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EVALUATION OF AIR TRANSPORTATION UNDER CONTROLLED ROOM TEMPERATURE FOR PHARMACEUTICALS

ABSTRACT

Pharmaceutical industry like aviation is one of the most regulated industries today. Shipping pharmaceutical products under defined time and temperature conditions is a challenge deriving from regulatory and product quality aspects. Good distribution practice should be valid throughout the distribution chain but regulatory issues are still short of strength in practice. Transportation should be considered as extended warehousing, still compliances are business rather than regulatory driven. The paper demonstrates deviations between shipping requirements and realistic capabilities of today's commercial aviation in terms of maintenance of the controlled room temperature. Examples show cases of temperature deviations during transport realization. Suggestions are made on future research in the field of air transportation.

KEY WORDS

good distribution practice, regulatory issues, controlled room temperature, temperature deviations, process qualification

1. INTRODUCTION

In order to secure pharmaceutical product's original quality during its validity period, it is essential to secure storage and distribution under specified conditions. These conditions comprise predefined storage and distribution temperatures, level of humidity and protection against light exposure. While primary packaging protects the product from moisture and light, shipments of pharmaceuticals might get exposed to atmospherics conditions during distribution. This makes temperature major constrain in securing and defining the appropriate traceability process [1]. Warehousing and transportation processes need to be designed in such a way to secure the product from any temperature exposures outside the defined regimes in which product stays in its original quality thus protecting the end users' health.

Distribution chains are very often a set of complex processes which include several stakeholders and locations [2, 3]. Regulatory issues to be complied with emphasize further its complex structure. Logistical support only could comprise more than one stakeholder even in a point-to-point distribution scenario. Transportation companies as well as handling terminals further deepen this structured pattern. Simple distribution pattern consists of producer to consumer distribution realization. However, this mode of distribution is seldom the case. Far more often a scenario considers a process which includes several warehouses, some at remote sites with shorter or longer storage processes, handling terminals, different transportation modes, integral or multimodal solutions, waste number of manipulations from fully automated to hand manipulation thus generating a set of complex and design-demanding processes.

Additional complexity of distribution processes is emphasized by the diversity of transport models as well as the capability of adaptation to controlled temperature conditions. Transportation means are selected according to the volumes and routes planned. Road transportation, where available and plausible, using cool trucking presents a good solution in the preservation of a defined temperature regime. Sea freight might be accounted for where low costs for shipping are prerequisite and time-defined shipping is not a must, but the transport mode changes in reaching the port of departure remain the critical point in realization. *Graph 1* presents a relationship between time consumed by transportation processes and costs related to different transportation modes. Shipping

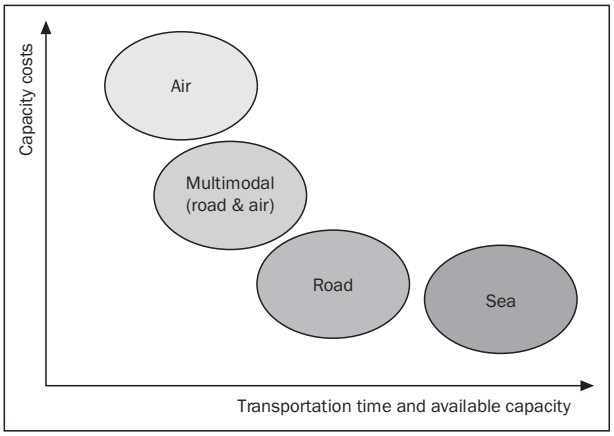

Diagram 1 - Time spent in distribution related to costs for different types of transportation modes

by air proves to be difficult in terms of securing the required temperature regimes or at least the costs of applying safe models are the highest. Still, this means of transportation stays in focus of pharmaceutical industry in long-range shipping solutions due to its capability of covering high distances in the shortest possible time, thus safeguarding the goods from being in distribution for a long period of time (sea freight might take four weeks between Europe and North Atlantic). Air and sea modes presented by the graph consist not only of one transportation means and service provider. Allocation of the goods in the sea or air ports still comprises trucking in most of the cases but does not mean automatically a multimodal transportation solution.

2. REGULATORY ISSUES IN TRANSPORTING PHARMACEUTICALS

The pharmaceutical industry is one of the most regulated industries in the globalized world market today. Effects of globalization resulted in the need for even stricter regulations in distribution thus aiming to harmonize standards for good manufacturing, storage and distribution practices [4, 5]. Pharmaceutical product shall be kept under the prescribed temperature, humidity and light conditions during storage and distribution thus preserving the original quality of the product throughout the distribution channels [6, 7, 8]. This requirement is today in the focus of all the national and international regulatory bodies.

The most important milestones in the United States of America regulative in the field of pharmaceutical products distribution are contained in the USP[1] document *General Chapter 1079 Good Storage and Shipping Practice*. The document consists of standards and defined procedures in the field of medicinal products distribution accepted by the FDA[2] [9]. This USP document publishes the results of research in the field of storage processes for pharmaceuticals, validation of transport means and applicable distribution processes. Good Storage and Shipping Practices developed by the USP is directed through this document towards manufacturers, distributors, wholesalers, package producers and transport logistics providers [10]. It also comprises risk analysis in the distribution of time and temperature sensitive pharmaceuticals related to the effects of temperature, humidity and vibration exposures and defines the conditions for distribution from the producer to the end user. The document carries out the obligation which all involved stakeholders have towards the shipping requirements defined by the producer. The processes defined to address these requirements are generally considered as *Cool Chain Management*[3].

