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OPTIMAL DESIGN OF PHAREMACEUTICALS SUPPLY CHAIN

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ABSTRACT

It is very known that the availability of drugs is the major problem faced by patients. Therefore, this article deals with the optimization of a pharmaceutical supply chain, i.e. we need to reorganize the entire current pharmaceutical network with a main objective of no patient suffers as long as the medicine exists somewhere. Achieving this requires a strategic organization of the geographic network in order to gain a better distribution. It is based on the information that must be received after a general study on the entire health sector in a specific area. The problem is formulated in a nonlinear model (MINLP) and in order to solve it we resort to using optimization solvers to show the effectiveness of this approach

Keywords: Supply chain; optimization; medicines; pharmaceutical network; distribution.

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1. INTRODUCTION

According to the World Health Organization, "Any pharmaceutical policy aims to develop, within the limits of national resources, the potential aptitude of pharmaceutical products to control common diseases and to mitigate suffering".

The drug industry gather little pharmaceutical companies, their supply chains is a complex structure because of customer requirements, traceability, time limit of consumption, the choice of therapy forms, marketing and distribution.

The pharmaceuticals supply chains PSC refers to the circuit of drugs from production to distribution, in other words from the laboratory to the patient via wholesalers, distributors and pharmacies.

The PSC is a multi-service organization working for a single purpose; to appease the patient while having his share of gains.

The PSC is very complex and difficult to manage than other chains owing to specifics methods to conserve many drugs, for example, insulin requires a refrigerator while Doliprane can be stored in an ambient temperature... Drug consumption is the only way to know if the product P is destined for that patient C. The PSC is very important compared to other chains because of its impact on the life of the individual.

In order to reach the customers, pharmaceutical products move through multiple players, which constitute a supply chain (SC). The complex and dynamic nature of relationships and competition among these members as well as the uncertainty at different levels of PSC requires the use of advanced while efficient optimization techniques to provide a great suite for informed decision making. Therefore, it is essential to have a solid understanding about the pharmaceutical industry and the mechanisms by which this industry works.

In Sousa et al [20] the study aims to provide useful information about the context of pharmaceutical supply chains as well as key characteristics of this industry.

Rodrigues [17] shows in his work, the possibility to reduce travelling costs, allowing the generation of the not greater quality services and hence improving customer satisfaction.

In this work we will try to optimize the overall drugs costs. In the first part, we will see some generalities of the pharmaceutical supply chain, later we will present our problem, the method of resolution and discussion.

2. STATE OF ART

1. Generalities on the supply chain:

The pharmaceutical supply chain occupies a significant part of the global industry because of its impact on the health and even the life of the individual.

Health is not only a fundamental universal right, but also a major resource for social, economic and individual development.

The objectives aimed by the drug policy are complicated. The patient is penalized by the disruption of the drug distribution chain. Distributors are affected by the problems encountered by the laboratories, including the concomitant sale that led distributors to retain drugs to facilitate sales and compel pharmacists to buy nightingale products by various means and to favour pharmacists according to their turnover, which goes against the pharmaceutical ethics that must ensure the drug to the patient. [4]

Shortages and waste are due to failures in the drug supply system that affect health or economics because total health expenditure is determined by drug purchases and the development of access to essential drugs requires the reliability of a supply system.

The management of the pharmaceutical supply chain is complex and different from the manufacturing supply chain; it is not possible to have a centralized structure (a platform that delivers directly to patients). In terms of requirements on quality and traceability, as well as on seasonality and variability of demand, the pharmaceutical and agri-food logistics chains are similar but they diverge immediately on the large price difference of the drug, the rupture of stock, waste [18].

Physical structure and decision making can be centralized or decentralized. Indeed the physical structure can be centralized in the sense that a supplier delivers directly to the care units without going through the wholesalers while the decentralized decision is that each link in the chain tries to minimize its cost, whereas, the centralized decision it is a whole set of links that tries to minimize the overall costs. Several companies have adopted the multi-step optimization method thanks to its strategy and its reduced cost.

