set C was 19.47%. This shows that the data for week 45 shows a ratio of about

three times for the "C" and "B" sets and four times for the "D" and "C" sets compared to the total 2020 data.

Therefore, based on the Week 45 data, between 0.26% one-quarter and one-third (i.e. 25-33%) of all inbound shipments in 2020 may contain a drug or medicine, which could be approximately 19.000 – 25.000 shipments per year and 50 – 70 shipments per day. Based on the my study data from two and a half days, my aim was to determine the aggregate DDD of the 101 opened shipments (containing a total of 205 medications or apparent medications). This was calculated by multiplying the dose of the total quantity received (unit of presentation and number of boxes) and using the DDD value in the WHO database. For legal preparations, it is usually possible to determine the DDD of a box of medicines. For counterfeit and illegal products, in most cases this is not possible because the products do not have secondary packaging or, if they do, they are not tamper-evident boxes. In most cases, the products simply arrive in blister packs or blister fragments. For my calculation, I therefore use the total number of units or quantities actually received for the pharmaceutical form (e.g. tablet, capsule, ampoule, etc.) of a preparation. I was able to determine the DDD value of a preparation for 183 products. I calculated the total daily DDD value for each study day separately, and from this I calculated the average DDD value per shipment for my research team's study, which was 221. I identified 22 products containing active substances with no available ATC codes, and these products was not included in my calculation. From all data in 2020 we estimated that 4 ampoules per 1000 person-years of unidentified, possibly illegal medicines or health products without DDD and approximately 40 solid dosage form (tablet, capsule) per 1000 person-years of unidentified, possibly illegal medicines or health products without DDD may have reached the Hungarian population. Based on the previous average, I assume that the results of the two and a half day study can be extended to the calculation of the annual data. Based on the average number of shipments per day, as previously determined from the data received from the NTCA Airport Directorate, this represents a volume of 1.2 DDD/1000 inhabitants/day of counterfeit drugs. According to a study by Berterame and colleagues published in the Lancet in 2016, this means that this value is equal to one third of Hungary's opioid analgesic consumption (3.984 DDD/1000 inhabitants/day) [6].

IV. Questionnaire survey to find out practitioners' experiences and opinions on illegal drugs

IV.1. Methods

My research was a cross-sectional pilot survey with a total of 4 blocks and 14 questions. The first block was the basic information collection, which consisted of 3 questions. The second block also consisted of 3 questions and was intended to assess the physician's opinion and attitude towards the problem. The third block asked about the practices used during patient admission. This block contained 4 questions. The last, fourth block asked about the physician's options and actions after the problem - or health problem - had been identified. This block also consisted of 4 questions.

Thirteen of the 14 questions were open to pre-set answer choices. The last question of the questionnaire gave the respondents the opportunity to express their opinions and thoughts on the problem in a free-word response.

The pilot survey was sent via Google Forms questionnaire in March 2021 to the heads of the Department of Primary Health Care of the Faculty of General Medicine and the Department of Emergency Medicine of the Clinical Centre of the University of Pécs, to the physician’s working in the units.

IV.2. Results

The pilot questionnaire was sent to 59 doctors in March 2021. It was completed in March and April 2021, during which time 20 responses were received. 35% (n=7) of the respondents work in primary care, 60% (n=12) in emergency care and 5% (n=1) in both. 20% (n=4) of respondents have been practising for 5 years or less, 45% (n=9) for 6-15 years, 10% (n=2) for 16-25 years, 15% (n=3) for 26-35 years and 10% (n=2) for 46 years or more.

75% of the respondents (n=15) consider the use of fake or illegal medicines or medicines that look like fake medicines to be a real danger, 15% (n=3) do not consider it a real danger and 10% (n=2) cannot assess the problem.

40% of respondents (n=8) have experienced problems with the use of falsified or illegal medicines in their practice or operation. While 45% (n=9) have heard about problems with the use of fake or illegal medicines from patients or colleagues.

When asked whether the patient's examination (taking a medical history, etc.) includes a check to see what other medicines are used by the patient is in addition to those prescribed by the

doctor, 20% (n=4) of respondents always ask, 45% (n=9) ask if they suspect the use of a falsified or illegal medicine, 20% (n=4) sometimes ask, and 10% (n=2) do not ask but think it is a good idea. None of the respondents selected the option "no, because it is not necessary" and 5% (n=1) could not answer this question.

