Patient safety risks and pharmaceutical quality of ophthalmic products distributed online

Theses of doctoral (Ph.D.) dissertation

Dr. Sára Merczel

Programme lead and supervisor: Prof. Dr. Lajos Botz professor

Co-supervisor: Dr. András Fittler associate professor

Head of doctoral school: Prof. Dr. Erika Pintér professor

University of Pécs

Medical School

Doctoral School of Pharmacological and Pharmaceutical Sciences

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List of abbreviations

ATC = Anatomical Therapeutic Chemical classification system

BAC = benzalkonium chloride

DZA = dorzolamide hydrochloride

FIP = Fédération Internationale Pharmaceutique - International Pharmaceutical Federation

FMD = Falsified Medicines Directive

HPLC = high-performance liquid chromatography

NNGYK = National Centre for Public Health and Pharmacy of Hungary Hungarian pharmaceutical governmental agency since 1st August 2023.

OGYÉI = National Institute of Pharmacy of Hungary Hungarian pharmaceutical governmental agency until 31st July 2023.

Ph. Eur. = European Pharmacopoeia

Ph. Hg. VIII. = Pharmacopoea Hungarica VIII.

RSD = relative standard deviation

TIM = timolol maleate

USP = United States Pharmacopeia

WHO = World Health Organization

I. Introduction

Online shopping of physical products and services has become an everyday and popular activity for individuals of the 21. century. Pharmaceuticals as "special products" are not an exception either.

But what is the motivation of patients and consumers for the purchase of such a "special product" as pharmaceuticals via the internet? Mostly simple and convenient access, many times lower price compared to those in traditional pharmacies, access to products which can not be obtained via traditional routes, access to medications requiring prescription without a prescription. According to previous investigations patients and consumers do not understand or sense nor "quality" differences nor risks between the purchase via traditional, closed pharmaceutical chain and via illegal (but resembling traditional) online "supply chain" (Abanmy, 2017; Fittler et al., 2018a; Long et al., 2022).

We have limited scientific data regarding how medicine shortages determine patients' willingness to obtain pharmaceuticals from the internet. International investigations confirmed the expansion of online purchase of pharmaceuticals after the COVID pandemic, in addition to the increased internet use and online shopping in itself (Chereches, et Popa, 2021; Gu et al., 2021). If a pharmaceutical shortage occurs, patients, consumers and their relatives may turn to self reliance instead of traditional medical and pharmaceutical supply chains.

Increased and "ignorant" demand for and access to counterfeit or falsified medicines is affected by the shortage-inducing transactions of mostly over-regulated official pharmaceutical supply chains of developed countries.

Moreover, increased interest for a simpler online market is influenced by the wider range of products at lower prices, and popularity of miracle drugs which seem to aid self-treatment or prophylaxis (Long és mtsai., 2022).
Risks are known, but the collection of real life data in this “scientific field” is extremely difficult. Most available literature on online distribution of pharmaceuticals focuses on web pages and their legality and try to simulate the purchasing behaviour of a single potential consumer with test purchases. Thus, the most information originates from those investigations, which analyse the online availability and quality of pharmaceuticals and other healthcare products procured via internet (Orizio et al., 2011; Norbutas, 2018; Vida et al., 2017; Vida et al., 2019).

II. Aims

This dissertation aims to introduce an investigative system consisting of complex quality analysis encompassing the motivations of distributors and consumers, risk evaluation of patient and drug safety, online purchase methodology and pharmaceutical approaches. Necessarily it involves the professional evaluation of extensive online “pharmaceutical supply chain”, which provides patient-initiated solutions for the medicine shortages becoming more and more frequent.

1. Our purpose was to investigate the national shortage status of a given pharmaceutical category, methods of notification of professionals, patients and consumers about medicine shortages, occurrence of actual medicine shortages and subsequent possible online pharmaceutical distribution, pharmaceutical procurement via internet and the characteristics of the

purchases of products affected by shortages. We focused on a product category involving high risks as well as medicine shortages: ophthalmic products.

2. Our aim was to develop and use a complex risk evaluation methodology as an investigative device, which is able to identify high risk pharmaceuticals distributed online based on objective parameters. We intended to evaluate patient safety risk associated with the online purchase of the chosen pharmaceutical category with the developed methodology, which encompasses general pharmaceutical risk, therapeutic risk and the risk originated from the probability of microbiological contamination.