The comparison to the decentralized setting, centralized decision-making creates more economic profitability for the entire PSC. Nevertheless, joint decision-making does not necessarily result in more benefit for the two PSC members. Moreover, the proposed centralized model optimizes the decision variables in order to maximize the economic profitability of the whole PSC and may not satisfy the required fill rate for the patients. In pharmaceutical supply chains, due to their responsibility towards society, it is of high importance to consider social consequences of decisions in addition to the costs or benefits of those [13].

In development of a dual-purpose MILP model for a multi-product and multi-period supply chain network design problem in which strategic decisions (numbers, locations and production technologies of secondary manufacturers, numbers, locations and capabilities of key developing countries). As well as the number and location of local CDs;lk and tactical decisions (ie product flows between institutions at different levels in each period) are taken into account simultaneously [11].

Most mathematical models of PSC allow for an adequate conceptualization of the structure and the behavior of a supply chain and the conditions must under consideration for a given problem. The models do not adequately specify current unit operations or future production technology’s options, and are unable to answer critical questions about alternative products or processes technologies [19].

The current geographic distribution of pharmacies in the national territory ensures the availability of drugs to populations in an anarchic way.

The work we present in this article aims to address the problem of a real industrial case. We sought to optimize overall costs. To do this we will reorganize the entire circuit of the pharmaceutical network of the city of Tlemcen for a better distribution of drugs by opting for multi-echelon optimization.

Several companies have adopted multi-level optimization method owing to its strategies and its low cost.

a- Supply chain design :

Supply chain design responds to a need for businesses to meet changing and unpredictable customer demand with limited resources and complexity, as both system components and modeling need to be mastered to reduce costs: production, storage and transport costs.

Supply chain design issues are often complex because of their direct relationship to the economic, organizational and social sector. For this reason, industrial companies and the scientific community are attracted by the design of an efficient logistics network [3].

A good design of the supply chain (production, distribution, location / allocation, choice of suppliers) ensures the flexibility, reliability and efficiency of a company as well as optimization of the overall costs of the product.

b- Location problem :

The location theory formally began in 1909 when Alfred Weber investigated a warehouse location problem to minimize the total distance between warehouses and customers. In 1960, Hakimi considered a more general problem that considers the location of one or more sites in a network to minimize the total distance between customers and those sites, or to minimize the maximum distance.

The location term refers to the determination of the locations of sites that may be production sites or distribution sites of the company.

c- Allocation problem:

The allocation is well known to the world of economists. It is a concept relating to the use of resources and in particular, the factors of production (labor, capital, raw materials) to satisfy in the short and long term the consumption needs of the population. The allocation is an operational research that optimizes a function, the problem of allocation is the allocation of activities to production sites or customers to distribution centers.

d- localisation-allocation problem :

A location-allocation problem consists in determining the location of one or more sites whose objective is to optimize a mathematical function that depends on the distances between these sites and a set of potential users.

In most cases, location decisions and allocation decisions must be made simultaneously. A location-allocation problem consists in determining the location of one or more sites whose objective is to optimize a mathematical function that depends on the distances between these sites and a set of potential users.

To balancing the demand and supply in a transplant organ supply chain decreased the waiting list needs certain scheduling and management. The main contribution consists of considering recipient regionsas another component of the supply chain; in addition, importance of transportation time and waiting lists hasled us to consider a bi-objective model. In addition, uncertainty of input data has led us to consider a stochastic approach [8].

Chaves [5] presented a solution for the CCCP (capacitated centered clustering problem), using the CS (clustering search) algorithm that uses the concept of hybrid metaheuristics, combining metaheuristics with a local search in a clustering process.

Barreto et al [2] discuss in their paper, the location routing problem (LRP) and consider a discrete LRP with two levels: a set of potential capacitated distribution centers (DC) and a set of ordered customers.

