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Study of the Evaluation Process of Class II Devices in the United States and the Relation with the Origin and Preparation of the Manufacturers

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Estudio del proceso de evaluación de dispositivos de Clase II en los Estados Unidos y la relación con el origen y la preparación de los fabricantes

Estudo do processo de avaliação de dispositivos de Classe II nos Estados Unidos e da relação com a origem e desenvolvimento de fabricantes

***Abstract*—**The global production of medical devices has increased due to growth in developing countries, hence the evaluation of pre marketing medical devices is needed to provide safety for patients and operators of such technology. In the US evaluation of medical devices is done before marketing depending on the type of device to be introduced. To market Class II devices the developer must present the application 510 (k) by which a study of "approval" of the new device is made to an existing one. However, many producers from different countries take more time to fulfill the requirements of the study indicating that they might not be fully prepared. This article aims to return the number of devices, the duration of study time and device manufacturer's countries applying the study to know the countries that are best prepared in assessing their technology. A database of the FDA was used to establish the countries applying the test 510 (k). A hierarchical classification of countries by discriminating variables as the average length of study and number of studies requested by each country was used. Three groups of countries which are discriminated according to the study duration and the number of devices presented were classified. The first group contains countries that had large amounts of equipment evaluation and had short duration of the study period. Such countries are traditionally recognized as strong producing countries of medical devices. The second group is contrary to the first, countries that submitted few devices and the duration of the study was higher indicating that they are not well prepared for technology assessment. The third group presents variability in the amount of devices presented; however the duration of the study is relatively constant for all countries in this group, which can be classified as developing countries for the production of medical devices.

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It is necessary to strengthen the production of Class II medical devices in Latin America. The duration of the studies evaluating devices is a great source of information to predict the best prepared countries when assessing their technology manufacturers.

***Keywords*—** Production of medical devices; Technology assessment; Class II devices; 510 test.

***Resumen*—**La producción mundial de dispositivos médicos ha aumentado debido al crecimiento en los países en desarrollo, por lo tanto, es necesaria la evaluación de los productos sanitarios previos al ingresar al mercadeo para proporcionar seguridad a los pacientes y a los operadores de este tipo de tecnología. En los EEUU la evaluación de dispositivos médicos se hace antes de la comercialización en función del tipo de dispositivo a ser introducido. Para la comercialización de dispositivos de Clase II el promotor debe presentar la solicitud 510 (k) por la que se hace un estudio de "aprobación" del nuevo dispositivo a uno ya existente. Sin embargo, muchos productores de diferentes países toman más tiempo para cumplir con los requisitos del estudio indicando que no están preparados por completo. Este artículo tiene como objetivo analizar el número de dispositivos devueltos, la duración del tiempo de estudio y los países del fabricante del dispositivo que aplican al estudio para conocer los países que están mejor preparados para evaluar su tecnología. Se utilizó una base de datos de la FDA para establecer los países que aplican la prueba de 510 (k). Se utilizó una clasificación jerárquica de los países discriminando variables como la duración media de estudio y el número de estudios solicitados por cada país. Tres grupos de países fueron clasificados divididos de acuerdo a la duración del estudio y el número de dispositivos presentados. El primer grupo contiene países que tenían grandes cantidades de evaluación de equipos y tuvieron corta duración en el período de estudio. Esos países son tradicionalmente reconocidos como países productores fuertes de dispositivos médicos. El segundo grupo es contrario al primero, los países que presentaron dispositivos y la duración del estudio fue mayor, lo que indica que no están bien preparados para la evaluación de la tecnología. El tercer grupo presenta una variabilidad en la cantidad de dispositivos presentados, sin embargo, la duración del estudio es relativamente constante para todos los países de este grupo, que pueden ser calificados como los países en desarrollo para la producción de dispositivos médicos.

Es necesario fortalecer la producción de dispositivos médicos de Clase II en América Latina. La duración de los estudios de evaluación de dispositivos es una gran fuente de información para predecir los países mejor preparados en la evaluación de sus fabricantes de tecnología.

