Short study

Value creation by the pharmaceutical wholesaling industry by means of superior delivery capacity when compared with direct sales by the pharmaceutical industry

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Contents

1. Starting hypothesis and goal setting

In the context of the pharmaceutical supply chain, which has been extensively described and systematically investigated in a wide range of publications and studies, the pharmaceutical full-line wholesaling sector fulfils a central role. An expert report has been commissioned by the European Association of Pharmaceutical Full-Line Wholesalers (GIRP) and carried out by the Institute for Pharmacoeconomic Research, Vienna (IPF), to illustrate the economic value added offered by the European pharmaceutical full-line wholesaling sector. Within the framework of this expert report, the Institute for Pharmacoeconomics and Medication Logistics (IPAM) at the Wismar University of Business, Technology and Design has been commissioned to conduct a specific analysis focusing on the importance of the immediate availability of medicinal products for patients. The present study aims to complete the picture of the pharmaceutical, medical and economic value contribution the pharmaceutical full-line wholesaling sector makes through its superior capacity to deliver medicinal products to patients.

The IPF expert report reveals that pharmaceutical full-line wholesalers, with their very closely meshed network of branches, are in a position to deliver the required and ordered medicinal products to a pharmacy in an average time frame of 4.53 hours (according to the perceived delivery time data collected through pharmacy questionnaires) or even 2.66 hours (according to wholesalers and taking pharmacies' opening hours into account). By comparison, the pharmaceutical industry's direct delivery services need 57.94 hours on average to deliver the products (according to the pharmacy questionnaires). This yields a difference of 53.5 hours or more than 2 days. The time discrepancy is the result of the use by the pharmaceutical industry of a logistics model based on centralised warehousing (in a country such as Germany this typically means 1-2 warehouses) and the relatively infrequent deliveries to pharmacies.

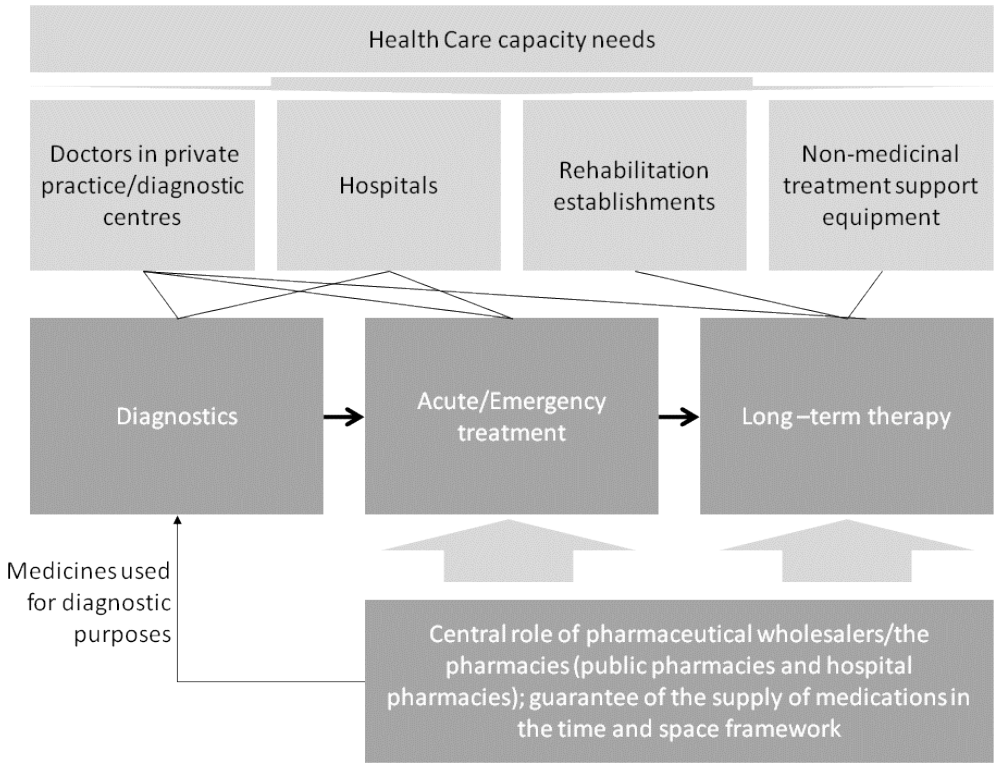
In countries where pharmaceutical full-line wholesalers are active, the intricate logistics network maintained by them, which is responsible for their outstanding ability to deliver the goods, is much more efficient, but at the same time cost-intense due to the large number of branches and personnel resources. If delivery times of more than two days would theoretically be sufficient, it may be reasoned that current service

levels of pharmaceutical full-line wholesalers are higher than necessary to an extent that, to the knowledge of the authors, hardly exists in any other branch of commerce. It is obvious that this high service level is necessary for the healthcare system. Pharmaceutical full-line wholesalers have adopted the existing model because it has a superior ability to supply the demands of patients Therefore, the value of the high capacity to deliver is not only to be measured in pharmacy-based financial ratios, but also in terms of the healthcare of the population.