When asked if they had encountered a patient in their practice who was suspected to have entered the health care system or needed health care due to the use of counterfeit or illegal drugs, the following responses were received: 20% (n=4) said "yes", 30% (n=6) said "I have not experienced this in my own practice but have heard of such a case", 5% (n=1) said "I have not experienced this in my own practice and have not heard of such a case". Also 30% (n=6) answered "no, but I consider it a real danger", 10% (n=2) stated "no, and I do not see such a danger at the moment". And 5% of respondents (n=1) said they could not answer the question.

I also asked whether it could be proven that some symptoms or complaints were caused by the use of counterfeit or illegal medicines, would there be any possibility of this being properly accounted for to the funder? This question was answered by 90% of the respondents (n=18). 5.6% (n=1) responded "yes, I choose this settlement in all such cases", 11.1% (n=2) "yes, but it is not the primary settlement option", 5.6% (n=1) "yes, but I have never used this settlement option". 38.9% (n=7), answered "no, but I think it is a good idea" and also 38.9% (n=7) could not answer the question.

At the end of the questionnaire, I gave respondents the opportunity to express their views on what interventions they think could be taken to reduce or prevent the use of falsified or illegal medicines. The majority called for prevention, awareness-raising and 2-3 minute media campaigns, information for professionals, training lectures, publications, more strict controls, and credible sources of information or at least recommendations. It is considered important to provide medical universities with a thorough education and training on the problem, to carry out stricter monitoring and regulation, and to educate and inform the public, highlighting the harmful consequences and cases of health damage, in order to discourage the use of products of dubious origin.

V. Costs of implementing a system to combat counterfeit medicines in the EU Member States

VI.1. Methods

Based on a literature review and interviews with experts in hospital pharmacy, I developed a 41-question questionnaire to evaluate the serialisation scheme that came into force in February 2019 and the subsequent stabilisation period. The questionnaire was sent to all (n=96) Hungarian hospital pharmacies in September 2019 via the Hungarian Society of Pharmacy and Hospital Pharmacy through the Hungarian Society of Pharmacy and Hospital Pharmacy.

The questionnaire consisted of three main sections: institutional data and human resource requirements; infrastructure and IT improvements; and tasks related to serialisation. Employees work hours dedicated to FMD related duties are expressed in full-time equivalent (FTE). At the end of the first three phases, I offered respondents the opportunity to freely express their comments, share their experiences and any other information that led to additional costs in their unit for implementing and running FMD.

I used data from 43 responding institutions to estimate the FMD-related cost burden of all Hungarian hospital pharmacies based on the number of hospital beds available from the Hungarian PULVITA Health Data Warehouse using a multivariate linear regression model [7]. Based on the resource utilization and unit cost reported by the survey respondents, my research team and I developed a multivariate linear regression model to identify parameters that have a significant impact on the total cost of serialization. Descriptive statistics and statistical analysis were performed using SPSS software version 26.

V.2. Results

V. 2. 1. Introduction of respondents, workflow of serialization in hospitals and additional human resource requirements

Due to the high response rate (n=43, 44.8%), the data obtained can be considered representative. Respondents cover approximately half of all active (42 194) and chronic (24 514) beds within the country.

Human resource requirements for serialisation tasks I measured in terms of working time and expressed in full-time equivalents (FTE) instead of monetary units. In February 2019, at the launch of the Anti-Counterfeiting Directive, the average increase in pharmacist workload was 0.92 (± 0.98) hours per day, and respondents estimated that this would increase by 1.13 (± 1.65)

hours during the stabilisation period since launch. In addition, the FMD appeared to significantly increase the workload of assistants compared to pharmacists' workload. In February 2019, at the start of the scheme, a 2.25 (± 1.42) hour increase in workload was estimated for pharmacy assistants working with FMD, and in the long term an additional 4.01 (± 3.88) hours of work was estimated. Consequently, the increased workload due to serialisation will result in a full-time equivalent of approximately 0.25 pharmacists and 0.75 assistants per institution by the end of the stabilisation period.

V. 2. 2. IT and infrastructural developments

The majority of hospital pharmacies needed a computer or laptop (60.8%) or monitors (67.4%) in the initial phase, while some hospitals (<20%) reported having made such investments during the stabilisation period. The average investment cost per institution for IT equipment up to the start-up period was €1,410 (SD: €335), including computers and scanners, with an additional €301 (SD: €577) expected to be spent on this during the stabilisation period, according to the responses. In Hungary, the National Healthcare Service Center has provided two scanners per institution to the pharmacies of the hospitals it runs.