Different decisions may be incorporated in the model, such as numbers, locations and production technologies of manufacturers' plants; numbers, locations and capacities of main distribution centers; numbers and locations of local distribution centers [11] as well as location and allocation of secondary and primary sites and also products [20].

3. PROBLEM DESCRIPTION

Production distribution networks are an effective tool for modeling a company's manufacturing and logistics activities. The design problem of the distribution system involves determining the best configuration on the location, size, technological content and product range to achieve the long-term goals of the company [6].

In Kumar work, a two-echelon inventory system with a single warehouse and a single retailer is considered. The mathematical model is developed for the retailer, the warehouse, the entire chain by integrating order / configuration, carrying and transportation costs and numerical example is considered, and the model is solved using the computer program written in MATLAB [9].

In the continuity of Mehralian work in the management of independent members sharing common objectives is a frequent concern in all supply chains. Specifically, because of the crucial role of the pharmaceutical industry in producing and delivering the right product to the right people at the right time, coordinating members of the pharmaceutical supply chain (PSC) is a critical factor [10].

The objective of the work is to reconfigure the network of multi-level pharmaceutical supply chain, multi-product, in order to stabilize drug prices throughout the study area and at the disposal of patients. This network has three players; suppliers (see Figure 4), wholesalers (see

Figure 2), retailers (pharmacy). Pharmacists (see Figure 1) place orders near wholesalers with precise quantities and for desired delivery dates. To satisfy these orders, the wholesalers make requests for deliveries to the suppliers, in the same way, these orders have precise quantities and arrive at agreed dates, it is important that it has as a coordination between the actors to align the offer on demand in terms of services (quality, costs, time, quantity, service ...) [14]

First, retailers must be grouped together. This step allows us to define the different clusters of customers (retailers) (see Figure 3), then we deal with the problem of location / allocation of wholesalers with a specific capacity.

Fig.1. Map of pharmacists

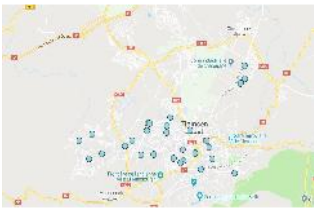

Fig.2. Map of wholesaler

Fig.3. Map of customers cluster

Fig.4. Map of suppliers

This optimization allowed us to locate the wholesalers as well as the allocation of wholesalers to suppliers and the assignment of different clusters of customers (pharmacies) to localized wholesalers. The aim is to minimize the number of open wholesalers and the cost of transportation between suppliers and wholesalers as well as wholesalers and pharmacies by respecting the capacity of wholesalers and the capacity of delivery vehicles. We use the optimization software LINGO 12 for the resolution of this problem which has been broken down into several sub problems.

Differents solutions methodologies have been deployed to solve developed models in the context of PSCs. For example, in a multi-objective network design problem, Mousazadeh used constraint method to achieve the final compromise solution and also to provide trade-off analysis between the conflicting objectives in the MILP problem. In addition, the well-known

TH approach Torabi & Hassini was employed to obtain a compromise solution in accordance with the decision maker preferences [21].

The branch and bound technique through CPLEX solver to find the solution of the formulated MILP model was used in Gatica et al work [7].

As we know, the majority of the mathematical models developed for the real world problems are intractable in solution procedure. Hereupon, the researchers attempted to employ differents strategies (such as decomposition, heuristic methods, etc.) to handle the problems in large-sizes [20].

Nagaraju proposed a three-level supply chain with a single-manufacturer supplying a single kind of product to a single-distributor and then to a single-retailer is considered [12]. Mathematical model is developed for optimal net revenue of the coordinated three-level supply chain by incorporating ordering cost, carrying cost and transportation cost. In the proposed model, the demand at the retailer is assumed as a cubic function of unit selling price. Prajapati in his paper talk about successful PCs is not only the performance achieved, but also customer satisfaction and financial performance. In addition, the financial performance is also attributable to customer satisfaction [16].