The European regulation issues are related to the production and distribution of medicinal products as stipulated by the EMEA[4]. The Agency produced and published a series of documents which regulate the obligations and liabilities of all the participants in the distribution chain for medicinal products [11, 12]. The recommendations about Good Distribution Practice[5] account the conditions under which the transport of pharmaceuticals should be performed with a particular emphasis on the indication of unacceptable degrees of heat, cold, light, moisture or other adverse influences. Those pharmaceuticals which require controlled temperature storage should also be transported by specialized means in order to appropriately and successfully address those requirements. Several documents address those issues in particular [13]. The Directive 2001/83/EC accounts for wholesale distribution chain. Directive 2004/93/EC as well as Directive 91/356/EEC contain the principles and recommendations on good production practice for medicinal products. Guidelines on good distribution practice of medicinal products are included in Document 94/C 63/03.

Regulatory issues related to GMP (Good Manufacturing Practice), GSP (Good Storage Practice) and GDP (Good Distribution Practice) for pharmaceutical products in the Republic of Croatia have been regulated by the Law on Medicines[6] which in the section *General Provisions Article 2* defines the GMP as part of the quality assurance system which provides consequent and permanent manufacturing and checking according to adequate quality standards in compliance with their purpose [14, 15]. GDP has been defined as a standard for the wholesale storage and transport which include organization and conduction of the processes in compliance with the required conditions. Although the aforementioned law does not explicitly deal with the transport of medicals, the regulatory document dealing with GDP[7] states those products shall be transported in a way in which their identification is not lost, contamination is avoided, the breakage, leak or spilling does not occur, the goods are safe from temperature, humidity and light exposures or patho-

gen contamination. The products which have defined storage temperature must be transported according to the prescribed temperature regimes. Those conditions must be monitored and recorded. The manufacturers or distributors included in pharmaceuticals distribution are obliged to report in writing on any irregularity related to drug distribution that might affect its original quality as defined in the approved resume on drug's properties according to the Regulation defined for drug quality monitoring.

Each of the aforementioned definitions as laid down by the respective authority considers transport as an inseparable part of both good manufacturing and good distribution practice for pharmaceuticals. The need to design package and distribution processes capable of responding to strict regulatory conditions as well as specific characteristics of the transportation entity in terms of its sensitivity to various influences present in the distribution environment, remains the fundamental compliance task for the industry in general. Engaged stakeholders are expected to safeguard the product while in their custody by setting a number of transparent, defined and qualified processes.

The product stability data is basic information required to define the conditions under which the product remains in its original quality and effective until the predefined expiry time. This data comprises elevated levels of temperature and humidity as stipulated in guidelines issued by CHMP[8] and ICH[9]. The results of accelerated and stressed tests on stability, including but not limited to MKT[10] should be used in stability studies to cover the real ambient temperature values under which the product is preserved in warehouses, hospitals, pharmacy or at the end users' and in drug stores [16]. This data should be displayed on the product and packing label. Based on the data collected during the stability studies for each product, preservation conditions are evaluated and defined. These conditions are being regularly rechecked and confirmed by the regulatory agency as part of registration process the product is undergoing on a particular market.

Conditions under which the products are stored or distributed (including but not limited to transportation) are proven using the calibrated data loggers[11] Cool trucks might have data loggers preinstalled while in air and multimodal transportation cases, devices are placed on the packaging or inside the packaging itself. The accuracy of the instruments must be ±0.5 °C. Unlike other parts of GMP, the distribution processes are exempt from validation. This fact derives from the character of distribution process explained earlier in the paper. The USP 1079 document in chapter *Controlled Room Temperature, 9th supplement on Good storage and shipping practice*, defines the preservation conditions which can be displayed on the product label. Most common conditions found on labels for tablets, capsules and other oral use substances is controlled room temperature. Unlike the ambient conditions which are considered as conditions present at the working place, the controlled room temperature comprises more strict range of temperatures from +20 °C to +25 °C. Since the maintenance of such a narrow regime is difficult to achieve, approved deviations are defined allowing temperature fluctuations to occur in a wider range (+15 °C to +30 °C). In this case an MKT is calculated. If the gained values are within the defined regime of +20 °C to +25 °C, the goods are considered to be safe. No report on the temperature deviation occurrence is required; no investigation on the product quality will take place. Equally, should the temperature reach +40 °C but over a period shorter than 24 hours, or goods were subjected to exposures outside the +20 °C to +25 °C regime for more than 24 hours, but within the +15 °C to +30 °C regime all this time, the goods will be considered safe from harm.

The mean kinetic temperature is the calculated temperature which simulates the influence of different temperature deviations the product was subjected to during the monitoring period (storage and/or distribution). MKT represents isothermal temperature which simulates the effect of the real temperature within the observation period.