High standard medical care provision is always based on the interaction of the availability of diagnostic capacity (doctors in private practices, possibly also hospitals, radiologists, laboratory capacity, etc.), and therapeutic capacity (doctors in private practice, possibly also hospitals and other service providers such as non-medicinal goods supply specialists, etc.; Figure 1). The importance of the regional availability of all the elements of care provision is widely accepted and is also the declared aim of the healthcare policies in many countries. So, it is a common political demand that the availability of doctors in private practice should be increased or maintained in rural areas. This is obviously not a cost-minimising strategy in terms of logistics, but one which ensures the timely provision of medical care. It can even be considered a cost-effective strategy if one takes into account all healthcare costs in the event that some diagnostic/therapeutic facilities would not be easily available (e.g. costs of additional hospital admission). Developments such as the decrease of the network of doctors in rural areas are uniformly highly sceptically observed by politicians and the whole population, and result in an increase in efforts to promote the settlement of more pharmacies in these regions. The closure of regional hospitals is also regarded with disfavour.

Quite similarly, the well-timed and geographically appropriate availability of a medicinal product is a necessary element in the healthcare provision to patients, and thus provides an example of a situation where not only a “simple” financial ratio explains “everything”. The necessity is shown by the fact that medications form part of the therapy of almost all diseases. In a database search, IPAM was unable to find any evidence-based guideline for the treatment of diseases in which medication did not play a certain or even a major role.

Figure 1. The importance of the pharmaceutical wholesale trade in the value chain of the healthcare market



To this extent, the logistical achievement of pharmaceutical full-line wholesalers can be measured in their ability to provide urgently required medicinal products, which are not stored in pharmacies 2 days earlier than is possible in alternative direct delivery models. This is a care provision element that is central to the healthcare provision to the populations of the countries under consideration. In support of this line of argument, the care provision structure in developing countries often lacks a network of pharmaceutical full-line wholesalers. This has been critically evaluated. The lack of immediate availability of medicines has been found to have led to serious health problems.[1] It is therefore evident that the pharmaceutical full-line wholesaling sector cannot be compared to wholesaling in other branches, because

- It typically follows a pack-by-pack micro logistics approach instead of a bulk approach, and
- The consumption of medicinal products is more need-driven and more critically time dependent than it is the case with most other products.

[1] J Jitta et al. (2002) using Uganda as an example Cent Afr J Med. 1994 Oct;40(10):291-2; F Tobar et al. (2008) using Latin America as an example; Salud Publica Mex. 2008;50 Suppl 4:S463-9.

The purpose of this expert report is to measure the pharmaceutical, clinical and as far as possible also the economic advantages that can be obtained by being able to deliver the required medicinal products to pharmacies exactly when needed. The economic advantage of the pharmaceutical full-line wholesale distribution model is only partly related to pharmacies; a possibly much more important part is the positive health gains that can be realised because of the immediate availability of medicinal products through the services of pharmaceutical full-line wholesalers.

Consequently, the questions addressed in this expert report can be listed as follows:

1. Are there differences in the delivery capacity of existing logistics models, and if so, which ones?
2. What is the clinical value of the rapid availability of medicinal products? Are there empirical data that show what negative clinical effects occur if medication delivery for medical treatment is delayed by minutes/hours/days or the continuity of availability is interrupted?
3. Are there data concerning how frequently the superior delivery capacity of the pharmaceutical full-line wholesale trade is actually required, because the pharmacies do not carry sufficient stock? Can such demand be broken down differently for more and less critically needed forms of medication?
4. Can the combination of the answers to the questions 1-3 be used to derive the positive clinical effects of the superior delivery capacity of the pharmaceutical full-line wholesale trade?
5. Can the answers to the questions 1-3 be quantified in monetary terms (Euros)?

2. Delivery capacity of the European wholesale trade in comparison with direct sales

The differences in the delivery capacity of the two models, measured in terms of the time gap between an order for a medicinal product being placed and its availability in a pharmacy (definition B as outlined in the methodology section), are taken from the IPF study.[2] The results of this survey conducted in five European countries (France, Germany, Spain, UK, and the Netherlands), can be summarised as follows:

- In these five countries, pharmaceutical full-line wholesalers deliver to pharmacies on average three times per day.
- According to the pharmacies, the full-line wholesaler delivery time is between 2.85 and 16.35 hours with an average of 4.53 hours.
- By contrast, the time taken by the direct sales delivery model (according to pharmacists) is between 26.0 - 97.63 hours with an average of 57.94 hours.