4. METHODS AND MATHEMATICAL MODELS

a- Assumptions

The proposed hypotheses of this model are:

Consider a pharmaceutical supply chain network consisting of multi- echelons. There are some candidate locations for establishing required sites. In addition, different possible production capacity levels and storage capacity levels for manufacturing sites and local distribution centers are respectively available. Furthermore, all the drugs manufactured in each period must be transported to main distribution centers and cannot be stored at manufacturing sites. The demand is delivered weekly to customers on average in the order. The capacity of each local distribution centers must not exceed the capacity of vehicles, the processing capacity of wholesalers is always less than the sum of the orders for each cluster centers assigned to wholesaler I, The location / allocation plan covers a planning horizon in which no substantial changes are made to customer requests and transportation infrastructure The proposed model consists to minimize total costs. In detail, establishing more manufacturing sites, main distribution centers and local distribution centers with more production and storage capacity, in one hand would increase total costs. Finally, many strategic decisions, i.e. the location of manufacturing sites, main distribution centers and local distribution centers as well as some tactical decisions, production capacity of manufacturing sites and storage capacity of main distribution centers must be made.

b- The model parameters

(i) Index

The sets and indexes used in the model are as follows:

i : Index for classes of products i ∈ I

j : Index for supplier of pharmaceutical products; j ∈ J

k :Index for wholesaler pharmacy ; k ∈ K

l : Index for customers clusters (regions of pharmacy's); l ∈ L

m: Index for customers (which can represent pharmacies' shops); m ∈ M

x_m , y_m : Geometric position of the customer m;

x_l , y_l: Geometric position of the customer cluster l;

(ii)Data

The model requires the following data:

- Dc_{mi}: Demand on class i products at customer m.
- Dac_{li}: Demand on class i products at cluster of customers l.
- $C1_{jki}$: Euclidian distance (in km) from site j to site k of the class i products;
- $C2_{kli}$:Euclidian distance (in km)from site k to site l of the class i products;
- N_l: Number of customers in cluster l;
- Q_l : Capacity of the transportation vehicle allocated at the customer cluster l.
- Q_{ij}: Capacity of supplier j for class i products.
- Q_{ik}:Capacity of Wholesaler pharmacy k of the class i products;

- X_{ijk}: Quantity of the class i products shipped from supplier j to wholesaler pharmacy k;

For the mathematical formulation, we consider the following costs:

- FC_k: fixed cost of setting up and operating wholesaler pharmacy k.
- FFC_j: fixed cost for of setting up and operating supplier (wholesalers wholesaler) j;
- $opsp1_{cost-ik}$: Operational cost of the class i products at wholesaler k;
- $opsp2_{cost-ik}$: Expiry cost of the class i products at wholesaler k;
- $op1_{cost-ij}$: Operational cost of the class i products at supplier j;
- $op2_{cost-ij}$: Expiry cost of the class i products at supplier j;
- α: Transport cost per unit kilometer inter-city;
- β: Transport cost per unit kilometer in habitable areas;

The decision variables for the model are the following:

- Y_{ml} = 1, if the customers m is set up at cluster l, = 0, otherwise;
- Z_{lk} = 1, if customer cluster l is allocated to wholesaler k, = 0, otherwise;
- X_k = 1, if wholesaler k is located, = 0 otherwise.

(iii) First Step Capacitated Centered Clustering Problem

In a first stage, the problem of grouping the retailers into clusters is formulated as a capacitated centered clustering problem. The originality and efficiency of this approach come from the fact that it limits dissimilarity among the formed groups since these clusters are centered at the ”average” of their points’ coordinates,