Considering the short- and long-term workload growth, additional IT and infrastructure investments related to FMD in our nationally representative sample, my research team proposes the following metrics to illustrate, estimate and compare the burden, costs and costs of serialisation in hospital pharmacies:

- Pharmacist workload increase 0.28 hours/day/100 beds
- Technician workload increase 0.86 hours/day/100 beds
- IT investment costs 238.9 €/100 beds
- Infrastructure investment costs 80.7 €/100 beds

V. 2. 3. Workflow and procedures of serialization

The majority of institutions (74.4%) carry out deactivation of products in one step, while the remainder (25.6%) first verify the medicines and then re-scan the products' datamatrix code to check the medicine out of the system before dispensing to hospital departments.

After the first six months of experience following the start of serialisation, many institutions (41.9%) reported that they had experienced a price increase for serialised medicines. The majority of hospitals (88.4%) experienced supply problems for products covered by the FMD

regulation. 33 respondents (76.7%) experienced a shortage of medicines with unique codes and tamper-evident packaging in their institution. 23 respondents (53.5%) found that increased secondary packaging required an increase in the storage capacity of hospital pharmacies.

Based on a multivariate linear regression model, my research team extrapolated the results and estimated the total cost of serialisation for all Hungarian hospitals, with an estimated total cost of €266 596 and a mean cost of €2748 (SD: €3255, median: €1102, range: 167 - €13 250).

VI. Conclusions

In my research „Determining the real number of counterfeit or illegal medicines or products that appear to be medicines or products ordered over the internet that pose a threat to the safety of the Hungarian population", I considered as counterfeit or illegal medicines or products that appear to be medicines or products any product that is falsely indicated as such, has incorrect labelling, the name of the active ingredients and excipients, the composition of the product or its potency. It is of dubious origin as to the manufacturer, the country of manufacture or origin and the marketing authorisation holder. It has an unreliable history, a set of records and documents relating to its marketing [2, 8, 9].

My research team set out to estimate the number of shipments of medicine or products that appear to be medicine ordered by users from any of the online forums, or at least to estimate it more accurately than the data available so far. The scale of the problem is illustrated by the fact that in 2020, roughly 20,000 shipments were suspected to contain counterfeit or illegal medicines or medicines whose appearance mimics medicines. This equates to 50 shipments per day and 1.2 DDD/1000 inhabitants/day, which represents one third of our country's opioid analgesic consumption. In addition, approximately 4 ampoules and 40 per dose of non-DDD-containing preparations may reach the Hungarian population per 1000 persons per day.

Often the addresses on the senders address are misleading, so it is not possible to draw any far-reaching, objective conclusions from this data. The manufacturer of the products (or rather the country of origin) gives a more realistic picture of the manufacturers of counterfeit or illegal products, but the online space still provides complete anonymity and concealment for distributors.

On the basis of inspections at the postal premises of the Airport Customs Directorate of the National Tax and Customs Administration, I have seen cases of family members living abroad

seeking to care for their relatives at home by sending them medicines by post, and I have witnessed panic buying of medicines by lay people and professionals in the context of a pandemic, some typical "suo nomine" (to the doctor's hand) orders may be motivated by the need to obtain cheaper supplies, and of course users may turn to online sellers to hide vanity or shame. Some senders want to take advantage of Hungary's status as a member of the European Union, i.e. to facilitate transit and transit within the EU, but it is also clear that, as my research team has seen and experienced repeatedly, large volumes of counterfeit medicines are not primarily traded by international mail, but by some other means, such as smuggling across borders.

This study provides a more approximate estimate of the number of mailings that may arrive by post containing medicines of dubious origin or preparations that appear to be medicines, which may contain counterfeit or illegal pills or capsules that are difficult to estimate. The novelty of the research is that it seeks to ascertain the true extent of the problem by involving the National Tax and Customs Administration in the inspection of mail arriving by post. Unfortunately, the project cannot provide precise statistics, since there are no accurate statistics on the number of consignments containing medicines or products that appear to be medicines.
My pilot survey „Questionnaire survey to find out practitioners' experiences and opinions on illegal drugs" clearly showed that more than 80% of the doctors who completed the questionnaire consider the harm caused by the use of fake or illegal medicines or medicines that look like medicines to be a real danger and a problem to be solved. Interestingly, one third of the respondents have encountered problems caused by the use of counterfeit or illegal medicines in their profession or professional life, while 38.9% have heard of such cases from patients or colleagues. In principle, one would expect these two figures to be the same, but as is usually the case, more people have heard of the problem than have encountered it.