3. We strived to perform online test purchases of ophthalmic preparations, which are evaluated as most risky according to our risk evaluation methodology and are prone to shortages in our country. We performed test purchases based upon the results of our previous investigations.

4. We planned investigations to assess the pharmaceutical quality of eye drops obtained from the internet, with which, besides identification and content analysis, we can carry out quality assessment of pharmaceutical preparations in everyday practice in a fast, validated and cost-effective way, and to evaluate pharmaceutical risk.

III. Shortages of ophthalmic preparations for glaucoma

Medicine shortages are permanent, the only change is the range of pharmaceutical products. According to the investigated databases 26

publications and 4 authority notifications were addressing the shortages of ophthalmic preparations between 2000 and 2022.

News about the shortages of eye drops in the national press is often fake news, biased or incomplete.

In order to be able to evaluate the actual shortage status and/or officially announced medicine shortage of combination eye drops containing dorzolamid hydrochloride (DZA) and timolol maleate (TIM), we investigated the changes of the authority shortage list archives in the abovementioned time interval, and we assessed the wholesale and retail sales data of the products.

In summary we can declare that the appearance of the shortages of the combination eye drops containing DZA and TIM are separated in time from each other in the press, on the drug shortages list of Hungarian pharmaceutical governmental agency and at wholesalers and retailers. Among the 4 areas, logically, the shortage of single-dose and preservative free DZA+TIM eye drops first appeared in the sales data of Hungaropharma. Afterwards Hungarian press vividly reported about the shortages of these products in the subsequent months. In the investigated retail microenvironment (Szigethy Gyula Pharmacy) the same products became unavailable only 5 months later. Nonetheless, official notification of the shortages of these products on the shortage list of the Hungarian pharmaceutical governmental agencies (NNGYK/OGYÉI) appeared only 20 months after the temporary then permanent shortages detected at wholesalers.

IV. Complex risk evaluation and test purchase of eye drops available on the internet

In relation to products available on the internet there was no prior complex risk evaluation methodology published as a device to determine the quality and patient safety requirements and their risk values and/or evaluation. Therefore, we previously developed an investigative device, in which we merged different patient safety factors regarding products, general pharmaceutical risk, therapeutic risk, risk originated from possible microbiological contamination, risk induced by limited access to the products, falsification risk and the probability of online availability of the products (Vida et al., 2020). This analytical methodology that we developed in relation to medicine shortages of ophthalmic preparations served to objectify the patients' motivation for purchase.

We chose eye drops with MA in Hungary from 10 different therapeutic areas based on the sales data of community pharmacies.

Among the eye drops available via internet the highest patient safety risk in our case was shown for DZA+TIM combination single-dose and multi-dose eye drops. This coincides with the category of eye drops (S01ED51 timolol and its combinations, including DZA+TIM combinations) affected by the shortages announced by the authorities and the media. So, the category of eye drops warranted by the media and by our everyday practice unequivocally coincided with that affirmed by the risk evaluation methodology, namely single-dose and multidose DZA+TIM combinations.

We performed test purchases based upon the results of our previous investigations.

Eventually we received three shipments: Dorzox T eye drops from Trusted Tablets (www.trustedallovetheworld.com) and Buy Pharma (www.buy-pharma.md). Labels stated: dorzolamide hydrochloride (DZA), United States Pharmacopeia (USP) equivalent to dorzolamide 2% w/v + timolol maleate (TIM), IP, equivalent to timolol 0.5% w/v; Cipla LTD, Mumbai, India.
These are marked as Online sample No.1 and Online sample No. 3, numbers referring to order sequence. Second test purchase was Cosopt eye drops from GuysPharma (www.kiwidrug.com). Label stated: DZA, USP equivalent to dorzolamide 20 mg/ml + TIM, IP, equivalent to timolol 5 mg/ml; Santen OY, Finland. This sample was marked as Online sample No.2. The Online samples were preparations in multidose bottles, containing benzalkonium chloride (BAC) as preservative. Online sample No.1 and Online sample No.3 were obtained without a prescription, in spite of the statement of outer packaging requiring medical prescription by an ophthalmologist. Online sample No.2 according to outer label required prescription. Nevertheless, we obtained it without a prescription, though after the completion of a health-related questionnaire about the person who ordered it.