The capacitated centered clustering problem consists in minimizing:

$$\sum_{m\in M}\sum_{l\in L}[(x_m - x_l)^2 + (y_m - y_l)^2].Y_{ml} \qquad (1)$$

Such that:

$$\sum_{l\in L} Y_{ml} = 1 \quad \forall m \in M \qquad (2)$$

$$\sum_{m \in M} Y_{ml} = N_l \quad \forall l \in L \tag{3}$$

$$\sum_{m \in M} x_m Y_{ml} \leq N_l\, x_l \quad \forall l \in L \tag{4}$$

$$\sum_{m \in M} y_m Y_{ml} \leq N_l\, y_l \quad \forall l \in L \tag{5}$$

$$\sum_{m \in M} \mathrm{Dc}_{mi} Y_{ml} \leq Q_{li} \quad \forall l \in L, \forall\, i \in I \tag{6}$$

$$(\mathbf{x_m}, \mathbf{y_m}) \in \mathbb{R}, (\mathbf{x_l}, \mathbf{y_l}) \in \mathbb{R}, \forall \mathbf{m} \in \mathbf{M}, \forall \mathbf{l} \in \mathbf{L} \tag{7}$$

$$\mathbf{n_l} \in \mathbf{N} \quad \forall \mathbf{l} \in \mathbf{L} \tag{8}$$

$$\mathbf{Y_{lm}} \in \{0, 1\} \quad \forall \mathbf{l} \in \mathbf{L}, \forall \mathbf{m} \in \mathbf{M} \tag{9}$$

The objective function (1) represents the total Euclidean distance (square) between each client and the centre of the cluster to which it belongs. Note that the geometric position of the centre is unknown a priori since it depends on the clients assigned to the cluster. Constraints (2) specify that each client is assigned to a single cluster. Inequalities (3) define the number of clients in each cluster. The inequalities (4) and (5) define the geometric position of the centre of each cluster. The constraints (6) require that the volume of pharmaceuticals for each cluster does not exceed the capacity of the vehicles associated with that cluster. Finally, the constraints (7) to (9) define the space boundaries for the set of parameters and variables of the problem.

It should be stressed that after the customers (pharmacy) have been grouped into clusters, begins a second step calculation during which they have to be allocated to the wholesaler pharmacy to be open.

(iv) Second Step Location-Allocation Formulation

The problem of location-allocation at three levels and multi-products can be formulated as follows:

$$\min Z = \sum_{k \in K} FC_k * X_k + \sum_{i \in I} \sum_{j \in J} \sum_{k \in K} \left(\alpha * C1_{ikj} + op1_{cost-ij} + op2_{cost-ij}\right) * X_{ijk} +$$

$$\sum_{i\in I}\sum_{k\in K}\sum_{l\in L}\left((\beta * C2_{ikl} * D_{li}) + opsp1_{cost-ik} + opsp2_{cost-ik}\right) * Z_{lk} + \sum_{j} FFCj \ldots \quad (10)$$

Such that:

$$\sum_{k\in K} Z_{lK} = 1,\ \forall\, l \in L \qquad (11)$$

$$\sum_{k\in K} X_{ijK} \le Q_{ij},\ \forall i \in I\ \ \forall j \in J \qquad (12)$$

$$\sum_{j\in J} X_{ijK} \le Q_{ik}\ \ \forall i \in I\ \ \forall k \in K \qquad (13)$$

$$\sum_{j\in J} X_{ijk} = \sum_{l\in L} \mathrm{Dac}_{li} * Z_{lk}\quad \forall i \in I\ \ \forall k \in K \qquad (14)$$

$$Z_{lk} \le x_k\quad \forall l \in L, \forall k \in K \qquad (15)$$

$$Z_{lk} \in \{0,1\} \qquad (16)$$

$$X_k \in \{0,1\} \qquad (17)$$

Equation (10) denotes the objective function, constraints (11) and (15) indicate that all requests from a cluster of customer’s j must be satisfied by one and only one wholesaler. The constraint (12) ensures that the volume of product shipped from the supplier m to the wholesaler k is less than or equal to the capacity of the wholesaler k, the constraint (13) ensures that the volume of product shipped from the supplier m to wholesaler k is less than or equal to the capacity of the provider m, the constraint (14) indicates that the volume shipped from the supplier k to the clusters of clients j selected is equal to the order of the customers. Constraints (15), (16) and (17) impose binary conditions.