The MKT is calculated according to the following mathematical notation.

$$T_k = \frac{\frac{\Delta H}{R}}{-\ln\left(\frac{e^{-\frac{\Delta H}{RT_1}} + e^{-\frac{\Delta H}{RT_2}} + \cdots + e^{-\frac{\Delta H}{RT_n}}}{n}\right)}$$

In this formulation ΔH represents activation energy (typically from 60 to 100 kJ/mol for solids and liquids) in this case it is assumed its value is 83.144 kJ/mol. The R is universal gas constant and its value is 8.314472 kJ/mol. The temperature T_1 is the average temperature in degrees Kelvin during the first time period. The T_2 is the average temperature in degrees Kelvin during the second time period and T_n the average temperature in degrees Kelvin during the n^{th} time period. In this calculation it is assumed that intervals of data collection are identical during the observation period.

3. ANALYSIS OF TRANSPORT PROCESSES

The paper deals with a particular transportation in shipping pharmaceutical products from the warehouse in Zagreb, Croatia to the distribution center for the US market in Forest, Virginia. Commodity is bulk prepared tablets which need to be transported under controlled room temperature (agreed shipping temperature regime +15 °C to +25 °C). Transportation consists of trucking to and from the airport of origin and final destination and air transportation on Vienna, AT – Washington, US route. The average size of the ship-

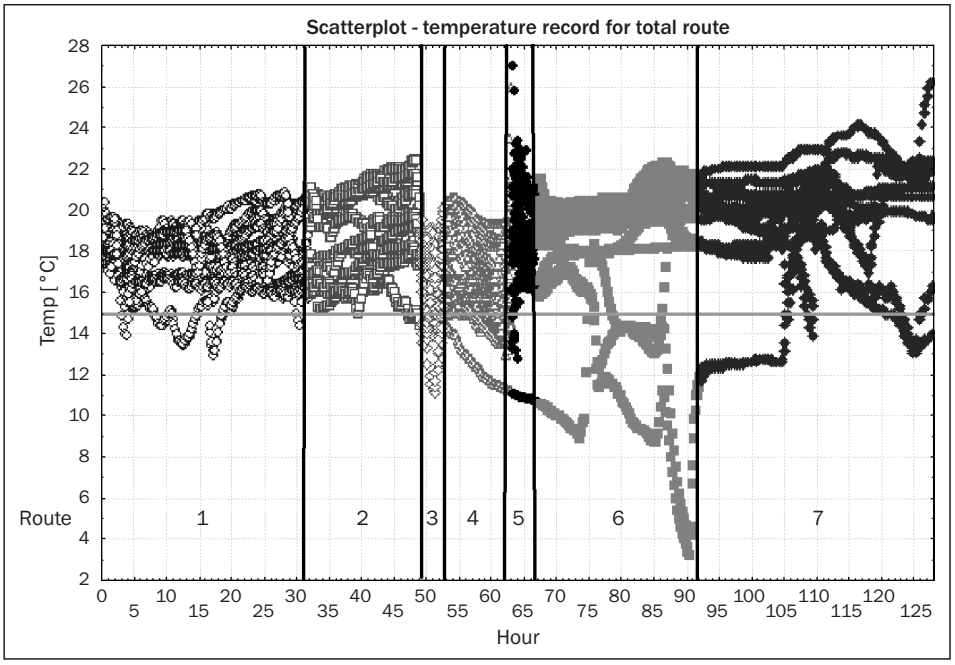

Figure 1 - Batch temperature record of all data loggers analyzed during the observed period

ment is 30 euro wooden pallets wrapped with nylon for additional protection. Each shipment is accompanied with two data loggers activated at the shipper's warehouse and deactivated at the consignees warehouse thus securing monitoring during the entire trip. Post realization analysis of the collected data is a prerequisite for the drug release process. A total of nine shipments was analyzed during the period from November 2009 till the end of January 2010. The evaluation consists of data collected from 18 data loggers. *Graph 4*.1 shows temperature records of all the shipments accomplished in that period. Temperature deviations are identified showing mainly lower than allowed temperature records.

Different sections in *Figure 1* (marked by numbers from 1 to 7) show records through specific phases in the transport process. The complete technological process can thus be divided into seven different phases or characteristic milestones of the process. Each of them can be observed separately since it consists of characteristic logistic and transportation processes. The first phase (*Figure 1* – section 1) is listed under number 1 in *Table 1*. The second phase, section 2 in *Figure 1* is the storage process at Vienna International Airport in Austria listed under number 2 in *Table 2* and so on. Trucking on route from Zagreb Airport to Vienna Airport is performed using cool trucks with a set temperature at +20 °C. The trucking to Vienna Airport comprises the short time between offload deadline and warehouse positioning (as per agreement between shipper and carrier) in order to minimize exposures which might occur during the warehouse storage at Vienna Airport. There is no controlled room temperature storage available at Vienna Airport. The total time spent between the truck offload and the aircraft loading is 11.5 hours. Approximately 4 hours positioning of the shipment prepared on the build unit load device[12] in the handling zone of the aircraft is included in this period. Total flight time might depend on the aircraft on route, weather conditions, total payload on the aircraft and route congestion. Published total flight time on this route for the particular carrier observed is 9 hours and 45 minutes. The offload process at the airport of final destination takes 4 hours after which the goods are stored in controlled room temperature provided by the refer positioned in the airport warehouse. During the storage, FDA and customs clearance is performed. Total transportation time which includes storage is 128 hours during which data were collected in 15-minute intervals.