***Palabras clave*—** Producción de dispositivos médicos; evaluación de tecnológica; dispositivos clase II; prueba de 510.

***Resumo*—** A produção mundial de dispositivos médicos tem aumentado devido ao crescimento nos países em desenvolvimento, portanto, a avaliação de dispositivos médicos antes da comercialização é necessário para garantir a segurança para pacientes e operadores deste tipo de tecnologia. Nos EEUU a avaliação do dispositivo médico é feito antes da comercialização de acordo com o tipo de dispositivo a ser introduzido. Para a comercialização de dispositivos de Classe II o promotor deve apresentar a solicitação 510 (k) com a qual se faz um estudo de "aprovação" do novo dispositivo a um já existente. No entanto, muitos produtores de diferentes países levam mais tempo para cumprir os requisitos do estudo indicando que eles não estão completamente despreparados. Este artigo tem por objetivo analisar o número de dispositivos devolvidos, a duração do tempo do estudo e os países do fabricante do dispositivo que aplicam o estudo para determinar os países que estão em melhores condições para avaliar a sua tecnologia. Um banco de dados do FDA foi usado para estabelecer os países que aplicam o teste de 510 (k). Foi utilizada uma classificação hierárquica dos países que discriminam variáveis, tais como a duração média de estudo e número de estudos solicitados por cada país. Três grupos de países foram classificados divididos de acordo com a duração do estudo e o número de dispositivos apresentados. O primeiro grupo composto por países com grandes quantidades de avaliação de equipamentos e que tiveram uma curta duração no período de estudo. Estes países são tradicionalmente reconhecidos como fortes países produtores de dispositivos médicos. O segundo grupo é contrário ao primeiro, os países que apresentaram os dispositivos e da duração do estudo foi maior, indicando que eles não estão bem preparados para a avaliação da tecnológica. O terceiro grupo apresenta uma variabilidade do número de dispositivos apresentados, no entanto, a duração do estudo é relativamente constante para todos os países neste grupo, podem ser classificados como países em desenvolvimento, para a produção de dispositivos médicos.

É necessário reforçar a produção de dispositivos médicos da classe II na América Latina. A duração dos estudos de avaliação de dispositivos é uma grande fonte de informação para prever o melhor preparado para avaliar fornecedores de tecnologia.

***Palabras chave*—** Produção de dispositivos médicos; Avaliação de tecnologias; Dispositivos classe II; 510 teste

I. Introduction

The global production of medical devices has increased due to scientific and technological sustained progress of the industry in addition to the demand for health services, in such proportion that rises to 635 Billions of Dollars a year, from this figure the participation in production in North America is 38.7%, while Latin America has a stake of 1.4%[1], hence the country with the largest medical device market is the United States and is therefore constantly doing assessment to devices to be marketed on its territory. Medical devices are regulated in the United States by the Center for Devices and Radiological Health (CDRH) belonging to the FDA. The objective of the FDA / CDRH is to promote and protect public health by making safe and effective medical devices [2].

According to the regulation, all medical devices are classified depending on the level of risk generated to the patient by a system of 3 levels (Class I, II or III), where level II devices can generate risk to the patient but to be marketed the manufacturer must first go through a certification of good manufacturing practices and a

study of "approval" in which it is checked whether the technology can be classified as similar to others that are already marketed in the country by application 510 (k). Manufacturers of various countries apply to this study to market their products freely, however, although the FDA said the results may take 3 to 6 months, in many cases this time is doubled due to the deficit of the manufacturer to demonstrate good manufacturing practices or a difference between their products and those already in the market. It is important to know in advance the preparation the medical device manufacturers have had in the development of their products and the ability to demonstrate the safety of the devices to be introduced to a market, in addition to observing the participation of certain countries in the market and its evolution over time. The study duration of acceptance for class II devices possibly allows to indicate which manufacturers tend to be better prepared to enter this market, which is why the focus of this article is to establish a relation between the time difference between the start and the end of the 510 (k) study with the country of origin of manufacturers that apply to it using classification of different groups of countries by cluster analysis.