(v) Third Step Cloud Computing

The main objective of this step, is that all informations we obtained previously are used in cloud computing, where this information is used by the doctor to refer his patient to the nearest pharmacist, to obtain their complete drug and in the short time (See figure 5).

We intend to offer better solutions by integrating new technologies such as cloud and fog computing. On our cloud computing, we will record large information; availability of medicines at any wholesaler distributor in the country so that we can start manufacturing near-consumed medicines to avoid waste and shortages. Concerning the connection between patients, doctors, pharmacies and wholesalers, this is done by fog computing so as not to clutter up the Cloud. The fog is therefore a local network linking the patient, the doctor and the pharmacist in order to check the availability of medicines in pharmacies and vice versa.

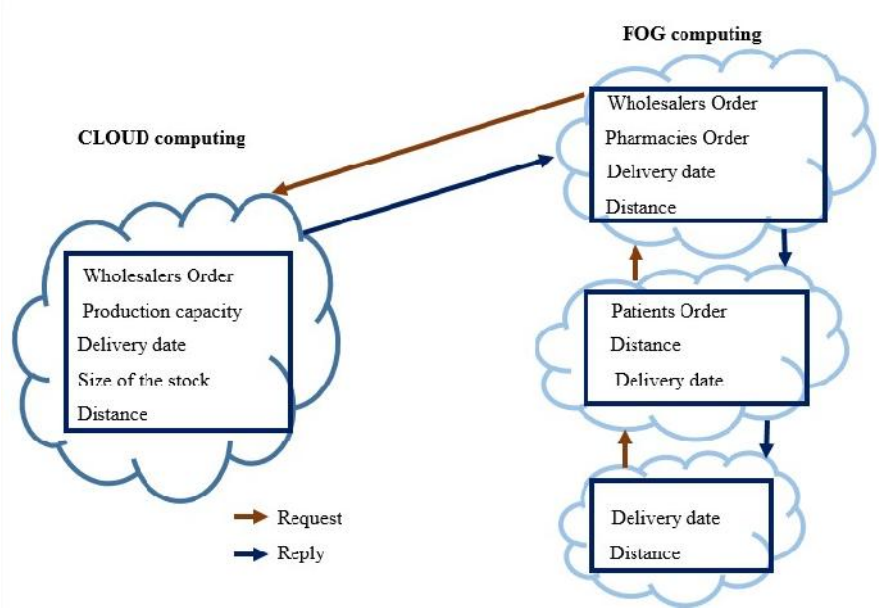

Fig.5. Illustrative diagram of integration of Cloud Computing and Fog Computing

5. EXPERIMENTAL RESULTS

In this section the model is applied to the problem. LINGO 12 has been used to solve the three programs and to obtain exact solutions by using Branch and Bound with default parameters of the solver.

We projected our study on a real case of the distribution of pharmaceuticals products in Tlemcen. The city of Tlemcen gathers 20 municipalities and 53 townships and counts more than 900000 inhabitants. Our study will be done on the three main municipalities located in the center of the map: Tlemcen, Mansourah, and Chetouane. (See figure 6)

Tlemcen is the capital of the city and has more than 140000 inhabitants; Mansourah follows with more than 49000 inhabitants and Chetouan with more than 47000 inhabitants.

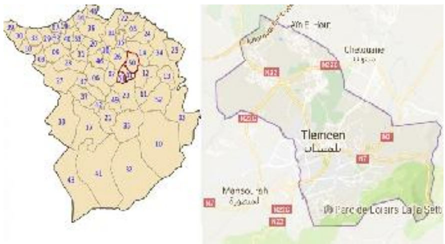

Fig.6. Map of Tlemcen City

Results of the first step calculations are summarized in table 1. The problem was to group 138 customers (pharmacies) into clusters. For each of the resulting customers' clusters, the number of assigned customers as well as their reference number is given. The coordinates of the cluster center also appear in the table. Out of the forty clusters generated, twelve have been assigned customers. The biggest clusters are cluster number elven. Results of the first problem, as well as the fixed investment costs, capacities at the wholesaler pharmacy, and distances between the potential wholesaler pharmacy and the center of each cluster are the data used for the second problem.

