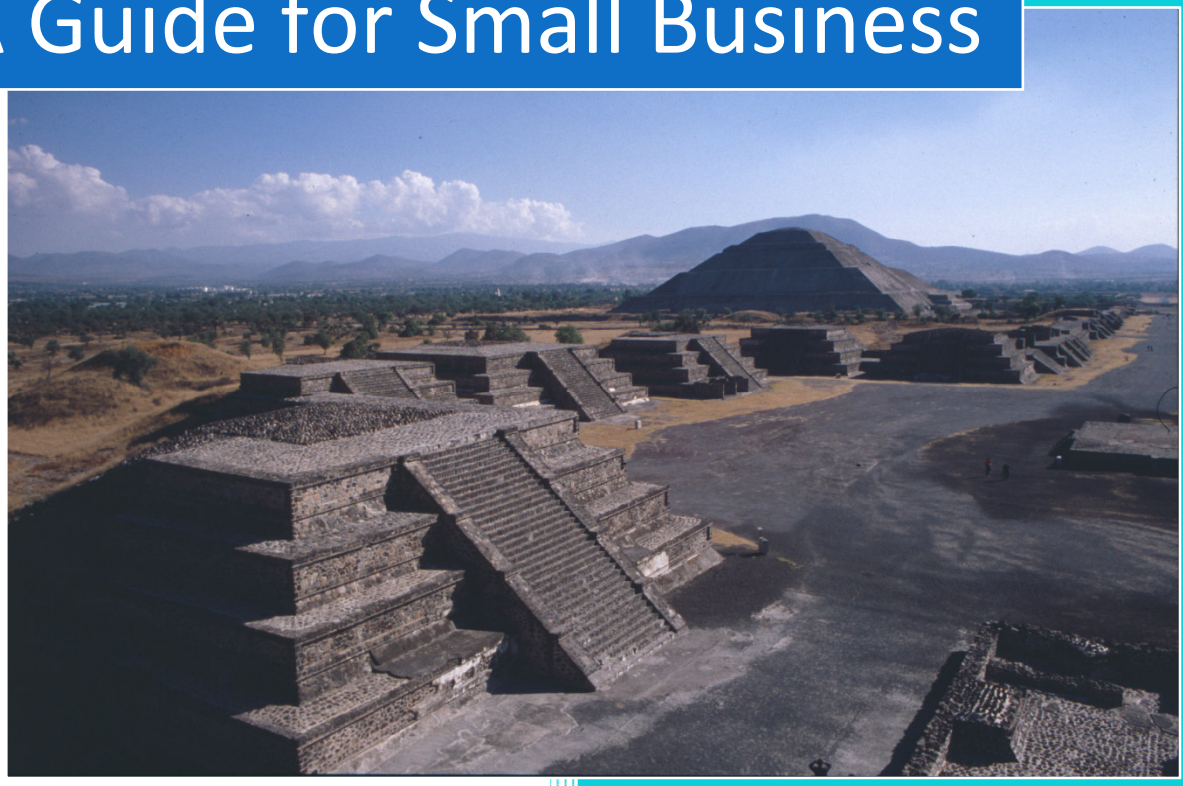
Dr. Sonja Bastian

Drug Regulation in Latin America
A Guide for Small Business



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INTRODUCTION

During the late eighties of the last century Multinational Companies (MNC) grew by mergers and acquisitions. During this process the portfolios of the MNCs were streamlined. The products were often outsourced or further marketed by management buy-outs or spin-offs. A lot of Small and Medium Sized Pharmaceutical Enterprises (SME) were launched with a variety of already registered generic drugs. Experienced and engaged employees developed the products for the European market. Nowadays these SMEs deliver their products to the European market with their niche products and look forward for new markets.

A special point of interest for these SMEs is the factor of "Cost Risk Effectiveness" (Siegel, 2008). Because of their limited resources (financial, human resources) their risk is much higher by entering new markets compared to MNCs. While starting expansion plans in SMEs the Latin American market is the less risky one, because the countries are more developed than the African countries, the language is more homogenous (Spanish or Portuguese) and the cultural difference is smaller compared to Asian and African states.

Besides the cultural and mercantile decisions a regulatory strategy has to be developed: "In the dynamic, global regulatory environment, a "one-size-fits-all" approach to strategy is simply inadequate. A truly effective global regulatory strategy that maximizes commercial opportunities while minimizing risk must address regional needs and take the larger global environment into account at the same time" (Jones, 2008). Although the Latin American market is always treated as one homogenous market, each country has its own history, market dynamic and its special regulatory framework. Therefore the country specific economical development, the market as well as the regulatory framework has to be analysed country by country to develop an approach expanding into these markets. Interviews with experts of different departments in a SME resulted in the following list of questions:

Marketing experts want to know if there exists enough purchasing power, are the consumers able to understand the advantages of the product, does an advanced health care system exist, who are the competitors in the market and are there special packaging requirements.

From regulatory departments the questions arise if the (e)CTD-format is accepted, and which requirements exist for the content of Module I, which studies (design, ethnics, investigators, sampling and laboratory parameters...) and specific data have to be submitted (analytical data, batch numbers, climatic zone adaption, stability..) and if the competent authorities follow FDA or EMA standards and decisions (based on interviews with VP RA and Director RA).

To answer such questions this guide for SME has been developed.

GUIDE FOR SMALL BUSINESS

This guide presented here addresses especially to small and medium sized business, located in Europe and offering generics as finished products to the market. To be economical the decision for special countries is made on three levels: Decision Level 1 elucidates the economic and developmental stage, Decision Level 2 analyses the market conditions in selected countries for generics and Decision Level 3 shows the basic efforts to be done during drug registration in a highly selective group of countries. This sequential analysis results in a identification of selected countries, where SME have realistic chances for a successful market access.

DECISION LEVEL 1: EMERGING LATIN AMERICAN MARKETS

The Latin American States are in North-America: Mexico, in Central America: Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama, in South America: Argentina, Belize, Bolivia, Brazil, Chile, Colombia, Ecuador, Paraguay, Peru, Suriname, Uruguay and Venezuela and in the Caribbean Cuba.

Out of this large group of countries with Spanish or Portuguese as the official language those with the highest Gross Domestic Product (GDP) were selected (Table 1). This indicator is the most valid figure, because "in most Latin American countries the growth of the pharmaceutical market is highly dependent on the growth of its GDP" (World Pharmaceutical Frontiers, 2010). The GDP is highest in Venezuela, Chile and Uruguay and most of the selected countries show relatively low inflation rates (< 5 %). Only Argentina, Uruguay and Brazil have higher rates (The World Bank, 2012).

KI	Argentina	Brazil	Chile	Columbia	Cuba	Mexico	Peru	Uruguay	Venezuela
GDP per capita (US$) (The World Bank, 2012)	9124	10710	12431	6240	5397 *	9133	5401	11633	13590
Health expenditure (% of GDP) (WHO, 2012)	8	9	8	8	11	6**	5	8	6
Health expenditure per capita (current US$) (WHO, 2012)	742	990	949	472	607	514 **	269	989	663
Life expectancy (SeBa World (1), 2012)	77	72,5	77,7	74,5	77,7	76,5	72,5	76,2	73,9
Poverty (% of population) (SeBa World (2), 2012)	30	26	12	46	n.a.	18	35	21	38
Urbanisation (% of population) (United Nations, 2012)	92,5	84,6	89,2	75,3	75,2	78,1	77,3	92,5	93,5

Table 1: Key indicators (KI) used for the selection of Latin American countries.