II. Methodology

A. Database Description

From a database generated by the FDA [3], a total of 64854 devices that applied for the 510 (k) form from January of 1996 to February 2015 were analyzed, data that relate manufacturer information, country of origin, study baseline, study end date, final decision and type of license granted. As a first step an exploratory data analysis was performed to recognize the number of devices tested by five year periods and the participation of manufacturers from different countries in this market. The interest of this study focused on evaluating the relation between the study 510 (k) duration and characteristics of the manufacturers who applied to it to observe the how well prepared the manufacturers were to meet the market requirements for medical devices in the United States and evolution of its participation over time. For this, the countries of origin were evaluated individually to know their level of participation per year and the average time of the evaluation of the devices of each country.

B. Database Pre-processing

The database underwent a pretreatment in which all the studies requested by the manufacturers of each country were taken into account. The number of studies was collected for each year for the total of studies requested by country from 1996-2015 Eq. (1).

$$S = \sum_{i=0}^{N} n_i \quad (1)$$

Where N represents total of years in the database and n_i the number of studies requested by each country in the year *i*. The duration of the studies was averaged for each country and the classification procedure was performed over this data. These two criteria were taken as the most influential at the time of making the classification.

C. Database General Processing

Following this a hierarchical cluster analysis was performed using Matlab® software with the mean and standard deviation of the duration of the evaluation 510 (k) to classify countries of manufacturers for the duration it took the study and the amount of requested studies. To verify the cluster analysis a graph by dendograms was performed and the distance between groups in relation to the average distance between neighbors was used, measurement known as the coefficient of inconsistency, so that the higher the value of this coefficient the better will groups be differentiated. To verify the statistical differences between groups a Wilcoxon - MannWithney analysis was made evaluating the differences between groups for each specific variable. It is important to note that to all the devices from the database were granted the license to market, however, was different type of licensing.

D. Cluster Analysis

The manufacturer's origin country was used as a variable for differentiation because it was of great importance of the study to establish the countries were the most devices are manufactured in order to classify countries that provide the better prepared the manufacturers from the countries that might need help on increasing the support to manufacturers for introducing a specific device in a market. The time it takes the 510(k) on giving a favorable decision can reflect the barriers that a manufacturer can overcome for introducing a device, meaning the less time it takes the study, the better documentation and proof of safety the manufacturer can provide. The duration of the study was used in order to classify the manufacturer's origin county that need more preparation when introducing a new device in a specific market from those who present better documentation and safety proofs. Due to the considerable high number of input variables, a data pretreatment was performed obtaining the mean and standard deviation of the study duration in days. Cluster analysis was used because it is a statistical technique that seeks to bring together elements trying to achieve maximum homogeneity in each group and the biggest difference between different groups that are unknown a priori, precisely what is to be determined. The initial choice of variables used to describe each country is done because for this study is very impor-

tant to know the delay of the evaluation 510 (k), so the mean and standard deviation of this measure are used as purpose classification. The normalized Euclidean distance between i and j individuals is defined in Eq. (2). Where t is the number of variables to characterize the classification, using this distance is equivalent to use the values changed to the scale of the standard deviation of the variables as starting data, using this kind of distance the drawback of the effects of different units of measurement of the variables is solved and a distance not dependent on measurement units is obtained [4].

$$d_{ij} = \sum_{k=1}^{t} (X_{ik} - \bar{X}_{jk})^2 \quad (2)$$

Although the classification variables are in the same units, the distance between groups is performed with Euclidean distance and the squared Euclidean distance that allow to use t variables without prior standardization, and also redundant information is eliminated to observe differences. The clustering method used is the method of minimal variance or Ward method in which the distance between two clusters is computed by the total sum of the squared deviations between each element and the mean of the cluster which integrates Eq. (3). At each step is minimized the sum of squares within groups on all the possible partitions obtained merging two clusters in the previous step [4].

$$SCI_K = \sum_{i=1}^{m} \sum_{j=1}^{n_k} (X_{ijk} - \bar{X}_{ijk})^2 \quad (3)$$

Where m is the number of variables and n is the number of elements of the group k. This method is also used because it is one of the most used in practice; it possesses nearly all the advantages of the method of the average and is usually more discriminatory in determining the levels of aggregation. Research done by Kuiper and Fisher [5] obtained as a result that this method could succeed better with optimal classification than others (minimum, maximum, average and centroid) methods.