Results of the second step computations are presented in table 2. Twelve wholesalers have been open out of the twenty height existing locations. The sixteen remaining wholesalers had to be closed.

Table 1 : Results of problem 1

N	**A**	**Assigned customers number**	**Number**	**X(A) Y(A)**	**Cluster demand**	**Adress**
1	A1	48, 51, 52, 66, 68, 75, 82, 85, 86, 91, 95, 110, 128, 130.	14	8266.501 5418.353	11970	Allée des pins
2	A2	60, 76, 84, 89, 96, 102, 107, 119, 131, 138.	10	7707.119 9599.026	8553	Oudjlida
3	A3	22, 28, 30, 33, 45.	5	3665.246 5174.464	6134	Bouhannak
4	A4	23, 24, 26, 31, 34, 37, 43, 49, 53, 69, 97, 112, 125, 132,	14	6998.288 5043.383	12600	Makhokh
5	A5	25, 47, 50, 59, 64, 70, 73, 77, 80, 87, 88, 100, 113, 127,	14	8156.378 6464.487	11553	Fedden sbaa

6	A6	3, 4, 5, 6, 9, 10, 11, 14, 15,	9	10915.75 10071.38	8610	Ouzidane
7	A7	19, 20, 21, 32, 35, 38, 39, 40, 41, 42, 44.	11	5257.482 5559.980	11303	Imama
8	A10	57, 81, 93, 104, 105, 106, 114, 117, 122, 126, 133,	11	7567.026 5519.598	10900	Pasteur
9	A13	62, 74, 83, 90, 98, 99, 103, 109, 124, 129,	10	8980.829 6317.433	7586	Sidi Othmane
10	A23	27, 29, 36, 58, 65, 79, 94, 108, 116, 118, 121, 123, 134, 136,	14	7359.619 5212.774	13284	Bel horizon
11	A24	46, 54, 55, 56, 61, 63, 67, 71, 72, 78, 92, 101, 111, 115, 120, 135, 137.	17	8452.675 5680.352	12593	Bab wahran
12	A25	1, 2, 7, 8, 12, 13, 16, 17, 18,	9	10266.70 8908.583	7870	Chetouane

Table 2 : Results of problem 2

Wholesalers	**Location decision**	**Allocated cluster number**	**Capacity**
1	Opened	A1	11970
2	Opened	A25	7870
3	Closed	None	0
4	Opened	A2	8553
5	Closed	None	0
6	Closed	None	0
7	Opened	A6	8610
8	Opened	A23	13284
9	Closed	None	0
10	Opened	A13	7586
11	Opened	A10	10900
12	Closed	None	0
13	Closed	None	0
14	Opened	A5	11553
15	Opened	A4	12600
16	Closed	None	0
17	Closed	None	0
18	Opened	A7	11303

19	Closed	None	0
20	Closed	None	0
21	Closed	None	0
22	Opened	A3	6134
23	Closed	None	0
24	Closed	None	0
25	Closed	None	0
26	Closed	None	0
27	Closed	None	0
28	Opened	A24	12593

6. CONCLUSION

The reactivation of logistics networks in companies has increased recently. The aim of our work is to reorganize the drug distribution network in the city of Tlemcen, as pharmacists complain of shortages and waste.

For this purpose, a two-step mathematical model has been constructed and solved sequentially. Once the pharmacies were clustered, the wholesalers to be closed or reopened were located and the retail clusters were allocated to them. LINGO 12 was used to solve all three programs and obtain exact solutions using Branch and Bound with the default solver settings. The encouraging results obtained in this work, suggest dedicating our additional research activities to introduce technological information systems, such as Cloud Computing and Fog Computing for an improvement of the system. We need to have a database containing all the necessary information:

- The requests of the customers
- The orders of the pharmacies
- The stocks and the products in rupture.

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