All data are from the 2011 year if not stated otherwise; *2008; **2009 (based on 50% coverage); n. a. - not accessible

For pharmaceutical companies the total health expenditures are another interesting parameter reflecting the importance of health care in the country. The selected countries (Table 1) with percentages mainly between 8 and 11 % of GDP show nearly comparable expenditure rate compared to selected European Countries (Germany, France, Italy, Spain, UK; 9-12%). Therefore it is assumed that the overall awareness for the importance of health care is comparable to fully developed countries. Focussing on the health expenditure per capita it is obvious that the absolute data are on a lower level compared to fully developed countries (~ 10 fold (Index Mundi, date not available)) depending on lower income per capita. The effect of health care expenditure is visible in the direct correlation to the life expectancy data.

The last key indicators are the parameters "high urbanisation" and "low rate of poverty": For both parameters the selected countries rank, with exception of Columbia, Cuba and Peru, within the top 10 of all Latin American countries. Urbanisation on the one hand reflects the development of the country (education, industrialization, middle class), whereas the poverty stands for the opposite: illiteracy, unemployment and slum population. High urbanization and low poverty correlates to an enhanced awareness of the population for health care.

Taken together the selected countries (Table 1) represent markets with realistic chances for pharmaceutical companies to successfully enter the local market, because the economies are stable and increasing, a health care system exists, people are educated and therefore able to be aware of the importance of health and finally they are willing to spend money to protect their own health and the health of their families.

DECISION LEVEL 2: MARKET SITUATION IN SELECTED COUNTRIES

The market situation in the selected countries varies because of the different developmental stages of the country's market itself, the presence of local as well as foreign pharmaceutical industry and the resulting competition, the political framework in general, regulatory authorities, intellectual property rights as well as pricing/reimbursement and health care system. Influencing factors of regulatory affairs, regulatory authorities, intellectual property

KI	Argentina (*1,13*)	Brazil (*2,13*)	Chile (*3*)	Columbia (*4*)	Cuba (*5*)	Mexico (*6*)	Peru (*7*)	Uruguay (*8*)	Venezuela (*9*)
Market size (bill. US$)	3,0 (*10*)	12,2 (*10*)	1,5	2,2	n.a.	8,8 (*10*)	0,8 (*14*)	0,4	2,1 (*15*)
Growth rate and	21 (*1*)	13 (*18*)	~30	5	n.a.	6 (*18*)	16 (*14*)	23 (*19*)	n.a.
Forecast (*16*); (%)	14	10	7,5	9		7,5	9		26
Generics (% market)	10	20	80	60	High	<10 (*18*)	3-25 (*20*)		
Generics Gov. support		yes	yes		yes	yes	yes	yes	yes
% local players	53-57	30	30	55	~85	n.a.	n.a.	n.a.	n.a.
Gov. Support	yes	yes	yes		yes	n.a.	n.a.	yes	n.a.
Prices	moderate	low	low	lowest	low	low	low	moderate	very low
Pharma-Import from DE (bill €) (*12*)	0,11	0,47	0,04	n.a.	n.a.	n.a.	n.a.	0,09	n.a.
Mercosur	M	M	A	A		O	A	M	(M)
CAN	A	A	F	M		O	M	A	F
WTO	X	X	X	X	X	X	X	X	X
OECD			X						
FTA (EU)			X			X	X		
FTA (USA)	X	X	X	X		X	X	X	(X)

Table 2: Important variables of country specific pharmaceutical markets

(1) (Nandin, et al., 2011) , (2) (Thuot, et al., 2012), (3) (Collet, et al., 2011), (4) (Santos Pereira, et al., 2010), (5) (Espicom Cuba, 2012), (6) (Medrisch, et al., 2008), (7) (Espicom Peru, 2012), (8) (Laboratorio Athena, 2009), (9) (Espicom Venezuela, 2012) (10) (IMS Health, 2012), (11) (IMS Health, 2007) (12) (AHK, 2010) (13) (World Pharmaceutical Frontiers, 2010), (14) (IHS, 2008), (15) (The Free Library, 2008), (16) (Sheftelevich, et al., 2010), (17) (Espicom Argentina, 2012), (18) (Bourne Partners, 2012), (19) (Uruguay XXI, 2011), (20) (Economist Intelligence Unit, 2011)

Abbreviations: n. a. - not accessible, CAN – Andean Community, M – member, () – depending on the vote of Paraguay, A – associate member, O – observer country, F – former member, FTA (EU/USA) – Free Trade Agreement with EU or USA

rights and the pricing/reimbursement system are discussed in "Decision Level 3". Here market size, market development, factors influencing the market (competition, economy,

geography...) and visions for the future are summarized and analysed to select those markets with the highest possible success for market access and penetration from the view of SMEs.

Table 2 summarizes key indicators of the selected countries with the aim to compare the data and to elaborate possible chances and risks for the entrance into the market. Country specific factors influencing the market are summed up country by country in the subchapters resulting in a recommendation to chances and risks integrating the special point of view of SMC.

To complete the pictures of the selected countries their membership to organisations and Free Trade Agreements with EU and USA are included in table 2, too.

ARGENTINA

Based on European immigration in the end of the 19th century and again after World War II, many national pharmaceutical companies have been founded which are present in the Argentinean market until today and cover a market presence of 53%. After several crises in the market history (Falkland war, economic crisis in 2001/02) many multinationals left Argentina and the local companies overtook the production sites, the employees, the knowledge and the vision of high quality products.

MARKET CHARACTERISTICS

Today 71% of the production of Argentinean pharmaceutical products takes place in local production sites. The multinationals returned and started to use the local production sites as well as the distribution channels of national companies to enter the market. But until now the market is dominated by local, family owned companies producing innovative products, supported by the government. (Nandin, et al., 2011)

Ranking (sales)	Company	% Market Share
1	Roemmers	8,3
2	Bago	5,3
3	Bayer	4,8
4	Ivax Argentina	4,2
5	Elea	3,8
6	Gador	3,5
7	Sanofi-Aventis	3,2
8	Pfizer	3,1
9	Phoenix (GSK)	3,1
10	Montpellier	3,0

Table 3: Top 10 pharmaceutical companies in the Argentinean market

(Nandin, et al., 2011)

Generics in Argentina were more or less copies until Argentina followed thereafter the EU and Japan with regulations on biosimilars based on the EU model (Greer, 2012; Espicom, 2006). Generics are mainly sold to the hospital (72%) and not to the pharmacy market (Espicom, 2006).