In so far, it is assumed for the purposes of this report that, following the receipt of an order from a pharmacy, the pharmaceutical full-line wholesaling logistic model is in the position to deliver medicinal products more than 2 days earlier compared to a direct sales delivery model provider.

[2] IPF (November 2011; Distribution profile and efficiency of the European pharmaceutical wholesale industry, interim report).

3. Analysis of the value of superior delivery capacity

Despite a detailed review and an extensive database search, evidence concerning the pharmaceutical/clinical effects of a delayed or interrupted intake of medication must be regarded as rudimentary. To derive from such data the clinical effects of a delay pre-supposes that a comparison of test groups (for example early versus delayed medication administration) is possible, but to date this has hardly been a feature of clinical studies. Research into evidence-based guidelines also shows that as a general rule an immediate start to treatment and immediate availability are assumed to exist.[3] Table 1 comprises a summary of the publications that have been identified as relevant.

- Nearly all of the publications that mention the start of medication therapy show the clinical value of starting in a timely manner. The fact that the evidence on this theme can be called rudimentary cannot be attributed to a failure to address the theme at all. It is more the case that in most clinical studies the importance of an early or delayed start to therapy has for the most part not been considered.
- In the area of HIV treatment, there is considerable evidence that interrupting treatment for as few as 24-48 hours is clinically extremely dangerous. Whether the interruptions were due to the patients themselves, the doctors, or even the non-availability of the products was as a rule not the focus of the investigations. Nevertheless, it is clear that a delay or interruption of treatment can lead to an increase in the infection and/or increases the risks of viral resistance, complications, or death.
- Various publications are concerned with the clinical evaluation of the importance of an early start to antibiotic therapy (antibiosis). These show beyond doubt the extreme importance of as early an onset of medication as possible. In stationary treatment, one investigation showed that in the case of sepsis, a delay in the introduction of antibiosis by one hour increases the chance of death by 7 percentage points, and that with 36 hours of delay there is a lethality of 100 per cent (Figure 3). Sepsis is a potentially deadly clinical situation that is characterised by a whole-body inflammatory state. A lay term

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[3] No guidline known to the IPAM deals with situations in which medical facilities/medicinal products are not available for more than 50 hours.

for sepsis is blood poisoning, also used to describe septicaemia.[4] Similarly, if less dramatic patterns have been confirmed for other diseases requiring antibiosis, for example pneumonia, meningitis, etc. Indeed, the logic of using antibiotics at all is to maximise the effects of doing so by having an early start.

- Scattered evidence about the value of a treatment standard that prescribes an early start to medication is also available for other indications (Table 1: antithrombotic therapy, antidotes, etc…).
- In sum, the available clinical evidence shows that a 2-day delay in the start of medication therapy is in principle unacceptable in numerous indications. If such critically needed medicinal products were not available in 4-6 hours, it is to be assumed that many patients would have to be admitted to acute inpatient treatment facilities. There is not any empirical data about how many patients would likely be affected or what costs they would generate.

However, apart from the publication concerning sepsis, none of the clinical publications provide very detailed data about the indication-specific effects of a delay in the onset of treatment of more than 2 days. Consequently, it is only possible to develop a model for the whole field which reflects in total the clinical consequences of a 2-day delay in the delivery of medications under the most vague and general of assumptions.

Table 1: Overview of the scientific literature concerning the value added by timely medication provision

Authors, year	**Source**	**Indication/ medication group**	**Focus of research**	**Results**
A Pasquet et al. (2010)	PLoS One, 15;5(10): e13414	Antiviral HIV therapy	Analysis of the effect of medication stock-outs on the interruption of therapy and patient mortality	Stock-outs have an independent capacity to explain the incidence of therapy interruptions and mortality
J Thorpe et al.	AIDS; 25(7):	Antiviral HIV therapy	Analysis of the effect of interruption of the ART therapy on the	Interruption of the ART therapy leads to a higher probability of the

[4] Source: Wikipedia.