V. Pharmaceutical analysis, evaluation and results of the purchased ophthalmic preparations

Different analyses and evaluational methods used during the complex investigation of the purchased products were consistent with the methods known from the Hungarian and international literature (WHO, 1999; WHO,

2016; Newton et al., 2009; Aldrich and al., 2013; Veronin et al., 2014; Vida et al., 2017; Rahman et al., 2021).

We used Cosopt multidose eye drops (containing 20 mg dorzolamide as 22,26 mg DZA and 5 mg timolol as 6.83 mg TIM per ml, Santen OY, Finland) from the referential, closed pharmaceutical supply chain as control samples.

Complete investigations of the purchased products and controls consisted of outer visual check and general quality evaluation. Quality evaluation encompassed organoleptic examination, quantitative and qualitative analytical tests (HPLC), and sterility tests.

Eye drops are required to be sterile and free from physical-, chemical- and biological contaminants. (Ph. Hg. VIII. - Ph. Eur. 6.0-6.5, 2008; Uddin et al., 2017). Labels should contain the time period in which the product is suitable for use after opening (Ph. Hg. VIII. - Ph. Eur. 6.0-6.5, 2008). Quantity of the active ingredient in the product should be within the range of 90.0% - 110.0% of the quantity stated on the container label (Sharath et al., 2011; Kahook et al., 2012; Tatham, 2020).

On the FIP checklist that we adapted to ophthalmic products Online sample no.1 and Online sample no.3 did not comply with the requirements of 8 items (24%, n/N=8/34), and Online sample No.2 did not comply with the requirements of 6 items (18%).

In organoleptic examinations Online samples were consistent in terms of clarity and opacity and did not differ from the clarity and opacity of Control samples, thus complying with the requirements of the Pharmacopoea (Ph. Hg. VIII. - Ph. Eur. 9.2, 2017).

Every Online sample contained the active ingredients (DZA, TIM) and microbiological preservative (BAC). As shown in Table 1, concentrations of online samples ($C_{meas\ av}$) differed more than 10% ($p<0,05$) from the values measured in control samples in case of at least one component. Therefore, differences are not due to randomness. The eye drops purchased online contained 99.3-113.1% DZA, 112.8-139.2% TIM and 82.4-97.7% BAC compared to theoretical values of label claim. The eye drops purchased online contained 87.0-99.2% DZA, 91.7-113.2% TIM and 88.9-105.5% BAC compared to control samples.

Table 1 Theoretical (label claim) (C_{theor}) and measured average ($C_{meas\ av}$) concentrations of the active ingredients and microbiological preservatives in ophthalmic preparations, significance levels (p-values) and comparison of concentrations (C_{meas}/ C_{theor} és C_{meas}/ $C_{control}$)

		C_{theor} (mg/ml)	$C_{meas\ av}$ ±SD (mg/ml)	p-value	Average (C_{meas}/ C_{theor}) ±SD (%)	Average (C_{meas}/ $C_{control}$) ±SD (%)
Online sample No.1	DZA	20.00	19.85±0.07	0.0005	99.3±0.33	87.0±0.29
	TIM	5.00	6.96±0.08	0.0174	139.2±1.57	113.2±1.27
	BAC	0.075	0.069±0.0027	0.7829	92.0±3.62	99.3±3.91
Online sample No.2	DZA	20.00	22.63±0.27	0.6133	113.1±1.36	99.2±1.19
	TIM	5.00	6.15±0.032	0.9936	123.0±0.64	100.0±0.52
	BAC	0.075	0.062±0.0027	0.0104	82.4±3.59	88.9±3.88
Online sample No.3	DZA	20.00	20.22±0.58	0.0043	101.1±2.90	88.7±0.55
	TIM	5.00	5.64±0.25	0.1094	112.8±5.00	91.7±4.07
	BAC	0.075	0.073±0.0034	0.1405	97.7±4.53	105.5±4.89
Control sample	DZA	20.00	22.81±0.50	reference	114.0±2.52	100.0±0.00
	TIM	5.00	6.15±0.35	reference	123.0±7.02	100.0±0.00
	BAC	0.075	0.069±0.0012	reference	92.6±1.54	100.0±0.00

Validated sterility testing for all the three samples confirmed sterility of the sample, as microbial growth did not occur.