“There exists a great barrier for the import of generics into the Argentinean market. The country can only import pharmaceuticals from countries listed in two annexes. [...] Drugs can only be imported from these places if their companies’ plants and products have been deemed safe by the first set of developed countries.” (The Economist, 2010) Additionally to that, price

accords have been negotiated including pharmaceuticals (Office of the United States Trade Representatives, 2011). This may indicate that the government is protecting the local pharmaceutical companies by limiting generics imports. This assumption is supported by Law 25551 of 2001 which establishes a national preference for local industry for most government purchases on national and provincial level serving as a barrier for foreign firms (Office of the United States Trade Representatives, 2011). The costs to import to Argentina are calculated as US$ 1789 per container (regional average US$1495) (The World Bank and International Finance Corporation, 2012).

BRAZIL

The Brazilian constitution states:

"Article 196

[Health, Right of Assistance]

Health is the right of all persons and the duty of the State and is guaranteed by means of social and economic policies aimed at reducing the risk of illness and other hazards and at universal and equal access to all actions and services for the promotion, protection and recovery of health." (ICL, 1993)

Therefore the government of Brazil enforces the cooperation and collaboration between government, its authorities and the pharmaceutical companies present in the Brazilian market.

According to the World Bank "the Brazilian economy has been expanding with the help of booming commodity exports. However, the efficiency and overall quality of government services remain poor despite high government spending as a percentage of GDP. Barriers to entrepreneurial activity include burdensome taxes, inefficient regulation, poor access to long-term financing, and a rigid labor market. The judicial system remains vulnerable to political influence and corruption." (The World Bank Brazil, 2011)

MARKET CHARACTERISTICS

Brazil is the biggest pharmaceutical market in Latin America and ranks on position 9 worldwide. (Brazilian Government, 2012). The motor supporting this "is the change in social class distribution. Based on the increased stability of the economic situation, including employment and GDP growth there is a shift upwards in the social classes." (Nilton Paletta, country manager and vice president, Latin America for IMS Health, (Thuot, et al., 2012)). Because there is still a numerous amount of poor people (26% poverty), the need for low price medicine is present. Therefore the growth of generics has achieved an annual growth of 53% (Thuot, et al., 2012). "90% of the Brazilian retail market is out of pocket, therefore all these people need to have access to affordable and trustworthy medicines, and this what generics is all about" (Odnir Finotti, executive president of Pró Genericos, (Thuot, et al., 2012)). Because of the generics act which phases out "similares" without bioequivalence studies, it is expected that the generics market will strongly grow, but prices are low, taxes are high (33.9% consumer tax on pharmaceuticals) and the competition is hard (Bourne Partners, 2012; Thuot, et al., 2012).

Taken together the Brazilian generics market will continue to grow. IMS Health expects that Brazil will reach position 3 in the world's generics market in 2015 (Thuot, et al., 2012).

At least the government launched a program for low income citizens, called “Saúde Não Tem Preço”, which includes reduction of the copayment in Farmácia Popular for the most important diseases such as diabetes and hypertension (Thuot, et al., 2012) stimulating the prescription market and making medicine available for poor people.

A lot of manufacturers are present in the Brazilian pharmaceutical market. In the top 10 positions there are global players as well as local companies, which have been successful by M&A (merger and acquisition) activities with local companies (see table 4).

Interestingly the local companies show a positive trend, whereas the multinationals lost market share resulting in less favourable ranking positions. This may be caused by the following observation of Odnir Finotti, executive president of Pró Genericos: “You need to be here - plant here, manufacturing, developing formulations etc., here.” (Thuot, et al., 2012). One reason for this is assumed to be founded in the historical development of regulatory affairs (RA) and the introduction of intellectual property rights (IPR) in close cooperation with local pharmaceutical companies. Today the RA and IPR system is outstanding in the Latin American world.

Company	% Market Share	Ranking	Trend
EMS Pharma	7,53	1	↑
Medley (Sanofi)	6,90	2	↑
Ache	5,31	3	→
Sanofi-Aventis	4,78	4	↓
Eurofarm	3,97	5	↑
Novartis	3,61	6	↓
Neo Quimica	3,45	7	↑
MSD	2,52	8	↓
Pfizer	2,52	9	↓
Bayer Pharma	2,23	10	↓

Table 4: Top 10 pharmaceutical companies in the Brazilian market.

Especially the multinationals show a reduction in market share, whereas the local companies increased their market shares during the last 5 years. (Thuot, et al., 2012), ↑ - increasing, → - constant, ↓ - decreasing

Furthermore it is important to tailor the products to the needs of the Brazilian population by adapting package sizes, formulations, medications and specific communication with the Brazilian customer. As an example for this Nycomed/Takeda successfully launched their product Neosaldina®, an analgesic (OTC) for the treatment of various types of headache and today the leading brand (IMS Health, date not available) in Brazil, by a creative marketing campaign, using an especially small package size (4 tablets), combined with alternative strategies in cooperation with the points of sale in terms of assistance in presentation and promotion of medical products in the pharmacies (Thuot, et al., 2012). Multinationals often use unique marketing campaigns for the whole world, but SME might be flexible enough to adapt their strategy to the market needs or to find innovative ideas to support local pharmacies in their business.

Another approach to get access to the Brazilian market is to target on Brazilian generics companies for mergers and acquisitions (M&A). Due to this strategy MNC indirectly get access to the Brazilian generics market: Sanofi-Aventis owns Medley, which ranks on position 2 in the Brazilian market (Thuot, et al., 2012). For SME M&A is not an option, instead of that

cooperation or out-licensing has to be taken into consideration while entering the Brazilian market.

Import costs for Brazil are calculated as US$ 2775 per container compared to a regional average of US$ 1495 (The World Bank and International Finance Corporation, 2012). No FTA exists between EU and Brazil and its associations (Mercosur and CAN).

CHILE

Chile is the most politically and economically stable country in Latin America, with an A+ credit ranking. It is the only Latin American Country accepted as a member of the OECD (Collet, et al., 2011). According to the World Bank "Chile is one of the most open countries to foreign equity ownership, as measured by the Investing Across Sectors indicators.[...] It takes 11 procedures and 29 days to establish a foreign-owned limited liability company (LLC) in Chile (Santiago). This is one of the shortest processes among the [...] Latin America and the Caribbean countries.[...] Chile enjoys the highest degree of economic freedom in the South and Central America/Caribbean region. The Chilean economy has demonstrated great resilience in coping with the global economic downturn and the February 2010 earthquake. With openness to global trade and investment firmly established, economic recovery has resumed at a steady pace, and the earthquake caused only a transitory dip in Chile's healthy economic growth." (The World Bank Chile, 2011)

The Chilean constitution states in Chapter III, Article 19 (9) - The right to protection of health:

"The State protects the free and egalitarian access to actions for the promotion, protection and recovery of the health and rehabilitation of the individual. The coordination and control of activities related to health shall likewise rest with the State. It is the prime duty of the State to guarantee health assistance, whether undertaken by public or private institutions, in accordance with the form and conditions set forth in the law which may establish compulsory health quotations. Each person shall have the right to choose, the health system he wishes to join, either State or private controlled." (Republic of Chile, 1980).