(2011)	967-75.		progression of an HIV-HCV co-infection (hepatitis C)	progression of the observed liver disease and thus also to a higher mortality rate
J.W Bae et al. (2011)	Aids 25(3): 279-90.	Antiviral HIV therapy	Review: The effects of a therapy interruption on the antiviral treatment	A treatment interruption of 2-4 days (depending on the study; review of several publications) increases the probability of an increase in virus load and drug resistance; under most regimens, the treatment can be interrupted for a maximum of less than 6-12 hours (half-life of the medications)
A.R.E Fowles (1995)	Post-graduate Med, 97(5):135-138	Heart attack treatment	Summary; the research results on the importance of the early onset of anti thrombolytic therapy	Available data show that delay in using anti-thrombolytic drugs by 1-2 hours leads to a higher rate of complications/mortality
S.G Sakka et al. (2010)	Antibioti-ka-therapie in der Inten-sivmedi-zin, Deutscher Ärzte-Verlag, Köln	Antibiotic use in intensive treatment	The clinical effects of delayed antibiotic use on intensive treatment procedures	The early use of antibiotics markedly increases the survival rate in the high risk group (septic shock) described; every hour of delay increases the mortality rate by about 7 percentage points, until this reaches de facto 100% after 36 hours of delay
K.L Rodri-guez et al. (2009)	Jt Comm J Qual Patient Saf. 2009 Oct;35 (10):509-18.	Antibiosis in cases of pneumonia	Description of the clinical situation and evaluation of the beginning of the therapy	In many cases, the treatment was found to have been started too late; this was seen as having serious clinical consequences, without supporting data being presented

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J.M Pines (2008)	Emerg Med Clin North Am. 2008 May;26(2): 245-57, vii.	Antibiosis in specific indications/ diseases	Review of the importance of an earlier start to antibiosis in cases of emergency hospital admission	A variety of studies show the importance of early antibiosis (in terms of survival rates) in a number of illnesses that lead to emergency admission, including meningitis, pneumonia, and sceptic shock. However, an early start to antbiotic use could also be associated with medication overuse.
K.A Santucci et al. (1999)	Pediatr Emerg Care. 1999 Apr;15(2): 99-101.	INH toxicity in paediatric cases-	The availability of antidotes in hospital pharmacies	At most, only 50 % of pharmacies stock antidotes, and this increases the risk of treatment commencing too late

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Figure 3: Mortality rates in cases of sepsis/septicaemia; the role of the start of antibiotic therapy (from Sakka et al., 2010)

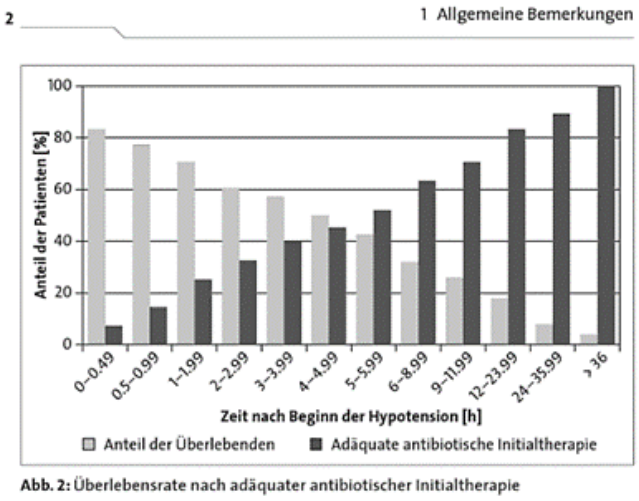


Abb. 2: Überlebensrate nach adäquater antibiotischer Initialtherapie

4. Relevance of almost immediately needed orders on demand in Germany

This study analysed data gathered by 106 German pharmacies on a package-by-package basis over an average period of 2.3 years. Data from these 106 pharmacies were available, because the IPAM is currently supporting these pharmacies in improving their replenishment. This data was anonymised to conduct the analysis described herein. Based on available turnover data, the pharmacies are representative of the average German pharmacy. Each ordered package was allocated to one of two categories; part of a regular order to stock or an almost immediately needed order on demand, based on current demand (and supported by the handing in of a prescription or a customer requesting a product). The alternative active ingredients in the products were classified in a very detailed manner into the internationally accepted ATC ("anatomic therapeutical chemical") groups (7 digits lead to 1 314 medication groups and, in more aggregated form, 5 digits of an ATC code lead to 478 medication groups and only 4 ATC digits lead to 192 medication groups). The codes with 4 digits were used to characterise the pharmaceutical nature of the active ingredients; the other codes were not used. Therefore, analysis was based on 192 different medication groups with specific order on demand quotas for each medication group.