The technique of cluster analysis provides a great differentiating tool for elements among lots of them, however, the technique itself provides some drawbacks because it is descriptive and not inferential technique, the solutions are not unique because they depend heavily on method of settlement. From the variables used in the cluster analysis the country of origin of manufacturers was set as a categorical variable, as shown in Table 1, and as quantitative variables average and standard deviation of the study duration.

Table 1. Codes of countries under study

	Country code							
1	'AD'	Andorra	23	'HU'	Hungary	45	'NL'	Netherlands
2	'AR'	Argentina	24	'ID'	Indonesia	46	'NO'	Norway
3	'AT'	Austria	25	'IE'	Ireland	47	'NZ'	New Zealand
4	'AU'	Australia	26	IL'	Israel	48	'PH'	Philippines
5	'BE'	Belgium	27	'IN'	India	49	'PK'	Pakistan
6	'BM'	Bermuda	28	'IR'	Iran	50	'PL'	Poland
7	'BR'	Brazil	29	'IS'	Iceland	51	'PR'	Puerto Rico
8	'CA'	Canada	30	'IT'	Italy	52	'RO'	Romania
9	'CH'	Switzerland	31	'JO'	Jordan	53	'RU'	Russia
10	'CN'	China	32	'JP'	Japan	54	'SA'	Saudi Arabia
11	'CR'	Costa Rica	33	'KM'	Comoros	55	'SE'	Sweden
12	'DE'	Germany	34	'KP'	Korea, Rep (N)	56	'SG'	Singapore
13	'DK'	Denmark	35	'KR'	Korea, Rep (S)	57	'SI'	Slovenia
14	'EG'	Egypt	36	'LI'	Liechtenstein	58	'TH'	Thailand
15	'ES'	Spain	37	'LK'	Sri Lanka	59	'TR'	Turkey
16	'FI'	Finland	38	'LT'	Lithuania	60	'TW'	Taiwan
17	'FR'	France	39	'MC'	Monaco	61	'US'	United States
18	'GA'	Gabon	40	'MG'	Madagascar	62	'VG'	Virgin Islands
19	'GB'	United Kingdom	41	'ML'	Mali	63	'VN'	Vietnam
20	'GR'	Greece	42	'MU'	Mauritius	64	'ZA'	South Africa
21	'HK'	Hong Kong	43	'MX'	Mexico			
22	'HR'	Croatia	44	'MY'	Malaysia			

E. Groups Validation and Analysis

Validation of clusters obtained was conducted to verify in which degree the final structure represents the difference between the objects of study. For this the inconsistency coefficient was used, which measures the correlation between the initial distances, taken from the original data, and the final distances with which the individuals have come together for the development of the method used. Higher inconsistency index values indicate that the separation of the groups in that distance is the greatest and the agglomeration result reflects the original data. After the validation an analysis over the groups was performed in order to present the main reasons that affected the time of the studies, according to the cluster analysis.

III. Results

In the exploratory data analysis a decrease in the number of manufacturers who applied for the form 510 (k) was observed as shown in Fig. 1.

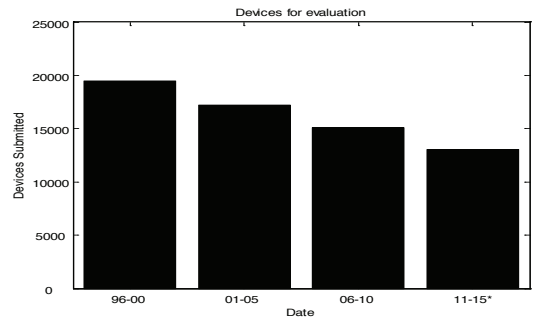

Fig. 1. Time variation of studied devices.