Since there were considerable temperature deviations recorded depending on the phase of the process, each of the phases as listed in *Table 1* was separately analyzed in order to evaluate the potential risk related to each phase.

The Zagreb – Vienna part of the route is operated by cool trucks. Temperature set-up is +20 °C. *Figure 2* shows some deviations occurring in the batch picture of all records, but those were of short duration and related to the door opening for operational reasons (customs inspection). The average recorded temperature was +17.8 °C and standard deviation 1.4 °C. The record obtained during the observed period shows relative stability of temperature within the defined regime thus marking this phase of the process as a stable one with acceptable level of variation. Red broken lines in *Figure 2* represent the temperature margin for 95% of all transportations. Having the lower margin at around +15 °C it might be concluded that this part of the pro-

Table 1 – Route details including share of different transportation mode

Part of the route	Duration[13] (h)	Cumulative (h)
1 Trucking Zagreb - Vienna	32	32
2 Vienna Airport warehouse	17	49
3 Loading of aircraft (goods positioned for loading)	4	53
4 Flight Vienna - Washington	10	63
5 Positioning in Washington airport warehouse	4	67
6 FDA and customs import clearance	25	92
7 Delivery to the consignee's warehouse in Virginia	36	128

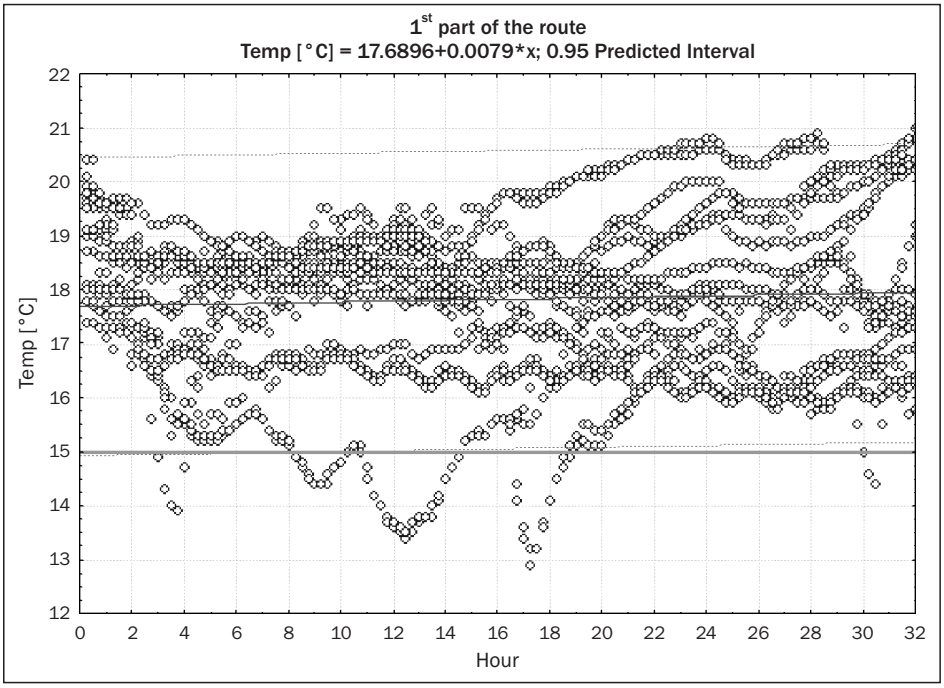

Figure 2 – Temperature records on Zagreb – Vienna route operated by cool trucks

cess does not represent high risk in temperature deviations. If the 17th hour is analyzed in particular as the one with the highest deviation, the value of standard deviation is 1.8 °C which may lead to a conclusion that there is high level of certainty the goods will not be exposed to the threatening temperature deviations. Moreover, the duration of deviations recorded proved to be short.

The second phase of the transportation process takes place at Vienna Airport. Transit airport Vienna does not have the infrastructure designed for storage under controlled temperature regime; however, it might be expected that indoor storage would provide sufficient protection to safeguard the shipment from environmental atmospheric conditions. *Figure 3* shows the record of all shipments realized in the observed period. The average recorded temperature was +18.7 °C with standard deviation of 1.9 °C which is within the requested temperature regime.

The third phase of the process as described in *Table 1* accounts for the processes related to the loading of the aircraft at Vienna Airport. Those might be considered as the most critical ones due to the fact that the prepared shipment is exposed to severe atmospheric conditions present at the apron. The shorter this process is the lesser is the danger the goods will be harmed by the atmospheric influences.