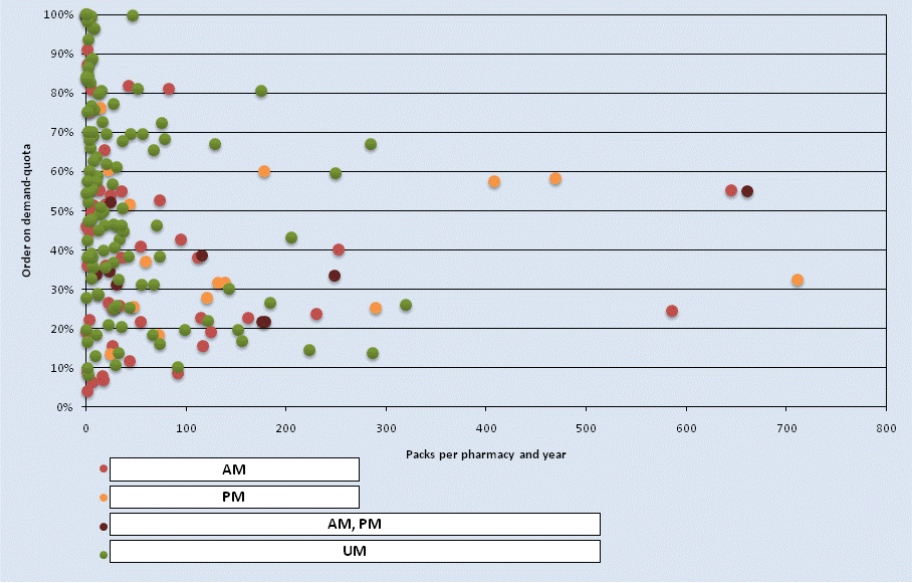
Appendix 1 shows the results in tabular form. The percentage of orders on demand varies according to the active ingredient group; they form between 4 % and 100 % of the total number of orders. The average is 30.3 %. The data shows that urgently requested orders are extremely important to German pharmacies. If it is assumed that each package ordered on demand affects one specific patient, the data indicates that, through these 106 pharmacies over 2.3 years, around 3 million patients were involved, but as certain patients are probably recipients of more than one package, the real number is likely to be somewhat lower. Nevertheless, per pharmacy and year, 12 247 patients are dependent on the superior delivery capacity of the full-line wholesalers and would have to wait 2 further days for their medication under the direct sales model. On the basis of the smaller range of available medications in other European countries in comparison to the German situation, the number of almost immediately needed orders on demand is likely to be smaller in these countries as well. The IPAM is aware of projects giving rates of 5-10 %; by comparison to the analysed German pharmacy, this would still mean that in the other

European countries between 2,000 – 4,000 patients per pharmacy and year are dependent on the delivery capacity of the pharmaceutical full-line wholesalers to ensure their health.

5. Simulation of the clinical/economic value added by superior delivery capacity

Appendix 1 shows the results of the pharmaceutical classification into the medicine groups, which are acutely needed (AM), long-term (PM) and on a mixed basis (AM, PM), formed by those active ingredients that fit into both former groups and a fourth group containing less acutely needed active ingredients (UM). To generate the table in the appendix, the evidence cited in this expert report has been combined with independent pharmaceutical expertise. The data show that the acute group is also affected by urgent orders; for this group, the data set shows an average order on demand quota of about 27 %. Figure 4 classifies all the 4-digit-ATC groups under consideration on the basis of their pharmaceutical class, the observed percentage of urgently needed orders on demand, and the number of packages per pharmacy and year.

Figure 4: Order statistics and the pharmaceutical classification of the medications dispensed in 106 German pharmacies



The existing clinical evidence is not applicable to all cases to clearly describe the number of complications for a 2-day delay in the commencement of medication. The authors of this expert report have decided to conservatively estimate the economic value of the superior delivery capacity of pharmaceutical full-line wholesalers (Figure 5). This is necessarily rough and the assumptions must be taken into consideration:

- For all the medicinal products classified as UM, it is assumed that a 2-day delay in delivery will not have any negative effect.
- In the case of medication that is acutely needed (AM), it is assumed that every 100th patient (1%) would have to be admitted to hospital as a result of getting the required medicinal products 2 days later. This could occur due to the worsening of symptoms or because of the need to initiate stationary treatment. The corollary is that 99% of patients are assumed, for whatever reason, to be able to cope with a 2-day delay.
- In the case of PM medicinal products, it is assumed that only 20 % of the patients do not have reserve supplies of medicines available in a quantity that would allow them to bridge a 2-day gap. Again, a hospitalisation rate of 1 % is assumed to result from a lack of product availability in this 20 % subgroup of patients.
- Medicinal products initially classified as mixed were on a pack-by-pack basis reclassified into 50% AM and 50% PM.
- The average hospital stay is assigned a cost of 2,935.78 €, the base case cost in Germany in 2010. This cost covers the whole inpatient treatment with an average case mix index of 1.0.

From the point of view of the authors, the resulting quantification is to be regarded as extremely conservative, for the following reasons:

- It is exceptionally optimistic to assume that in 99 out of 100 cases the non-availability of medicinal products, which are needed for acute or long-term treatment, will not cause either doctors or patients themselves to take counter-measures. It is probable that considerably more admissions to stationary treatment or more visits to prescribing doctors would take place. Many doctors and pharmacists would be likely to recommend to patients to admit themselves to hospital, both on medical grounds and because of their legal position (doctors and pharmacists will be afraid of recommending a delayed

start of treatment, so the risk-minimising strategy will be admitting patients to a hospital).