That means that the Chilean government is responsible for the protection of health and the reduction of health risks. In this circumstance the government and the health insurances (FONASA and ISAPRES) launched the GES (ex AUGE) program, which covers until today 69 diseases. (Bibliotheca del Congresso National, 2011).

MARKET CHARACTERISTICS

For many years the country was known to produce the cheapest pharmaceutical products, to disregard intellectual property rights (TRIPS) and to sell generics without sufficient bioequivalence studies. Besides that the distribution channels were concentrated on three different pharmacy chains, which nearly controlled the total market and the prices.

The local pharmaceutical industry was supported by the government (World Pharmaceutical Frontiers, 2010) and the market size was very small. Therefore Chile was not attractive for foreign pharmaceutical industry, although Chile had respectable growth rates. In 2006 the government started to reform the health care system. Today – the reforms are still ongoing – the country offers new opportunities for pharmaceutical companies:

The small market (3% of the Latin American market) is very dynamic and therefore companies active in Chilean pharmaceutical market should be flexible and innovative regarding prices,

services and product availability for the patients. The market is dominated by generics (80% of the pharmaceutical market).

Because of the economic development, the population is more and more interested in innovative medicine. Drivers of the market are first class medicine and niche segments. The market today is dominated by Chilean companies due to the governmental support. The local pharmaceutical industry is focused on production/contract manufacturing of innovative drugs and started the commercialization of their products, too. The Chilean companies are on a high developed standard (certified, GMP) and cover a broad spectrum of indications with licensed drugs as well as generics. In the market the patented drugs only have a market share of ~20%.

Under the Top 10 pharmaceutical industries only 2 Multinationals (Merck and Bayer) are directly listed. Teva got access to the Chilean market by the acquisition of Laboratorio Chile and therefore indirectly ranks on position 1. Multinationals are now starting in the Chilean market facing local brands and a highly competitive generics market.

Company	Ranking	% Market Share
Laboratorio Chile (Teva)	1	6,2
Laboratorio Saval	2	5,2
Andromaco	3	4,7
Recalcine	4	4,3
Laboratorio Bago	5	3,8
Medipharm	6	3,1
Instituto Sanitas	7	2,8
Merck	8	2,8
Pharma Investi	9	2,5
Bayer	10	2,4

Table 5: Top 10 pharmaceutical companies in the Chilean market.

Teva is the owner of Laboratorio Chile. All other Companies are Chilean (Collet, et al., 2011).

To provide the access to innovative medicine for the population – in order to guarantee best health care conditions - the governmental establishment of intellectual property rights and comprehensive regulatory framework, which is discussed later, was needed. This condition additionally allows the entrance of multinationals with their protected drugs. (Collet, et al., 2011)

“Non-Chilean companies operating in the country are required to contract the services of a customs agent when importing or exporting goods valued at over $1,000 FOB (Free on Board). The customs agent is the link between the exporter/importer and the National Customs Service and is responsible for facilitating foreign trade operations and acting as the official representative of the exporter/importer in the country. Customs agents’ fees are not standardized. This is an extra cost borne by non-Chilean companies operating in-country. However, companies established in any of the Chilean duty-free zones are exempt from the obligation to use a customs agent when importing or exporting goods.” (Office of the United States Trade Representatives, 2011). SME starting their business in Chile have to find out about the sizes of the payment to different custom agents, compare them and calculate these additional costs in their future pricing adjustment, alternatively a subsidiary in Chilean duty-free zones has to be established.

Import costs for Chile are the second lowest in Latin America with assumed costs of US$ 795 per container by a regional average of US$1495 (The World Bank and International Finance

Corporation, 2012). There exists a FTA between Chile and EU, signed in 2002 (European Community & Republic of Chile, 2002).

COLUMBIA

The Columbian pharmaceutical market is the fourth largest in Latin America. (Santos Pereira, et al., 2010). According to the Word Bank "Colombia is ranked 7th out of 29 countries in the South and Central America/Caribbean region and is one of the most improved economies in the 2011 Index. [...] Colombia continues to maintain strong economic fundamentals, including macroeconomic stability and openness to global trade and finance." (The World Bank Brazil, 2011).

The Columbian constitution states in Article 49: "Public health and environmental protection are public services for which the state is responsible. For all individuals access to services that promote, protect, and rehabilitate public health is guaranteed." (People of Columbia, 1991)

MARKET CHARACTERISTICS

In the past many multinationals closed their manufacturing plants in Columbia due to political safety concerns. They left behind business and technology knowhow as well as employees trained in pharmaceutical production. The plants and the employees were transferred to local companies developing home-grown operations, strong and expanding in Latin American markets. Today only a few global players (45% of total pharmaceutical market in Columbia) are actually present in Columbia (Genzyme, GSK, Roche). Genzyme entered the Columbian market in 2002 with success and respectable growth rates because of innovative and specialized niche products (orphan drugs, neglected patients). GSK on the other hand, selling blockbusters, sees the Columbian market as a stable market not expected to grow (Santos Pereira, et al., 2010).

60% of the pharmaceutical market is covered by generics, cheap (average price is the cheapest in Latin America) and easy accessible medicines, a demand of the expanding Columbian health insurance and the competition of the present companies. "This is because of strong competition that drives prices down", says Alberto Bravo Borda, Executive President of ASINFAR, National Association of Local Laboratories (Santos Pereira, et al., 2010)).

Because the Columbian constitution guarantees the access to health care the health protection Law 100 was established in 1993 to cover a basic health care program, depending upon income. This law was introduced to specifically reach the poor population. Especially children, single mothers, elderly and handicapped or chronically ill persons are included and benefit from this program (Krech, date not available). But "Plan 100 was criticized for making health care a commodity and not a right." (Anderson, 2009). During 2011 the Columbian government reformed the health care system (Act 1438 from January 2011 (Baker & McKenzie, 2011)) and in January 2012 167 new technologies were included in the plan of benefits especially for the treatment of diseases leading to greater disability and premature death such as cancer, hypertension, kidney disease, sexual diseases, reproductive system diseases and mental health with special emphasis on primary health care, health promotion and disease prevention. In 2011 the health care system reached coverage of 96 %. (Bolivar, 2012).
The import costs for Columbia are very high (US$ 2830 per container) compared to the regional average (US$ 1495), only exceeded by Venezuela (The World Bank and International Finance Corporation, 2012) and there exists no FTA between Columbia and EU.

CUBA

The pharmaceutical market of Cuba is rather small and has some special characteristics based on the political circumstances:

"Cuba is a totalitarian communist state headed by General Raul Castro and a cadre of party loyalists." (US State Department, 2011). Therefore the United States of America imposed a trade embargo on Cuba in October 1960, which is still ongoing. The trade embargo does not permit the sale of active ingredients or raw materials to Cuban pharmaceutical industry. Therefore the local pharmaceutical and biotechnology industry is very strong (Exports: US$520 mill in 2010). (US State Department, 2011)

The EU imposed an embargo on Cuba in 2003 which was not as strict as the US embargo. These sanctions were lifted in 2008 after Raul Castro took over the government from his brother Fidel. (BBC News, 2008).