As presented in *Figure 4*, the temperature is dropping every hour by 3.4 °C on the average while the lower margin of the reliability is dropping towards +12 °C. The average recorded temperature is somewhat lower than in sequences observed earlier +16.4 °C, but with acceptable value of 1.9 °C in standard deviation. Most significant deviations occur during the 51st hour where the average temperature recorded is +15.6 °C with the standard deviation of 2.0 °C. However, these values still demonstrate high level of probability the goods will be exposed to the acceptable levels of deviations during this phase.

The fourth phase or sequence of the process represents recorded conditions during the flight on route from Vienna to Washington. Despite the fact that a

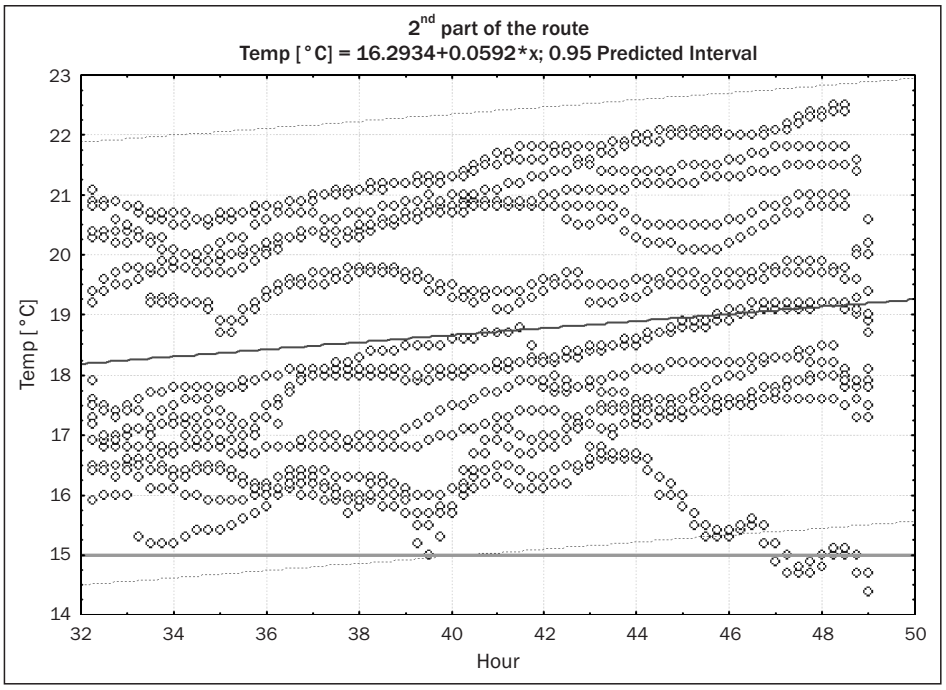

Figure 3 – Temperature records obtained during storage at transit station Vienna International Airport

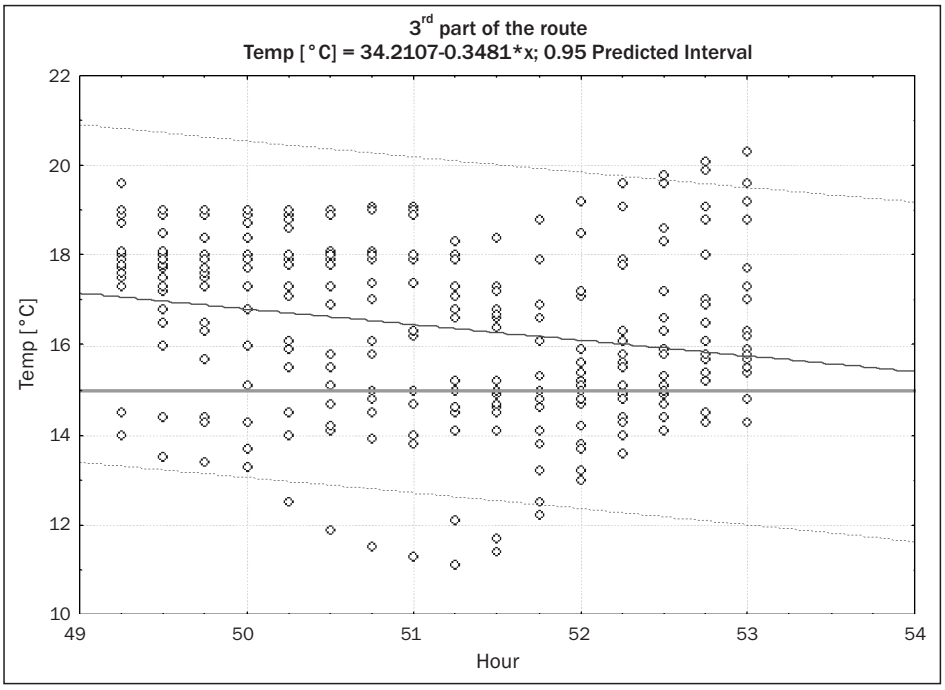

Figure 4 – Temperatures recorded during the loading of the aircraft at the apron

constant temperature drop has been recorded, its value of 0.1°C does not represent a significant impact since the cumulative value of 1°C might be recorded during the flying time. Aircraft on route was equipped with a system for maintenance of temperature but the accuracy of the temperature regime depends on the outside temperature the aircraft was exposed to during the loading process as well as on the profile of other load planned in the same aircraft hold. It has been noticed that the position within the hold itself plays an important role in maintaining a desired temperature level. Shipments loaded closer to the compartment door might be exposed to lower temperatures than those loaded on the positions far from the compartment door. Those however, might be subjected to the elevated temperatures due to the vicinity of the heating system source. During this phase in particular, the lower margin of the reliability interval of 95% is still around 12°C. This temperature was the exact value in which the phase before ended. Despite the fact that

the least of the deviations occurred during this phase, the connection between the protection of the goods under defined temperature regime prior to loading and the flight has been noticed.