- In this expert report, the economic costs are limited to those accruing due to an additional need for hospitalisation. In health economic evaluations, two other cost categories resulting from diseases/medical complications are discussed: indirect costs resulting from productivity losses of patients and intangible costs resulting from a diminished quality of life of patients and their relatives. These two latter cost categories are not considered in this report.

Figure 5: Value added by pharmaceutical full-line wholesalers by means of superior delivery capacity using Germany as an example

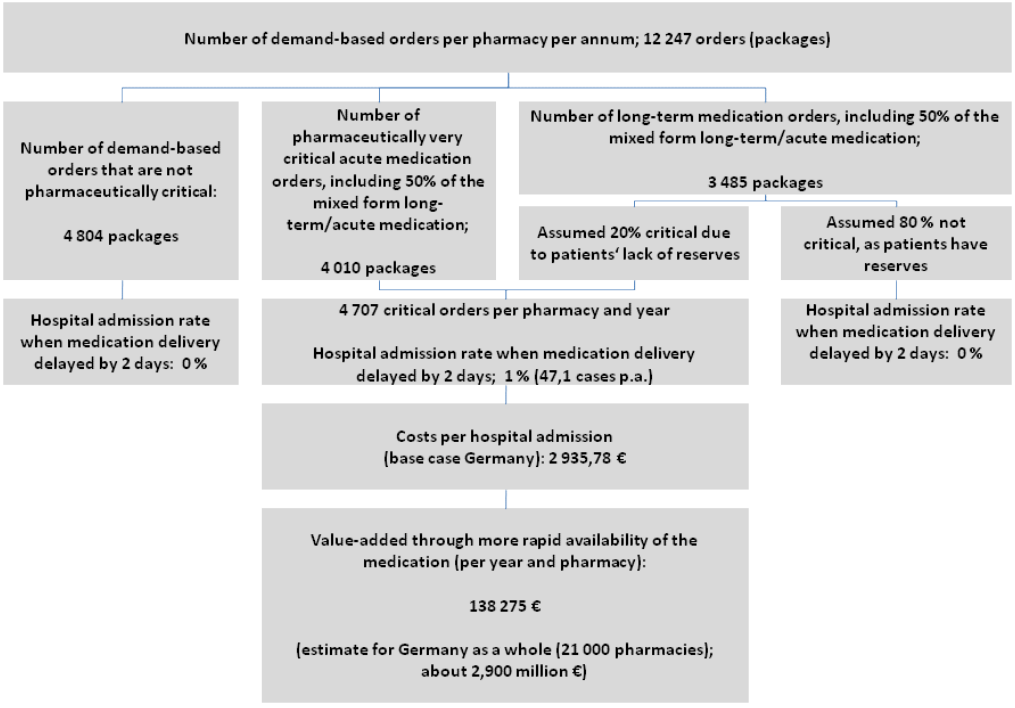


Figure 5 shows that on the basis of the available data, an absolute minimum of 4,707 orders per pharmacy and year in our observed 106 German pharmacies are critically needed from a pharmaceutical perspective. At a hospitalisation rate of only 1% due to medication non-availability, at least 47.1 people per pharmacy and year would be admitted to hospital on these grounds alone. Thus, the value added by the delivery capacity of the pharmaceutical full-line wholesale sector, interpreted as the non-occurrence of these admissions, is at least 138,275 € per pharmacy and year. If this

figure pertains to all the 21,000 non-hospital pharmacies in Germany, this is a value of approximately 3 billion €.

6. Summary of the results

The analyses contained in this expert report show that the pharmaceutical full-line wholesaling sector generates considerable added value because its delivery model is able to deliver urgently needed medicinal products at least 2 days earlier than is the case with direct sales. If the majority of the medicinal products presently supplied by pharmaceutical full-line wholesalers were in reality to be available 2 days later than originally needed, the result would be a considerable decline in healthcare and higher costs. Furthermore, bundling effects provided by the wholesalers would no longer exist; increased delivery costs and increased ordering efforts, as well as higher financial efforts to increase stock levels for pharmacies would be the consequence.

The discussion about the costs of pharmaceutical full-line wholesaling must be conducted with regard to its function in supplying the population with urgently needed healthcare resources. If medicinal products were not available within a few hours – and this is only possible through pharmaceutical full-line wholesalers – a large number of clinical guidelines would have to be revised, as the existing ones are based on the desired medicinal products being available in the short term instead of two days.

In this expert report, a demonstration of the value added by the pharmaceutical full-line wholesaling sector can only be made in a very cursory way. However, it is improbable that the clinical evidence concerning the consequences of a delay of medication therapy by 2 days will improve; the capacity to clearly derive the clinical effects of a delay in medication commencement of 2 days by the use of test groups formed per medication group is neither financially nor morally possible.