MARKET CHARACTERISTICS

In the response to the pressure of international sanctions and the disappearance of Soviet aid after the collapse of the Soviet Union, Cuba`s government was forced to introduce rationing of energy and consumer goods (including medicines). But this "Special Period" led to a continuous strengthening of local pharmaceutical and biotechnological industry. Today the Cuban pharmaceutical market is dominated by local companies. Cuba is the biggest exporter of medicals in South America with 50 countries on its clients list. The prices are much lower than the first-world-counterparts. Starting with the production of generics the development was followed by the introduction of intellectual property rights and the granting of patents. Today Cuban companies have granted more than 100 patents including 26 in US (Starr, 2004). The Cuban pharmaceutical industry is a very important financial as well as an image factor in the Cuban economy. A lot of economic co-operations are based on the export of high-quality/low price medicine (China, Malaysia, India and Iraq). Therefore it is strongly supported by the government. The mostly state-run companies are going to be certificated by ISO-9002 (first one was Biocen in 1999, (Grogg, 1999)). Further problems for foreign companies are dense regulations and impenetrable bureaucracy which deteriorates foreign business (US State Department, 2011; Starr, 2004) While Cuba offers low research costs and an opportunity for European companies to expand their product portfolios, obtaining patents or contracting continues to be complicated. (Grogg, 1999)

MEXICO

Mexico as one of the larger Latin American pharmaceutical markets has the most challenging forecast for sales potential, industrial growth and clinical research. Many of the global players are very much interested in Mexico: The healthcare expenditures of Mexico are in a high range and an increasing amount of the population has purchasing power. Although Mexico is neither a member nor an associate member of Mercosur, it signed free trade assignments (FTA) with the Members of Mercosur and with EU (European Commission, 2010).

MARKET CHARACTERISTICS

Comprehensive reforms in the health care system changes in the sector of intellectual property rights and drug regulation (bioequivalence studies for generics) have been undertaken and are ongoing, leading to higher quality products, cost effectiveness and a better supply of the population with pharmaceutical products.

Company	Ranking	% Market Share
Sanofi-Aventis	1	7,3
Pfizer	2	6,5
Schering Plough	3	4,8
Roche	4	4.7
Novartis	5	4,5
Johnson & Johnson	6	4,3
Bayer	7	4,2
Boehringer Ingelheim	8	3,9
GSK	9	3,8
BMS	10	3,6
...	...	...
Senosiain	17	2,4
Liomont	21	1,9
Sanfer	22	1,8
Rimsa	25	1,3
PiSA	26	1,1

Table 6: Top 10 pharmaceutical companies in the Mexican market added by local companies with highest rankings

(Medrisch, et al., 2008).

The market is dominated by global players (see table 6) and the local companies with the highest rankings start at position 17. Senosiain (EvaluatePharma, date not available), Sanfer (Sanfer, no date available), Rimsa (Rimsa, date not available), Liomont (Liomont, date not available) and PiSA (PiSA, date not available) are companies producing and selling generics for a variety of indications. Foreign companies are very successful with their branded drugs. The local companies are not active in R&D focused in the production of “similares” for which no bioequivalence study was necessary (Medrisch, et al., 2008). The stringent bioequivalence testing which needed new registration for all generics / similar drugs in the last years led to a massive reduction of products available on the Mexican market (estimated 7000 products vanished) after the deadline in February 2010 (Avena, 2012).

On the other hand quality is guaranteed by re-registration of drugs meeting bioequivalence standards. As a consequence, the number of companies present in the Mexican market, were expected to decline with the result that only those will stay who meet the economical and qualitative standards (Medrisch, et al., 2008).

The Mexican government initiated a campaign which reached full coverage in 2012 (Avena, 2012). The Mexican Institute of Social Security (IMSS) covers 44.3 % of the population, mainly workers in the private sector, Institute of Health and Social Services (ISSSTE) covers 9.8% of the population mainly government workers and representatives and Seguro Popular (founded 2003) for all Mexican not affiliated with any social security. (Avena, 2012).

To follow this trend and to meet customers needs the market needed low-price and high-quality products. Low prices were reached by a “reverse auction system” for the purchases by the Secretary of Health. (Medrisch, et al., 2008).

Interestingly the market share of generics in the Mexican pharmaceutical market in the past was very low compared to other Latin American countries, because people trusted more in patented drugs for safety reasons.

“Whether these rules (bioequivalence studies, re-registration) will lead to a shift away from the dominance of brands remains to be seen. Some pharmacies are so married to their brands that they maintain physicians on staff to offer free medical services for customers, who in return are given scripts for brands offered by the pharmacy.” (Bourne Partners, 2012).

In addition to that the suppression of the manufacturing plant law in 2008 made it easier for foreign companies to market and sell finished products without the presence of a producing plant in Mexico (Avena, 2012).
Trade with Mexico is simplified by FTA between Mercosur, USA and EU but the import costs are relative high (US$ 1780 per container) compared to the regional average (US$ 1495) (The World Bank and International Finance Corporation, 2012).

PERU

As one of the smaller markets in the Latin American region Peru is expected to be a small but stable market: “The sovereign risk is assessed as stable because of a low public debt burden (at 19.9% of GDP in 2011), the continuity of prudent fiscal and monetary policies under the administration of the president Ollanta Humala and rapid GDP growth. These factors support the A rating in this risk assessment.” (Economist Intelligence Unit, 2012)

Because the health expenditures per capita are still low the market is expected to have growth opportunities. Urbanisation and the gross domestic product are increasing supporting the growth potential of the Peruvian economy. But Peru, compared to the other countries, has a high poverty index. 20 % of the population cover 54 % of the total national income. Another 20 % live below the poverty line. To equate this situation the “Peru Healthcare Policy” was launched by the government. Therefore medicines at low prices with high quality are needed to achieve a full coverage for the Peruvian population (Maps of the World, date not available). In 2002 the Seguro Integral de Salud (SIS) was established to offer free healthcare to all the citizens. But the country itself with its jungles and mountains makes it very difficult to reach every habitant. Most of the hospitals and all 8 national hospitals are located in Lima (future years)

MARKET CHARACTERISTICS

Peru continues to implement its National Strategic Plan to combat counterfeiting and piracy to avoid drug copying. (Espicom Peru, 2012). But the penetration of the market with generics in Peru is very low. This may be caused by low confidence of patients into “copied drugs”. On the other hand, especially in Lima the self-medication has a volume of about 43% (Economist Intelligence Unit, 2011) indicating that there is a market for high qualitative generic drugs.

“Peru's key strength as a business location will be its openness to foreign trade secured by multiple free-trade agreements (FTAs with USA, Canada and EU) and its still-stable macroeconomic environment.” (Economist Intelligence Unit, 2011). Import costs are very low with US$ 880 per container compared to the regional average of US$ 1495 (The World Bank and International Finance Corporation, 2012).