The results provide a tool to relate the duration of study 510 (k) with the manufacturer's origin country. Countries were then classified using statistical agglomeration techniques by squared Euclidean distance and Ward's method. In Fig. 2 can be observed that the agglomeration technique differed total data in three main groups. Of all cases expressed in the database three distinct groups were obtained, these groups are made up of the countries listed in Table 2. The number of groups was chosen taking into account the coefficient of inconsistency which provides the greatest distance between the groups with a coefficient of 1.13, for which the distance has a value of 5.3.

Since the FDA is an organization from United States, the manufacturers of this country have greater access to such permits as presented in Table 2, it is why a cluster analysis was performed excluding the permissions requested by the manufacturers of this specific country, in order to observe the influence of this variable in the classification as shown in Fig. 3.

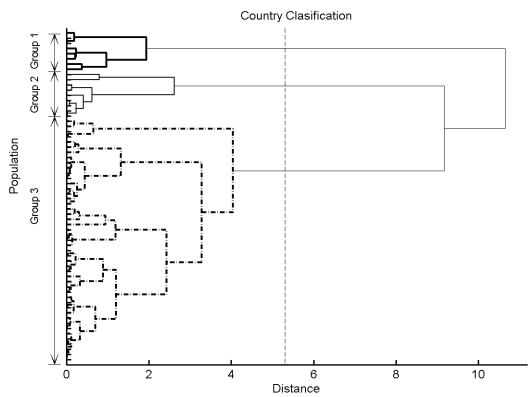

Fig.2. Country classification by mean and standard deviation of study duration and number of requested studies. Three groups are formed as shown in Table 2

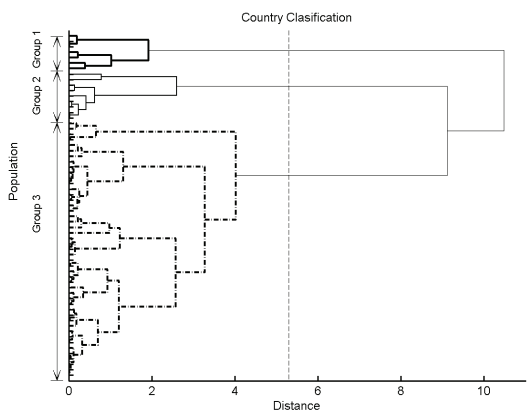

Fig. 3. Classification excluding the United States. The groups formed remain the same than the previous figure

Table 2. Classified countries

Group 1	Group 2	Group 3	
United States	Russia	Romania	Australia
Germany	Jordan	Gabon	Madagascar
China	Virgin Islands	Mali	North Korea
Netherlands	Comoros	Bermuda	Thailand
India	Turkey	Mexico	Malaysia
Israel	Poland	Sri Lanka	Iceland
Great Britain	Hungary	Iran	Finland
Canada	Egypt	Vietnam	Philippines
	Andorra	New Zealand	Indonesia
		Slovenia	Belgium
		Italy	South Africa
		Croatia	Taiwan
		Austria	Lithuania
		Mauritius	Hong Kong
		Brazil	Puerto Rico
		Spain	Pakistan
		Argentina	Japan
		Singapore	Sweden
		Norway	South Korea
		Liechtenstein	Costa Rica
		France	Greece
		Ireland	Saudi Arabia
		Denmark	Monaco
		Switzerland	

For this cluster analysis the same procedure mentioned above is performed. In order to verify the difference between groups a graph was performed, evaluating the mean duration of the decision and the number of studies. Fig. 4 shows in white the mean duration of the decision in days, and in black the number of devices submitted is shown.

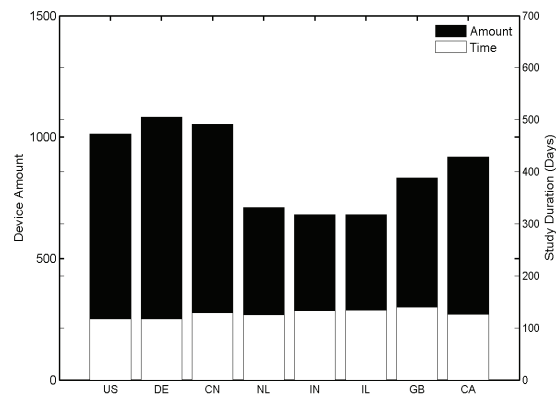

Fig. 4. Number of devices and duration of the study for group 1

Similarly for Group 2 it is plotted the number of devices submitted in white and the number of days of the studies in black as shown in Fig. 5.