In this report, an exemplary analysis of sales data of 106 German pharmacies showed that, on the basis of the available data, an absolute minimum of 4,707 orders per year in our observed pharmacies are critically needed from a pharmaceutical perspective. With a hospitalisation rate of only 1 % due to medication non-availability, at least 47.1 people per pharmacy and year would be admitted to hospital on these grounds alone. Thus, the value added by the delivery capacity of the pharmaceutical full-line wholesale sector, interpreted as the non-occurrence of these admissions, is at least 138,275 € per pharmacy and year (based on average costs per hospital stay in Germany). If this figure pertains to all the 21,000 non-hospital pharmacies in Germany, this is a value of approximately 3 billion €.

The pharmaceutical full-line wholesaling model in its present form is the only existing model to provide a service-level that is seen as necessary for the provision of vital medicines to the whole population. An example of such vital medicines are potassium iodide tablets, which must be administered to the population in case of nuclear catastrophes and therefore must be constantly available. In France, the government has signed a contract with French pharmaceutical full-line wholesalers[5], binding the wholesalers to hold both temporary and permanent stocks of potassium iodide medication. Full-line wholesalers must guarantee that stocks are accessible within 3 hours (7 days a week; 24/7), everywhere in France. In addition, they must ensure accurate reception and proper storage facilities in accordance with contract requirements. The contract stipulates that warehousing facilities must be strategically positioned all over France, ensuring, in case of emergency, the immediate availability of at least one tablet of 65 mg of sodium potassium per inhabitant. This guarantee can only be given by the existing logistic model of pharmaceutical full-line wholesalers.

In many European countries, the pharmaceutical full-line wholesaling sector employs a logistics model that can be described as complex in terms of the number of branches, number of deliveries per day, etc. However, this is the model that ensures access to medicinal products in the area of activity of pharmaceutical full-line wholesalers in the shortest possible time period. It is impossible to achieve this by using the direct sales model in its present form.

In conclusion, it can be said that the immediate availability of medicines is one of the many benefits with which full-line wholesalers contribute to the functioning of healthcare systems and their financing.

[5] SIRET 130 004 310 00038; Contract between Public Administration in 21st avenue French stadium Saint Denis La Plaine 93218, Paris, and French full-line pharmaceutical wholesalers.

7. Methodology

To the knowledge of the authors, there is no study that has answered the questions posed in this expert report. It was decided on time and capacity grounds not to collect primary data. In consequence, this expert report relies on the use of already published/otherwise available secondary data. For each of the questions addressed, it was necessary to follow a specific methodology, described as follows.

Question 1: Are there differences in the delivery capacity of existing logistics models, and if so, which ones?

The delivery capacity of a logistics organization can be described in terms of two dimensions:

- A) The number of medicinal products that can be delivered immediately (which the pharmaceutical wholesaler has “on stock”);
- B) For each delivered batch, the time between sending an order in a pharmacy and the delivery of a specific medicine pack.

It is dimension B) that is the focus of this study. Differences between the alternative models in dimension B) have not been independently researched in this report. Instead, the figures have been taken from an interim expert report of the IPF, assembled through the questioning of pharmacists. Neither the plausibility nor the reliability of these figures forms a focus of this expert report.

Question 2: What is the clinical value of the rapid availability of a medication? Is there empirical data that shows what negative clinical effects occur if medication delivery for initial treatment is delayed by minutes/hours/days or the continuity of availability is interrupted?

The complex theme concerning the pharmaceutical/clinical value of the earlier commencement of medication therapy or the avoidance of a longer interruption of medication therapy was investigated by means of a systematic review of the literature contained in the database Pubmed and Medline. Among others, the following search terms were used:[6]

[6] Because the literature search was done in German and English, the German search terms are also listed.

- Early medication/drug therapy [frühe Arzneimitteltherapie];
- Early initiation of medication/drug therapy [frühzeitiger Beginn der Arzneimitteltherapie];
- Value of early medication/drug therapy or early initiation of drug therapy [Wert/Bedeutung eines frühen Therapiebeginns];
- Early start of therapy [früher Start der Therapie].

All the existing scientific publications were then examined for relevance. The contributions judged to be relevant according to their abstracts were read in the full text version by two of the authors. The results of these publications are summarised in tabular form in this report. The normative pharmaceutical, clinical and economic aspects of the publications are documented as “outcomes“.

Question 3: Is there data concerning how frequently the superior delivery capacity of the pharmaceutical full-line wholesale sector is actually required, because the pharmacies do not carry sufficient stock? Can such demand be broken down differently for more and less critically needed forms of medication?