The next phase in the process comprises aircraft offload at destination airport and positioning in the adequate storage. Records obtained during this process (*Figure 6*) show similar stability observed earlier (*Figure 4* and 5). The lower margin of the reliability interval of 95% is still low at approximately +12°C. This can be explained as an occurrence deriving as a consequence from the exposure of the goods to lower temperatures during the previous phase. Only less significant changes (temperature deviation of 0.05°C per hour) have been recorded during this phase probably due to its short duration which is even below the error margin of the measuring devices. Yet the standard deviation is higher than the recorded one so far. Its value is 2.8°C which is a consequence of the dispersed input data.

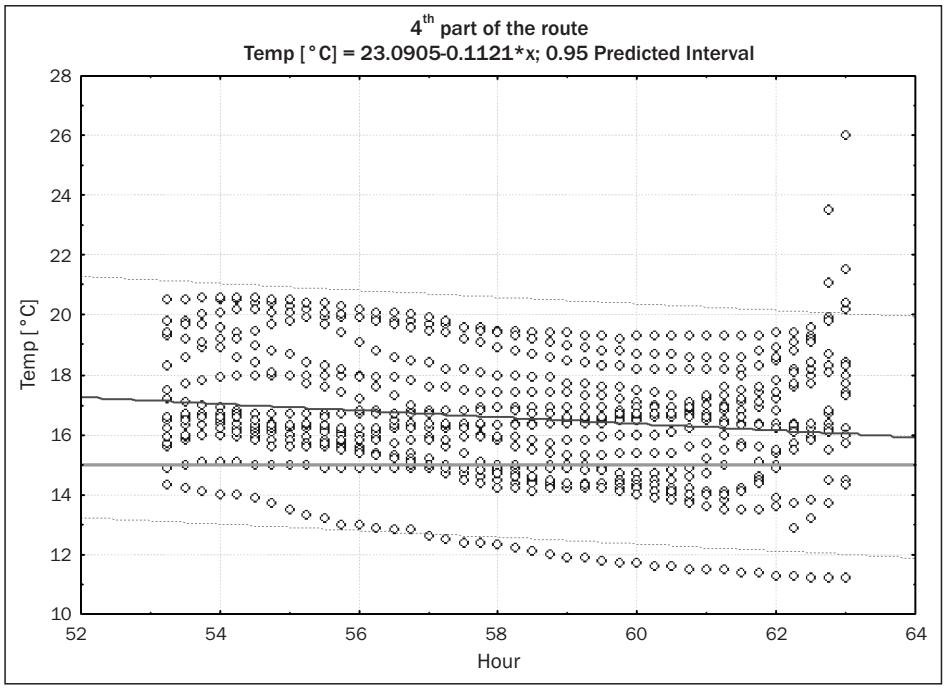

Figure 5 – Temperature records obtained during the flight on Vienna – Washington route