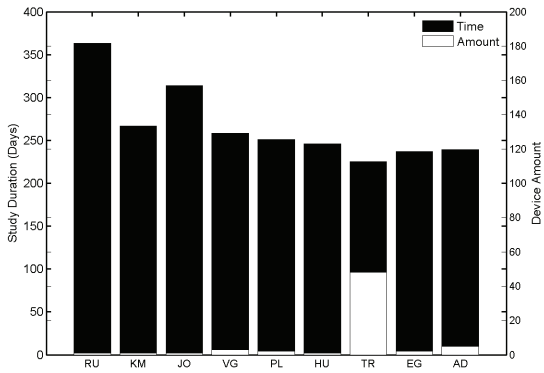

Fig. 5. Number of devices and study duration for group 2

For the verification a Wilcoxon - Man Whitney test was performed (Table 3) for which p values less than 0,05 reject the null hypothesis, i.e. the populations are different for the specific variable.

Table 3. Wilcoxon – Man Whitney test for number of devices and study duration

	Duration	Number of devices
P value	8,22706705e-05	8,22706705e-05

Manufacturers from countries in Group 3 had great variability in the number of devices tested, but the duration of each study remained on average 150 days. Fig. 6 presents the variables for Latin American countries.

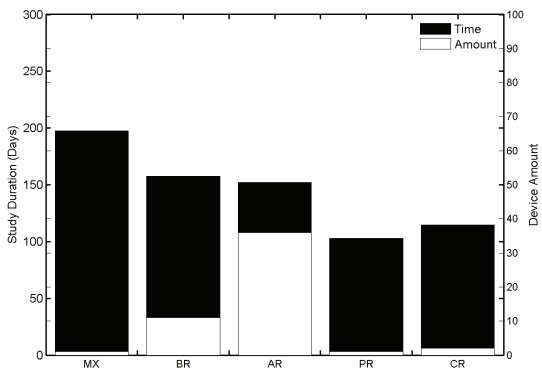

Fig. 6. Number of devices and study duration for Latin American countries

IV. Discussion

The total number of studies carried out for this type of risk classification (510 (k)), suggests that the number of evaluations conducted is decreasing with time, as shown in Fig. 1. The decline in the number of such studies might indicate the change in thinking of manufacturers that can shift from manufacturing devices of class II to devices of higher classes. This change may be due to the experience in the market that some manufacturers acquire that would push them to create more complex devices, moreover in the past decade, growth in the medical devices manufacturing industry has due mainly to changes in patient demographics; the economic rise of the BRIC (Brazil, Russia, India and China) nations has fueled the growth of this sector because it has increased the middle class who can access to improved health services [6][7]. Another reason that can explain this decline is that the type of study 510 (k) represents an evaluation to verify the new device is particularly equivalent to a class II device that at the time of the study already has marketing permits, the decrease in the number of studies over time shows that the number of sold devices is increasing and therefore it is not necessary to conduct the study of approval for certain new devices, i.e. the diversity of commercially available devices can be increased until reaching a point of "saturation" in which new devices always have an equivalence with any device already marketed.

From the total studied cases, a three group classification is seen using the highest coefficient of inconsistency with a value of 1.15, which relates an agglomeration distance of 1.16. However for distance values lower than 4 is not observed homogeneity in the groups which provides great variety and quantity of groups. Therefore inconsistency coefficient of 1.12 is chosen relating an agglomeration distance of 5.2 to which dissimilarity is small intragroup and large between the groups. Forming three specific groups.