“Peru's pharmaceutical market enjoys significant potential to grow during 2010, as there is much market space to develop businesses and sell products, according to Rey de la Cuba (Executive Director of Asociación Nacional de Laboratorios Farmacéuticos (ALAFARPE)). National firms will remain as the rising stars within the market, where their participation has soared in the past few years. Foreign firms are expected to continue showing interest to boost their participation and possibly buy local players. However, local firms are not expected to sell anytime soon, as they currently enjoy significant opportunities for profit making. As a result, the market is expected to remain fragmented with no major consolidations. As in many Latin American countries, the tendency of growth will remain in the generics' sector, states Rey de la Cuba.” (IHS, 2010).

Global Players like Abbott, Lilly, Merck, Novartis and Roche are active in Peru. Besides that some local pharmaceutical companies are present like Quality Pharma (vaccines, fertility, mistletoe products (Quality Pharma, 2012)).
The biggest pharmaceutical wholesalers are Química Suiza, Albis and Drokasa. Química Suiza is the representative for 13 pharmaceutical companies in Peru: Allergan, Ferring Pharmaceuticals, Leo and Solvay amongst others (Quimica Suiza, date not available). They distribute and market the products of the companies they represent in the Peruvian market.

URUGUAY

"...to become a leading productive sector in South America and a worldwide reference. We want to be recognized as a model sector due to the quality of our products, the technology we use and the specialization of our human resources, which enables us to gain access to the most demanding markets worldwide and continue to provide high quality medicine at affordable prices for all Uruguayans". (Uruguay XXI, 2011). This is the vision of the so called "Productive Cabinet" (Gabinete Productivo). The main objectives of this government associated cabinet are to enhance productivity and innovation and to enforce internationalization of Uruguayan pharmaceutical industry. After a transient period, where poverty increased in Uruguay, the country today has managed the economical crises from 2001 and 2008/09.

MARKET CHARACTERISTICS

The active players in the Uruguayan pharmaceutical market are multinationals producing patented drugs, small national companies manufacturing similars or generic products and sales companies serving the sales channels for diverse companies.

The growth of the Uruguayan pharmaceutical market is mainly driven by the changes in the age pyramid with increasing numbers of people in the age of >65 years. This population group needs more medications than the younger and therefore the market is expected to increase although the population growth rate is very low.

The government supports the pharmaceutical industry because it is the most dynamic and therefore the most important segment of the Uruguayan economy.

103 pharmaceutical companies are registered in Uruguay:

Subsidiaries of Abbott, Beckton & Dickinson, Boehringer Ingelheim, Merck, Pfizer, Roche, Sanofi and Serono stand for the group of global players with manufacturing sites and subsidiaries present in Uruguay.

Local generics manufacturing companies are for example Laboratorio Gautier (now a company of Europharma) and Gramon-Bago, belonging to the Bago-Group present in all Latin American countries.

Pure sales organisations are Beacio, Laboratorio Clausen, the Brazilian company Andromaco and the Argentinean wholesaler Laboratorio Dr. Gray.

The import costs are medium sized with US$ 1320 compared to the regional average (US$ 1495).

VENEZUELA

Venezuela belonged until 2006 to the Andean Community (CAN), the membership was withdrawn after the other members decided to enter a free trade agreement with the United States of America. In December 2005 Venezuela signed the agreement with Mercosur. To become a member the application has to be accepted by all Mercosur member states. Until now the Paraguayan congress denied the membership of Venezuela because of infringements of human law and restrictions of press freedom.

“Venezuela's business environment ranking will fall in 2012-16 to 80th place, making the country one of the least attractive investment locations in Latin America and globally. This reflects unpredictable state interventionism, a highly heterodox macroeconomic environment, sub-par legal security and difficulties accessing foreign exchange. Weak and politicised institutions, an unpredictable tax regime, an increasingly rigid labour market and deteriorating infrastructure will also impair the business outlook.” (Economist Intelligence Unit, 2012).

MARKET CHARACTERISTICS

“The Venezuelan health system remains financially fragmented and under-funded. [...] OTC and generic sales are expected to increase in the forecast period. There are about 33 pharmaceutical producers, most of which are local. Foreign producers have consolidated their regional operations in other countries in the last ten years, but Bayer, Daiichi Sankyo, Pfizer, Sanofi, La Sante and Teva remain.” (Espicom Venezuela, 2012). Additionally to the underfunded health care system the poverty rate is high and the prohibition of circulation of foreign currency, drug price controls and high inflation rates complicates trade with Venezuela, too.

SELECTION OF MOST PROMISING MARKETS

The final decision for each SME is dependent on the company size and internationality, the strategic orientation, the risk-taking of the management and the portfolio and therefore cannot be included in this guide.

But there are some important points to consider in the selection of the most promising markets:

POLITICAL AND ECONOMICAL SAFETY

The emerging countries are sometimes politically instable. That is founded in the history of the countries, where dictatorship still exists (Cuba), corruption is suspected (Venezuela, Argentina) and the rate of drug related crime is high (Mexico). There are some safer countries (Brazil, Chile, Mexico, Peru and Uruguay) compared to more risky states (Argentina, Cuba, Columbia, and Venezuela) with unexpected and unpredictable political and economical developments and/or governmental decisions.

MARKET SUCCESS

Growing and developing markets show the greatest possibilities for companies. But the population needs to be aware of health care and the access to healthcare products has to be possible. Therefore Peru for instance with geographical disadvantages (jungles, mountains), lesser educated people and hospitals mostly centralized in the capital city makes market access hard. Other countries like Venezuela have more political and economical hurdles which

makes market entrance more difficult. On the other hand in Argentina and Brazil global players cover the most interesting fields. This makes the market entrance for SME very challenging, laborious and expensive because of all kind of marketing & sales activities to strengthen the awareness of the company and its products.

GENERICS MARKET SUCCESS

Generics are the most interesting group of pharmaceutical products because their high quality, their market presence since many years and their low prices compared to patented drugs. But in Latin American countries the obligations for bioequivalence studies have been introduced in the recent past. Before that cheap but qualitatively poor copied drugs (similares) were available. Generics are now mixed up with these copied medicines by the population. Therefore the belief in the quality, safety and efficacy of the generic drugs in the population and the medical professionals is often very low.

Another point is that in many countries medicines are paid out of pocket. Therefore special packages should be developed for example with only a few tablets (Nycomed/Takeda and the launch of Neosaldina in Brazil) which lowers the price and makes it more affordable for the patient.

FINANCING HEALTH CARE

"With the exception of Cuba and Columbia, where the health expenditures are mainly issued by the government, the other countries pay out of pocket, through private insurance, charity donations and direct service payment by private corporations. That implicates that if economy decreases the pharmaceutical market will shrink too, because of a reduced purchasing power." (World Pharmaceutical Frontiers, 2010). A lot of reforms are ongoing in Latin America concerning health care: Brazil, Chile and Columbia guarantee health care for their citizens by constitutional rights. Mexico and Peru plan to reach coverage of more than 90% in the near future. But the majority has to pay for their treatments by their own.