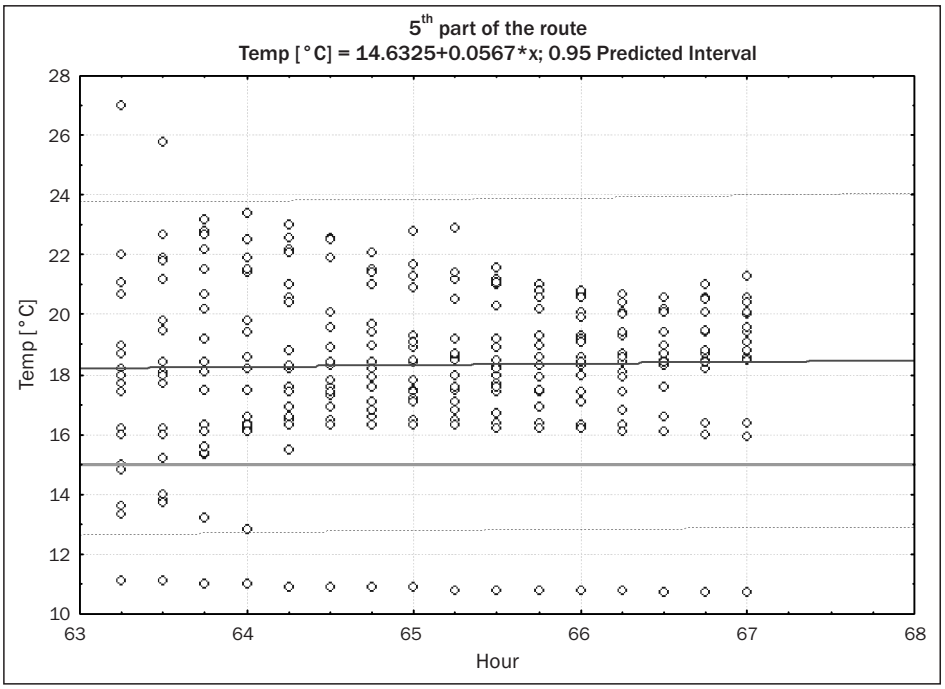

Figure 6 – Aircraft offload at Washington Dulles International Airport

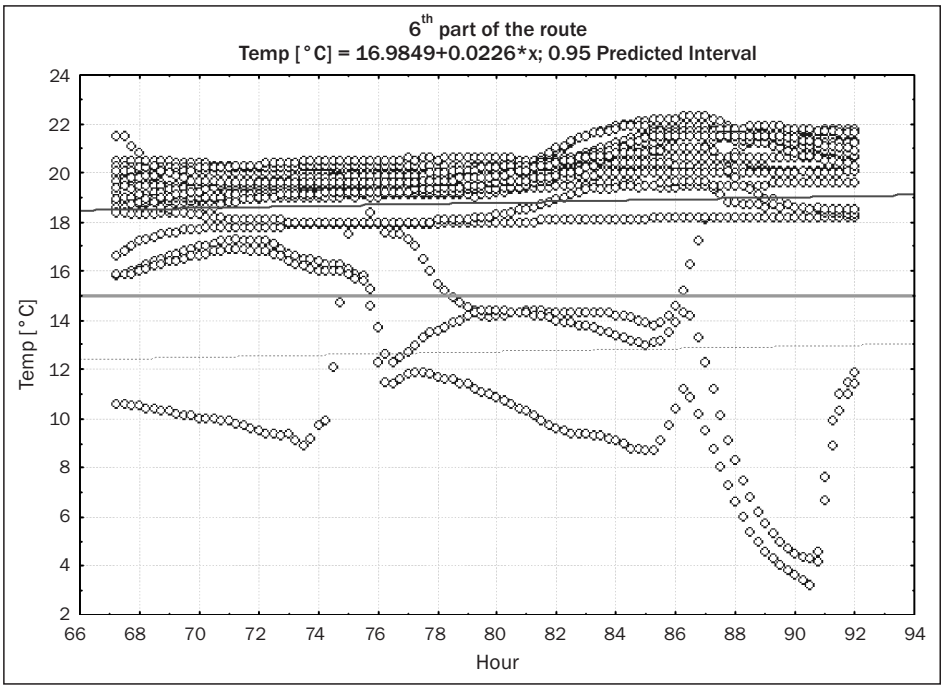

Figure 7 – Storage at Washington Dulles International Airport

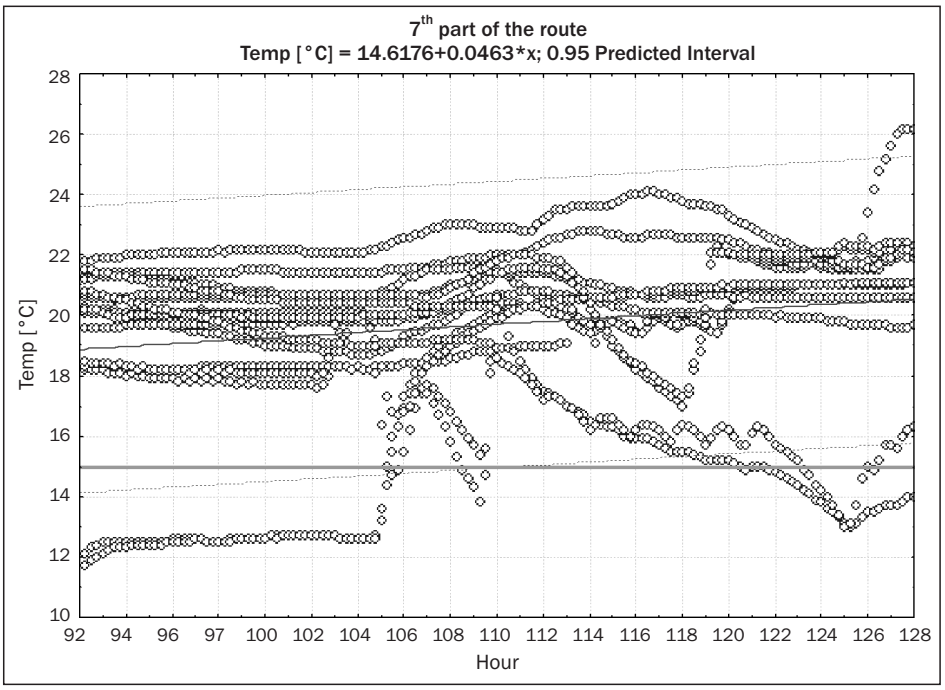

Figure 8 – Temperature recordings during road transportation from the final destination airport to consignee's warehouse

FDA and customs clearance is observed as the sixth sequence in the process. This part of the distribution chain might be considered as the critical one due to the process duration uncertainty. The shipment stays at the final destination airport until those processes are completed. Although the average recorded values are within the limits similar to the phases observed earlier, deviations occurred with significant values. The average temperature value is +18.7 °C but the deviations have peaks in the highest value so far. The minimal recorded temperature is +3 °C and the standard deviation value is 3.1 °C. Observing the 90th hour where the standard deviation has its peak at 5.1 °C, it might be concluded that this phase of the process represents the highest threat to the goods stability so far.