Because in the database most studies are requested by US manufacturers, the possibility that the number of devices were the only variable in separating influential groups was raised. Therefore a new classification with the exclusion of the United States was performed to check if the large number of devices that the United States brought to the classification of the remaining countries was significant. In Fig. 2 and 3 it can be noted that classification groups did not change, indicating that the number of studies is not the only criterion for classifying.

Cluster analysis classified 3 groups from which the first group was conformed by traditionally known countries for the production of medical devices among which are the US, Germany, UK, China and Canada. The second group associated countries with large differences, but there are two fundamental differences between the first and second group. Manufacturers of countries classified in the first group have similar characteristics, these manufacturers had many requests for the 510 (k) (mean of 400) and

the duration of the study had an average of 120 days as shown in Fig. 4 that can be compared to the studies considering fewer years [8].

Likewise, the countries in the group two share some similarities between them, in Fig. 5 the difference between the amount of studies presented and the study duration for each country is shown, and it can be observed how these countries present fewer devices to be evaluated but tend to exceed the duration of the study presented by the countries in Group 1.

On average, countries in group 1 presented a higher number of devices and the duration of each study is small compared to the duration of each study of group 2 countries, which have fewer devices than group 1. This suggests that countries in group 1 have a better preparation when facing a technology assessment process that the countries of group 2. It is notable that the manufacturer´s countries that have been classified within group 1 are countries that already have a standardized policy for marketing medical devices in their own markets as reported by Emergo Group [9] .

Manufacturers from countries in group 3 have a great variability in the number of devices they present, however the duration of the studies is not very variable with an average of 40 days. It should be noted that within this group are manufacturers from Latin America, which are Argentina, Brazil, Mexico, Costa Rica and Puerto Rico. The other Latin American countries do not appear in the database, i.e. have never applied for the evaluation 510 (k). As can be seen in Fig. 6 Latin American countries have introduced different amounts of devices to such evaluation, however study duration is similar in all countries. Something worth noting is that the mean duration in the study of Costa Rica and Puerto Rico is lower than that of the countries that traditionally have been the largest producers of medical devices in Latin America such as Argentina, Brazil and Mexico which might suggest the readiness of the two countries have to present the evaluation of devices could be higher.

Although in this paper two variables are treated, it might be of great importance to consider the effects of another variables in the duration of the evaluation such as the documentation presented, the clarity of the regulations of an specific market, the level of information about the device given by the manufacturer [10], the time of the year to apply for the evaluation, type of class II device submitted and political conditions among others, as the presented by the FDA in the review time for 510(k) submissions, which reported that 82% of all 510(k) submissions "contained at least one deficiency related to quality" defined as having at least one of the previous deficiency categories [11]. Furthermore, the results presented in this article can be useful as a basis for future studies where the manufacturer's major faults that may affect the evaluation time for their device can be considered, and also, it may help to find the best way to solution to these faults for future evaluations. Due to the available information in the database by the time this paper was written, in this study was not performed an analysis of the main factors that might affect the time of evaluation, which is will be considered for future studies.

Is worth of noticing that the inconveniences that may appear during the evaluation of the device could be extrapolated to other markets as well. However, this topic for its novelty and recent work time does not have much literature associated.

V. Conclusions

Although the variables used for the differentiation of groups of countries are few, using a multivariate tool, substantially simplified the information provided. Among the large number of countries applying for 510 (k) submission there are very few that actually show preparation for facing this study, as most substantially exceed the study time predetermined by the FDA which may involve incomplete documentation and lack of clarity in the description of the device.

It is necessary to strengthen the manufacturing industry of medical devices in Latin America, not only for class III devices but also classes II and I, which can be a market of great influence worldwide.

It is of great importance in future studies to deeply investigate the main factors that might be involved in the prolongation of the study of a specific device, which can be used to improve the level of preparation for manufacturers that could apply to a 510(k) submission to market their devices.

This kind of studies are important based on the creation of a technology assessment center that might advise on the process to obtain market registration or an approval for the FDA or any other market in minimum time, also can be useful for the creation of a model of background checks and requirements that minimize the time of study. This permits manufacturers to save time and money facing an evaluation process to their devices.

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