TRADE

For some countries there exist Free Trade Agreements (FTA) with Europe (Chile, Mexico and Peru) and for all but Cuba between the United States of America and the Andean Community (CAN) and Mercosur. Venezuela's position is not clear because it left the CAN in 2006 The CAN norms are accepted and were valid in Venezuela until end of 2009. On the other hand the Venezuelan membership in Mercosur is not accepted until now (Paraguay denied the membership) although Venezuela signed the framework agreement to join the community in 2005.

FTAs make trade much easier, therefore companies with their focus in European markets will rather expand to Chile, Mexico and Peru because of easier access and reduced costs. But the overall import costs vary much from US$ 795 in Chile to US$ 2868 in Venezuela compared to a regional average value of US$ 1495 per container.

Country	Pro	Cons	SME suitability
Argentina	Market share for generics is low (hospitals only) - pharmacy market may be evolved	Innovative patented local drugs dominate the market, import restrictions, price accords, high poverty rate, dominance of local	unsolved import regulations, possible only with partners (outlicencing to other pharmaceutical companies or partnership

Country	Pro	Cons	SME suitability
		companies supported by government, high import costs, no FTA to EU	with wholesalers or distributers)
Brazil	Constitutional right, prescription market low, but developing; out of pocket market high, need for affordable and trustworthy medicines, use of wholesalers as sales channels, introduction of generics act will enlarge the generics market (bioequivalence studies are obligatory)	Big and developed market, Presence of global players, high competition, low prices, high taxes, inefficient regulations for trade, presence (subsidiary) in Brazil is recommended, adaption of products to the patient's needs (package size, administration...)	hard to enter, high costs, possible only with partners (outlicencing to other pharmaceutical companies or partnership with wholesalers or distributers)
Chile	Politically and economically most stable LatAm country (A+), constitutional right, GES (ex AUGE) program, full coverage (government), flexible market, 80% of pharmaceutical market are generics, only a few global players, Low import costs, FTA with EU	governmental support of local companies with market knowledge, with exception of trade free areas a customs agent for foreign companies is obligatory	Very good chances for patented drugs and generics, especially for EU based companies
Columbia	Improved economy, constitutional right, Law 100 and Act 1438, 96% coverage (insurances), safe and constantly growing, Geographical localisation (Central America- South America)	Political safety concerns, instable political situation, low urbanisation rate, high poverty rate, no profitable market, lowest prices, generic market is constant, high import costs, no FTA with EU	Some chances because of stable market forecast, but very low prices
Cuba	No competition with US-based global players because of embargo	Totalitarian communist state, small market with established local companies, low urbanisation, low	Low chance, strong governmental control, difficult contracting, impenetrable bureaucracy

Country	Pro	Cons	SME suitability
		prices, strongly supported and controlled by the government, dense regulations, impenetrable bureaucracy, contracting is difficult	
Mexico	Most challenging forecast, population with purchasing power, reformation of drug regulation and health care system, elimination of "similares" without proof of bioequivalence, full health care coverage since 2012, need for generics (small, but developing market share), import of finished products facilitated by the government, FTA with EU	High interest of multinationals, large chain retail pharmacies, relatively high import costs, pharmacists stick to their known brands	Realistic chances with partners (outlicencing to other pharmaceutical companies or partnership with wholesalers or distributers)
Peru	Small but stable market, stable sovereign, growth opportunities, low penetration with generics (fear of copied drugs), open for foreign business, FTA with EU	Geographical structure (mountains and jungles), high poverty rate	Possible especially for EU-based companies, but problematic distribution of products
Uruguay	Change in the age pyramid (>65 years), high need for drugs, small local companies selling similar or generics, medium sized import costs	Strong support of local pharmaceutical industry, highly competitive, no FTA with EU	Some chances for geriatric products
Venezuela	Only local competition, (foreign companies have consolidated regional operations in other countries)	Underfunded and fragmented healthcare system, high poverty rate, drug price control, high inflation, no membership to Mercosur, CAN and no FTA with EU	instable economy, unsolved (trade) situation

Table 7: Summary of Pros, Cons and Suitability for SME

Based on the findings in decision level 1 and 2, the political and economical safety, market success, market situation, financing of health care and trade factors, summarized in table 7 and in addition to the FTA with EU Mexico is expected to be the most promising country to enter, if out-licensing to a partner is planned. If an entrance to Latin-America is planned without partnering Chile is selected as the most promising country, supported by the finding that the founding of a subsidiary is easiest in Chile. Each of the emerging markets (Table 7) offer many chances in the developing markets, but they too bear a lot of risks. Therefore the main factor in the decision level 2 was fixed to the political and economical stability, the competition and the existence of Free Trade Agreements (European Community & Republic of Chile, 2002; European Community & Republic of Mexico, 1997) between Europe and the selected countries, which makes trade much easier. Additionally the AHK of Chile and Mexico have strong interest in supporting especially small enterprises in their efforts to enter the markets of these Latin American countries and support SME in their start period.

DECISION LEVEL 3: DRUG REGULATION IN SELECTED COUNTRIES

Mexico and Chile are countries of the Pan American Health Organization (PAHO), a subdivision of the World Health Organization (WHO). Under this organisation the Pan American Network for Drug Regulatory Harmonization (PANDRH) was "established in 1999 to support processes on drug regulatory harmonization. PANDRH includes the national authorities of countries in the Americas, various pharmaceutical interest groups, industry, and academia" (FDA, 2011). Working groups of PANDRH are actually: Bioequivalence, Biotechnological Products, Combat Counterfeit Medicines, Good Clinical Practices, Good Laboratory Practices, Good Manufacturing Practices, Plants, Medicines Classification, Medicines Registration, Medicines Promotion, Pharmacopoiea, Pharmacovigilance and Vaccines. (PAHO, 2012).

The harmonization goes along with the membership of Mercosur and CAN in the Global Cooperation Group (GCG). „The Global Cooperation Group (GCG) was originally formed as a subcommittee of the ICH Steering Committee in 1999 in response to a growing interest in ICH Guidelines beyond the three ICH regions. A few years later, recognising the need to engage actively with other harmonisation initiatives, representatives from five Regional Harmonisation Initiatives (RHIs) were invited to participate in GCG discussions, namely, APEC, ASEAN, EAC, GCC, PANDRH and SADC." (ICH, 2012).

The Third Pan American Conference recommended the formation of a Medicines Registration Working Group, „which prepared a survey on technical and legal requirements for drug registration that the different countries could be requesting and evaluating for the granting registration of drugs. […] The proposal encompasses the drug registration requirements for new or generic drugs. In this regard, it bears mentioning that registration requirements for similar or generic products were made uniform. Accordingly, there is no distinction between the two products (similar and generics) since, from the sanitary standpoint, there should be no differences in requirements for drug quality. The proposal also covers the registration of new drug dosages, new concentrations, new combinations, and registry renewal" (PAHO/PANDRH, 2004).

The objectives of the Pan American Network for Drug Regulatory Harmonization are; "(1) To promote and maintain a constructive dialogue among regulatory agencies, the pharmaceutical industry, and other sectors, through periodic Conferences. (2) To encourage convergence of drug regulatory systems in the Pan American Region. (3) To adopt recommendations for

implementation at national and regional levels. (4) To encourage and facilitate technical cooperation among countries. (5) To promote harmonization of medicinal drug regulation requirements and guidelines for specific regulatory issues" (PAHO, 2004).