VI. Statements

Illegal online distribution and purchase of medicines, including ophthalmic products is a process affected and motivated by multiple factors. Therefore, it is considered a complex field, that fundamentally determines patient and mediaction safety, a novel challenge. In line with the aims of this dissertation we make the following statements:

1. According to Hungarian and international literature the complexity, partial inconsistency and deficiency of the regulations by the competent authorities may result in the expanding use of the internet for medicine trafficking. Distributors and consumers alike, are mostly lead into this system of falsified and counterfeit medicines by the legal supply chain. Most incentive factors are the unlimited, unhindered and free access to prescription-only-medicines, the weak regulations of developing countries and the too rigid regulations of pharmaceutical supply chains in developed countries, which often lead to shortages, the wide, simple and cheaper availability of products, and last but not least the lack of common interests of stakeholders.
This is aggravated by the fact that in case of shortages, as a possible motivating factor, strategies of resolution of shortages are heterogeneous on national and international level. Multiple appearance of ophthalmic product shortages in the media were mostly incoherent with authority notifications, registers. Even though shortages should be present in the register of shortages of the pharmaceutical governmental agency, based upon the official,

compulsory notification by the distributor. So, they far not appear in every case, or just with significant delay. Many times, shortages are noticed merely upon feedbacks from pharmacies (community and institutional). Moreover, there is a massive time gap between the central, administrative solution of shortages and the availability of medicines for patients.

This is corroborated by the fact, that in our retail microenvironment (Szigethy-Gyula Pharmacy) patients temporarily could not be supplied with their medicines. Continuous supply of preservative free and single-dose DZA and TIM eye drops was impossible in September and October of 2017. This may lead even those patients with proper adherence towards the illegal online purchase of ophthalmic preparations endangering the safety of patients and medications alike. (So far, we did not encounter such cases, but among the motivations revealed by surveys this is one of the most dominants, thus we deemed it important to investigate and recognise it professionally in time, in order to make timely preventive actions.)

2. In order to determine and objectify the consequential patient risk factors, with the aid of previously existing literature data and our pharmaceutical professional expertise we developed a complex risk evaluation methodology, which may be a recommended reference methodology for investigative or control test purchases. With the help of this methodology online distributed pharmaceutical products posing patient risks can be objectively identified. According to our knowledge this may be considered as a gap-filling methodological recommendation in this field. During our previous investigations we have not met such a comprehensive methodology, which would address the risk evaluation of online distributed medicines before test

purchase. We can declare that by using it, patient safety risks and the probability of online availability can be determined. By the standardization of inclusion criteria, we can elaborate better control systems and we can perform test purchases with better efficacy.

The methodology is a general investigative framework. Its objective criteria of selection are based upon pharmacological-, technological- and biopharmaceutics properties of pharmaceutical preparations and characteristics of online medicines market. So, they are suitable for the preliminary risk evaluation of different formulations and pharmaceutical categories before test purchase. We think that the integration of this methodology, which uses pharmaceutical approach as well, helps fast, cheap and objective determination, quantification of patient safety risks even before test purchases by the use of easily accessible information and data. Although the developed framework is suitable for every pharmaceutical class, it should be individually tailored to the specific area of products depending on the preparation intended to investigate. This complex risk evaluation methodology considers patients' and consumers' aspects also, when it evaluates legal and illegal online pharmaceuticals market before test purchase. In summary, it compounds the characteristics of pharmaceutical preparations and online pharmaceutical market. The investigative methodology also gives an example for the evaluation of legal online pharmacies holding authorisation for online distribution of medicines, which may serve to identify products with potential patient safety risks with some proper supplementation regarding the given therapeutic area and product range.

3. We carried out our purchases of single-dose and multidose DZA and TIM containing eye drops - which were unequivocally identified by our everyday work experiences and the array of ophthalmic pharmaceutical preparations signalled by the media, and the results of risk evaluation methodology - according to literature methodology and the results of our previous investigations (Orizio et al., 2011; Norbutas, 2018; Vida et al., 2017; Vida et al., 2019). We could not obtain single-dose preparations from the abovementioned range of eye drops. We were able to purchase eye drops requiring prescription without a prescription on two occasions, and in one case upon the completion of only a health-related questionnaire. Corroborating the fact, that these days the availability of every therapeutic (pharmaceutical) category is unlimited (Mackey et Nayyar, 2016; Fittler et al., 2018b). When purchasing Online sample No.3 we could pay only in bitcoins and the suspected online pharmacy withdrew an additional 78,79 Euros apart from the price of the eye drop from the bank account of the payer.