The final phase of the process consists in road transportation to the consignee's warehouse. According to the gathered temperature values an improve-

ment could be concluded compared to the previous phase; however, the standard deviation remains at high 2.4°C which is partly consequence of the dispersed input data. The average recorded temperature compared to the earlier phases is also elevated to +19.6°C. Deviations recorded are of a short duration and the lowest value reaches +12°C.

According to data available it might be concluded that the processes which include preparation of the shipment for the loading, flight and storage at final destination represent the highest risk to the temperature regime maintenance. The reason for this might be found in the complexity of this part of the distribution channel. A number of different stakeholders appeared in this phase of the process thus bringing the complexity of the processes to a higher level. In order to determine the level of risk each of the distribution phases is representing, the designed temperature mapping should be done for each infrastructure and transport means used. Mapping should be done for both winter and summer periods, thus marking the possible highest and lowest deviation temperatures the goods might be exposed to. Based on the conducted temperature profiling, processes should be designed and qualified to address the issues related to regulatory aspect as well as to quality assurance for the product being shipped. Such qualified processes should be evaluated periodically and questioned for their compliance. The technical solutions available on the market which could be used to solve the temperature deviations are often not cost-effective and thus seldom used. In addition, simple and relatively cheap solutions (compared to other technical solutions available) such as thermal blankets for aircraft pallets are not qualified for the temperature regime maintenance and therefore not considered as the ultimate solution.

4. CONCLUSION

Pharmaceutical products are time and temperature sensitive. A requirement to maintain the controlled temperature regime for certain pharmaceutical products during their distribution processes derive from the regulatory obligation stipulated by the national and international regulatory bodies. In general, GMP and GDP processes defined for these products comprise also defined storage and transportation conditions. Transportation should be thus considered as an extended storage during which a defined temperature regime should be safeguarded. The risk evaluation of the multimodal process described in the paper offers possibility to contemplate on the quality of used transportation means in terms of temperature stability. Cool trucking and controlled room storage where available could be considered as relatively stable distribution environment. Processes related to aircraft operations might be marked as less stable, as well as storage under uncontrolled conditions during the FDA and customs clearance.

As a solution to overcome these shortcomings, the use of thermal protection in form of thermal blankets or even isolated unit load devices might be considered. This however should be subject to previous cost-effectiveness evaluation. A separate research is suggested in this respect to show the effectiveness of one or the other technical solution used to prevent negative influence of temperature exposures. Particular focus could be put on the conditions to which shipments are subjected during the flight in order to determine the level of risk related to this segment of the distribution chain.

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SAŽETAK

VALORIZACIJA PRIJEVOZA FARMACEUTSKIH PROIZVODA ZRAČNIM PUTEM U UVJETIMA KONTROLIRANE SOBNE TEMPERATURE

Farmaceutska industrija je kao i zračni promet jedna od strogo reguliranih industrija današnjice. Prijevoz farmaceutskih proizvoda u definiranim vremenskim i temperaturnim uvjetima predstavlja izazov koji proizlazi iz regulatornih obveza i potrebe osiguranja kvalitete proizvoda. Dobra proizvođačka praksa mora se primjenjivati kroz ukupan distributivni proces, no propisane regulatorne obveze još uvijek nisu u punoj mjeri na snazi. Prijevoz se mora promatrati kao produženo skladištenje, međutim stupanj usklađenosti procesa ovom pitanju izvor nalazi u ekonomskim umjesto regulatornim aspektima. Rad prikazuje razlike između definiranih zahtjeva održavanja kontrolirane sobne temperature i realnih tehnoloških mogućnosti u zračnom prometu danas. Primjeri pokazuju slučajeve temperaturnih devijacija tijekom transporta. Obrađeni prijevozni zadaci prikazuju devijacije u zadanom temperaturnom režimu po pojedinim fazama obrade pošiljke. Predlažu se daljnja istraživanja koja za cilj imaju valorizaciju svakog pojedinog dijela distributivnog lanca.

KLJUČNE RIJEČI

dobra distributivna praksa, regulatorna pitanja, kontrolirana sobna temperatura, temperaturne devijacije, kvalifikacija procesa

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11. Data logger is an instrument designed to measure temperature, humidity, vibration or light exposure during distribution processes.
12. Unit load device, ULD - a pallet or container used for load on the aircraft. Part of aircraft equipment.
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[14] Republic of Croatia, Ministry of Health and Social Welfare: "*Zakon o zdravstvenoj zaštiti*", Zagreb, July 2003

[15] Republic of Croatia, Croatian Parliament: "*Zakon o lijekovima*", Zagreb, June 2007

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