The potential of the higher capacity to deliver evident in the wholesaling model only has its most positive effect for a patient if the order under consideration is one where the need for the medication is almost immediate (order on demand). The so called order-on demand quota measures how many packs (out of all ordered packs) were urgently needed by patients (either because of a patient OTC demand or because of a prescription handed in by the patient). In a dynamic perspective, a pharmacy`s order on demand quota depends positively on the total number of medications available in the country and the delivery capacity of the wholesale sector, for the more able wholesalers are to deliver the goods, the less critical it is for pharmacists to make storage provision.[7]

In the experience of IPAM, orders on demand form 20-40 % of the German market, where the range of medications available (more than 100,000 different products) is

[7] It would only be possible to fully explore the above-mentioned roughly sketched dynamic effects by means of a detailed model. This study instead follows a static approach, probing the importance of almost immediately needed orders on demand in practice. That means that possible changes in pharmacy stock levels (number of medicines) because of the existence/non-existence of a full-line wholesaler are not taken into account. To date, reliable data concerning even the static approach has scarcely been published.

the largest (compared with other European countries). In other countries, order on demand quotas of 5-15 % are more common.

In this study, the percentages of urgently needed orders on demand were estimated on a package basis in 106 German pharmacies over an average period of 2.3 years. Pharmacy data was available because the IPAM is running a project with these pharmacies in order to improve their replenishment. Data were only analysed in an aggregated and anonymous form. The packages were allocated to ATC medication groups, and then with the assistance of pharmacists, into the following groups:

- Pharmaceutically uncritical medications (UM), where a delay of 2 days in delivery was not necessarily to be regarded as critical;
- Pharmaceutically highly critical acute medication (AM), where a delivery delay of 2 days is very critical and in principle unacceptable;
- Long-term medication (PM), where the interruption of supply can lead to critical results if the patient does not have reserve supplies and a delay of 2 days exists. The evaluation of this group of medicines depends on the actual situation of the patient, but this study does not include data concerning this topic.
- Mixed forms (AM, PM), which are used as both acute and long-term therapy.

The analysis outlined above is not based on the records of individual patients, and in consequence can only generate an early guideline. In this context, it is important to mention the limitations of the method:

- In the case of long-term therapy, the authors are unaware of any study that quantifies how many patients lack reserve supplies of medicinal products that would last for 2-3 days when they ask for such medicines in a pharmacy or hand in the relevant prescriptions. In these cases an immediate availability of the products is not needed.
- The division into critical/uncritical medicinal products by means of ATC codes based on a pharmaceutical review is necessarily very rough and cannot replace a detailed analysis made on a patient-by-patient level. Medications described in this expert report as uncritical can indeed, in a specific context, be of critical importance and the reverse case is also true.
- In any European country, unavailable medicinal products can to a certain degree be substituted in the pharmacy by available ones with the same or

similar active ingredients. How far such substitutions would have been possible in the case of the almost immediately needed orders on demand under consideration is unknown. In many countries, the law obliges pharmacies to carry a minimum supply of critical medicinal products. It is to be assumed that these supplies are accessed to fill the most critical orders on demand. However, this is already the case nowadays. So, orders on demand in our dataset cannot include these medications.[8]

- Particular groups of patients, for example those released after the acute treatment phase in a hospital or patients who receive emergency supplies from a hospital pharmacy, cannot be considered because it is not possible to relate the almost immediately needed orders on demand to a specific patient.

Questions 4/5: Can the combination of the answers to questions 1-3 be used to derive the positive clinical effects of the superior delivery capacity of the pharmaceutical full-line wholesale sector? Can the answers to questions 1-3 be quantified in monetary terms (Euros)?

This expert report aimed to prove the importance of the pharmaceutical wholesaling sector, by using Germany as a reference case. The two above mentioned questions dealt with clinical evidence concerning the importance of an early start to medication therapy in a particular medicinal product group and the quantitative importance of urgently needed orders in different medicinal product groups. The answers to these questions are meant to show the superior delivery capacity of full-line wholesalers from an economic and monetary perspective. For this purpose, simplified assumptions are used, as the detailed data concerning patients/cases is not available. In particular, we assumed that a hospital stay induced by a delayed start of medication treatment causes costs comparable to the average costs per hospital stay in Germany (Case Mix Index of 1.0).

In a technical sense, this study does not take into account second-line effects of a scenario without any full-line wholesalers. For example, if pharmacies would need to

[8]It cannot therefore be argued that the percentage of almost immediately needed orders on demand given in this expert report overstates the importance of the delivery times.

rely on direct deliveries only, they would probably increase the number of stocked products and the stocked value. Consequently, costs resulting from these second-line effects (higher stock costs/stock losses; higher process costs) are also not included into this study.

Prof. Dr. Thomas Wilke

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