4. In case of letters or small packages sent via postal services the quality assurance of shipping conditions is not ensured for the whole duration of the journey. Therefore, shipment conditions and the preservation of product quality until delivery to the patient - which is fundamental in closed supply chain - can not be reportedly ensured. It is unknown, what was the temperature and moisture level during shipment process. There are no identifiable manufacturer and/or transporter responsibilities, which would guarantee the quality parameters described in product leaflets and product

responsibility of the preparation. So, this shipment chain holds medication safety risks at every instant.

Thorough visual check of outer and immediate packaging, labels and patient information leaflets is indispensable for the identification of irregular, quality deficient and falsified medicines. All the three online samples deviated from the FIP checklist, that we adapted to ophthalmic preparations, all of which deviations involve potential patient safety risk concerns. Online sample No.2 arrived relabelled from Italian to English, which means, that the origins as well as proper usability may be questioned. Labels on the outer packaging and immediate container were not consistent and were not readily legible. As per literature data, manufacturers of falsified medicines in most cases may care less about smaller, but important details of packaging and labelling, as these are difficult and expensive manufacturing processes (FIP, 2013). If the pharmaceutical preparation does not hold a marketing authorisation in the given country, then it increases the probability, that the patients obtain reliable patient leaflet, and receive authentic information on the manufacturer of the product. Online sample No.1 and Online sample No.3 are not authorised in our country. Additional suspicious sign of falsification is that all three samples were sent via postal service to a Hungarian address. This route of distribution is illegal.

During qualitative and quantitative analysis of ophthalmic preparations obtained with test purchases we found slight discrepancies between claimed and measured concentrations of the active ingredients and the microbiological preservative. The concentration of the active ingredient in Online sample No.1 and Online sample No.3 was not compliant with the international threshold value of ±10% ($p<0,05$) (Sharath et al., 2011; Kahook

et al., 2012; Tatham, 2020). Online sample No.2 also deviated from requirements, as the real concentration of microbiological preservative (BAC) was only 82% of claimed value ($p<0,05$). Lower amount of the active ingredient was presumably due to inadequate shipping and storage conditions, as all eye drops and their active ingredients and excipients can be stored at room temperature. Reference eye drops used as Control samples obtained from national community pharmacy source, as a closed supply chain, were compliant with every professional requirements according to qualitative and quantitative analytical examinations.

A frequently neglected aspect of online test purchase of medicines is the sterility of preparations, which is a requirement of utmost importance in case of ophthalmic preparations. In our investigations we found that the test purchased preparations were sterile. Sterility is key during the manufacturing process of ophthalmic preparations, and this is a fundamental requirement, as it is the most predominant aspect of medication safety and quality of eye drops. Although every sample was free of microbiological contamination based upon the sterility test of the pharmacopoeia, sterility alone is not sufficient for product safety. Adequate shipment, storage and packaging conditions are indispensable factors in the stability of pharmaceutical preparations.

Falsified medicines are hard to identify, as they sometimes differ only in some of the product requirements from real pharmaceutical preparations. Packaging and labelling were non-compliant, but sterility testing revealed no microbiological contamination. At least one ingredient - active ingredient or microbiological preservative - of the eye drops purchased from the internet were not present in the concentrations stated on the label.

In summary, our results proved that the purchase of medicines from uncontrolled sources, especially for those requiring prescription and those that hold high patient safety risks, involves healthcare hazard.

Great advantage of this complex risk evaluation methodology is, that by using it, investigations may be more cost-effective, as test purchases may not be made for every single medicine. Nevertheless, with this easy and cheap method much more test purchases can be made, which in turn increases the efficacy of control and investigation of pharmaceutical market.