It is also clear from my work that the majority of respondents consider the fight against counterfeit medicines to be important. Similar to the wishes expressed by lay people and professionals in other countries, the same expectations are expressed by Hungarian professionals, such as that education, public education and the promotion of conscious consumer behaviour are part of a successful fight. There is a need for professional training, information materials, campaigns, training for prospective and practising professionals and awareness-raising among the public.
It was also clear that professionals lacked the knowledge of where and how to report medicines that were considered suspicious.

My work is a pilot study. A national survey would be needed to ensure that the views of professionals working in emergency and primary care, who are the first to encounter the consequences of counterfeit medicines, are representative of those in Hungary. However, it is clear from these data that our respondents identify the same areas as urgent to be addressed as those identified by their colleagues practising in similar areas and responding to similar questionnaires elsewhere in the world. The clear message from my work is that counterfeiting of medicines needs to be more intensively researched and discussed, and cases need to be collected to prevent the potential, yet preventable, harm that can occur.

In my research on „Costs of implementing a system to combat counterfeit medicines in the EU Member States", it was useful to carry out a cost-benefit analysis of anti-counterfeiting measures, taking into account all direct and indirect costs and benefits. Unfortunately, data on the penetration rate of counterfeit products in the supply chain, data on the actual global and national market for counterfeit medicines, data on the consumption of counterfeit medicines by patients, and real data on the actual incidence of patient risk and health outcomes are missing. The limited amount of data available is derived to varying degrees from unrepresentative national data and from studies, estimates and extrapolations from expert opinions and forecasts. As a consequence, health economic analysis of the global issue of falsified medicines is extremely difficult, and it is not yet feasible to extrapolate the data obtained to a single patient, medicine or geographical area.

Mandatory and increasing serialisation will increase the traceability of medicines, making the pharmaceutical supply chain safer and less attractive to counterfeiters.

Serialisation was previously argued to have many advantages in increasing patient safety. Yet these benefits (such as faster product recall or the expected rapid response in pharmacovigilance) are not obvious.

The European Alliance for Access to Safe Medicines (EAASM) has previously indicated for large hospitals that additional human resources, i.e. 2-4 full-time equivalent pharmacy assistants per institution, will be needed to carry out the serialisation workflow and to report false negative and positive indications after the FMD is activated. Additional costs to operate the system will depend on the deactivation method selected and used, the number of medicine boxes, and the system scan and response times used [10-12].

My work is also a gap-filling study, as previously only preliminary estimates of the costs of introducing, operating and maintaining serialisation were available, particularly for units at the

end of the pharmaceutical supply chain, such as public and hospital pharmacies. Hospital pharmacies did not have even an estimate of the size and scope of the investments needed in the preparatory and stabilisation period.

In order to assess the impact of the Falsified Medicines Directive on the entire pharmaceutical supply chain, a detailed data collection covering all actors, including implementation and maintenance costs, would be needed, as in my study.

The methodology I have developed could also be used to conduct surveys of hospital pharmacy sector actors at the European level in order to obtain detailed data on the hospital pharmacy sector actors in the EU Member States.

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IX. List of publications

Articles related to the thesis:

Vajda P, Richter K, Bodrogi Z, Vida RG, Botz L, Kovács S, Zemplényi A, Bella R, Fittler A. Survey of workflow and cost implications of decommissioning regarding the Falsified Medicines Directive in Hungarian hospital pharmacies. BMJ Open. 2021 Nov 23;11(11):e047193. **(IF: 2.692)**

Péter Vajda, Eszter Ábrahám, Zsolt Bodrogi, Tímea Dergez, András Fittler, Róbert György Vida, Lajos Botz. Data-based assay of the quantity of counterfeit and falsified medicines purchased online. **PUBLICATION IN PROGRESS.**

Presentations related to the thesis:

Vajda Péter, Botz Lajos. A magyar lakosság biztonságát veszélyeztető, az internetről rendelt hamis gyógyszer vagy gyógyszernek látszó készítmények valós számának meghatározása. Kajos Luca Fanni, Bali Cintia, Preisz Zsolt, Polgár Petra, Glázer-Kniesz Adrienn, Tislér Ádám, Szabó Rebeka (szerk.). 10. Jubileumi Interdiszciplináris Doktorandusz Konferencia = 10th Jubilee Interdisciplinary Doctoral Conference: Absztraktkötet = Book of Abstracts. Pécs, Magyarország: Pécsi Tudományegyetem Doktorandusz Önkormányzat (2021) 347 p. pp. 220-220., 1 p.

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