We performed the test purchases not only based upon the shortage motivating it, but according to a predefined risk evaluation. Pharmaceutical analysis of the purchased ophthalmic preparations consisted of simple outer visual check, organoleptic examination, then complex, fast, yet cost-effective HPLC testing and efficient sterility testing. HPLC examination of DZA, TIM and BAC and sterility testing methods are accurate and suitable for small sample, routine quality control.

A limiting factor for the conclusions made upon our investigations is, that we included only one pharmaceutical formulation, based upon the products available on the market in our country, and according to national shortages.

Regarding the selection process, the fact, that it was based upon consensus and experience of pharmacist investigators and not on comprehensive, country-wide data, may express a bias. Further limitations of our work are the low number of samples, and that the combined method is rather time-demanding, which limits its use on the spot and its suitability for generalisations with regards to qualitative evaluation of medicines distributed via internet. Nevertheless, usability and adaptation of our methodology in

other regions is feasible, due to the universal and global character of online distribution.

Evaluation of the online pharmaceutical market has become widely popular among pharmacists and authorities in the past 20 years, mainly because of the increased interests of patients and consumers. These investigations induced a series of regulations, although their effectiveness is often questionable and debated (E.g.: Falsified Medicine Directive, EU logo) Therefore, professionals are trying to fight against illegal online medicines distributors with more, novel, but individual techniques and methodologies, to protect patients and consumers. Besides new models against falsification („Big data", „infoveillance", web mapping and deep learning models with artificial neural networks, etc.) further development of traditional methods also supports the struggle against illegal online distribution of medicines. Based upon our investigations we can establish that the method developed by us is suitable for the objective preparation before the test purchase of medicines or healthcare products, based on patient and medication safety risk evaluation, by researchers or market surveillance investigators, for the realisation of test purchases with the simulation of online purchase methodology and for the qualitative evaluation on the basis of pharmaceutical aspects.

VII. Conclusions

Our investigations into patient safety risks and pharmaceutical quality of ophthalmic preparations distributed via internet, although did not corroborate the purchase of a medicine containing a major qualitative defect, may not be regarded as useless. As lack of success does not mean that we can not learn from it. Maybe even more, than from success.

1. Online purchase of medicines is a global phenomenon, it spreads rapidly, and it affects every healthcare system. This form of distribution of medicines offers more and more products, with increasing accessibility. Consumers who purchase from the internet are frequently ignorant of the fact, that these products are not subject to quality control, which otherwise is an indispensable requirement in case of authorised pharmaceutical preparations. Therefore, they are not worried about the quality of the products bought this way. They are in lack of suspicion and knowledge to consider and evaluate the prevailing patient and medication safety risks.

2. Authorities are taking steps to control the professional adequacy of this area on national and international level, but due to ever increasing incentive factors for consumers, they are still exhibiting limited effectiveness. Not even the prevailing healthcare risk can be accurately determined, continuous monitoring is or would be necessary to assess it.

3. To decrease the incentive factor of online purchase of medicines one of the easiest options would be a collaboration between the stakeholders of the national medicine supply chain for the early, “alarm chain”-like exploration of medicine shortages. With the regulated follow up of shortages through a joint alarm chain involving all the stakeholders of pharmaceutical supply chain (pharmaceutical governmental agency, pharmaceutical wholesalers, community- and hospital pharmacies, pharmaceutical distributors) the system could earn some weeks before actual shortages occur.

4. Patient safety risk associated with online purchase of medicines - especially in case of ophthalmic preparations - is remarkable. In order to confirm the actual usability of the risk evaluation methodology, as a device, we performed successful test purchases after a patient risk-based evaluation

of the online availability of ophthalmic preparations and qualitative and quantitative evaluation based on pharmaceutical approach.

5. In summary, we developed a complex pharmaceutical methodology, that is suitable for the practical investigation and quantification of medicine shortages and patient and medication safety risks caused directly or indirectly. With the aid of available literature data, we developed a recommended reference methodology, which may serve as the basis for test purchases performed with the purpose of research or for authority inspections.

In order to decrease the prevailing hazard and patient and medication safety risks, raising public awareness is vital. Authentic, evidence-based information from healthcare professionals may help to increase health-consciousness and to decrease individual risks. Regular inspection of the online market is necessary in order to reduce healthcare risks of patients. There is a need for easily performable investigations to simply and rapidly rule out falsified medicines. These evaluations may promote the development of international regulations, awareness campaigns and legal requirements.

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