The flow of information is depicted in figure 1:

Figure 1: Information- and work-flow for harmonization of drug registration in Latin America (GCG = Global Cooperation Groups of the ICH)

Based on this situation the states of the CAN as well as of Mercosur mostly accept the ICH registration documents used in the CTD. Only in Module 1 regional specific information is needed.

FOUNDING A LOCAL SUBSIDIARY

There are a lot of benefits arising when companies start their business with their own local subsidiary: The subsidiary gets access to services and institutions provided by the government, it has insights in the market dynamic and steers the activities of the sales and marketing. Especially in the emerging Latin American countries a product adaption (smaller packages, special administration) sometimes is suitable and profitable.

Many of the Latin American countries made the registration of a pure sales organisation easier. Especially Chile ranks on position 1 for starting a business in their countries (The World Bank and International Finance Corporation, 2012).

CHILE – MARKET ACCESS BY FOUNDING A LOCAL SUBSIDIARY

Under the Chilean "Ministerio de la Salud" the "Instituto de la Salud Pùblica" (ISP) including the Agencia Nacional de Medicamentos (ANAMED) is responsible for the registration of all drugs to be imported into Chile. The applicant has to present complete documentation on preclinical and clinical studies during all phases of development. The CTD format is accepted

for Module 2-5 and it is expected that in this first decade of the new millennium Chile will comply with the CTD which is planned already for years (Marovac, 2001). Additionally an expert's opinion should be included, covering the whole set of studies performed with the product. The revision by the Chilean authority needs 12-18 month. Internal revisers and a commission of external experts participate in this process. (Marovac, 2001).

DRUG REGULATION PROCESS

The process of drug registration in Chile is mainly regulated by the Decreto 3 (D.S. 3/2010) "Aprueba reglamento del sistema nacional de control de los productos farmacéuticos de uso humano" (Ministerio de Salud; Subsecretaria de Salud Publica de Chile, 2011) and in the Decreto 1876 "Aprueba reglamento del sistema nacional de control de productos farmaceuticos, alimentos de uso medico y cosmeticos" (Ministerio de Salud de Chile, 1996).

D.S. 3/2010 describes the registration of pharmaceutical products in detail and regulates labelling, import, distribution, information and pharmacovigilance. The most important parts are summarized in the following text, which is mainly a translation of parts of D.S. 3/2010. Unfortunately the document is only available in Spanish:

The "Instituto de Salud Pùblica" (Institute) is the authority to control pharmaceutical products covering the whole territory of Chile, based on regulation D.S. 3/2010, the "Códico Sanitario" (Chilean Government, 1968) and all related regulations. The control of medicinal products covers all phases of the product value chain (Article 3). The "Secretarías Regionales Ministeriales de Salud (SEREMI)" serve as the regional authorities for application and verifying pharmaceutical products (Article 4).

Day	Action
0	Submission of request for authorization, electronical submission is possible (Instituto de Salud Publica de Chile, date not available) payment of the corresponding tariff.
1	Start of procedure Submission is recorded: „the time and date of presentation are noted" „a reference number for the entry and future tracking is given" Upon payment of the fees the procedure starts.
1-10	The Institute reviews the application
10	The applicant receives a revision: In the case of admission of the request for evaluation and review it shall notified to the applicant and the tariff corresponding to the next phase of the procedure hast o be paid. If it is determined that the application is not admissible the institute will give a period of five working days for revision.
180 for patented drugs **120 for basic health care and generic drugs**	Technical information, information on quality, safety and efficacy is evaluated by the Institute and the final decision about the application is made.

Table 8: Timeline for the evaluation of an application in Chile

The registration of a pharmaceutical product is a process of evaluation based on systematic studies covering pharmaceutical properties, pharmacology, toxicology and clinical experience

to verify the quality, safety and efficacy of the product. The registration can be requested by any natural of juridical person, national or foreign, which must be domiciled in Chile (Article 18).

The registration process is independent from the commercial aspects of industrial or intellectual property (Article 19), which is regulated by Ley N° 19.039 “Propiedad Industrial”, Ministerio de Economía, Fomeneto y Reconstrucción. (Ministerio de Economía Fomento y Reconstrucción de Chile, 1991)

All medicinal products imported to or manufactured in Chile for the distribution or the use in the national territory have to be previously registered by the national authority (Article 20)

D.S. 3/2010 further contents a list of documents needed for registration (Article 28 – 42, annex 1 Chile) and a description of the application procedure (Article 43 - 50). A check-list for the evaluation of the completeness of the documents needed for the application is provided by the Institute (Instituto de Salud Publica de Chile, date not available).

VARIATIONS

Variations have to be announced to the competent authority by a petition, which in turn has the right to enable or disable. This applies to technical aspects (labelling) and to changes in the formulation, modification and all administrative aspects like addresses and names (Article 63 – 70).

IMPORTATION

D.S. 3/2010 further regulates the importation of medicinal products into the territory of Chile (Article 95 ff): Import is only possible for authorized pharmaceutical laboratories, pharmacies, drug stores and pharmaceutical warehouses by natural or legal persons in accordance with the current legislation. To import into the national territory, an authorized location is required like authorized pharmaceutical laboratories, pharmacies, drug stores and pharmaceutical warehouses corresponding to the kind of material to be imported (Article 95 – 97). For the import of any medicinal product the company should apply for a certificate to the SEREMI, corresponding to the Customs Office of entry of the product. It should cover all relevant information on material, amount and nature of the product, as well as the route and means of transport shall be indicated for the shipment from the customs premises to an establishment approved for this purpose (Article 98). The SEREMI decides on the request within a period of three working days from the date of filing of the petition. For any destination of pharmaceutical products, the certificate issued by the respective SEREMI should be submitted to the Servicio Nacional de Aduanas (National Customs Office). The National Customs monthly informs the Institute about the import (quantity, importer) of the medicinal products (Article 99).

PRODUCTION (GMP)

The production of proprietary medicinal products shall correspond exclusively to pharmaceutical companies regulated and authorised in accordance with regulation D.S. 3/2010. These pharmaceutical companies are enabled to the import, production, packaging, conditioning or quality control of the medicinal products (Article 106 - 112). All pharmaceutical companies shall observe the regulation contained in Good Manufacturing and Laboratory Practices, as appropriate to the activities for which they are authorized. The foundation as well as amplification and modification of a pharmaceutical company have to be authorized per resolution by the Institute and are valid for three years with the possibility for renovation

(Article 108-112). The procedure for the authorization to install a pharmaceutical company in Chile is described in Article 113 – 194. The distribution of products is only possible for pharmaceutical companies, drugstores and warehouses of medicinal products, under defined conditions and for the purpose the products and distributors are authorized (Article 195 - 198).

SUMMARY OF PRODUCT CHARACTERISTICS (INFORMATIÓN AL PROFESIONAL)

The "Informatión al Profesional" (corresponding to SmPC) is a document containing the characteristics of the medicinal product, pharmacokinetic and pharmacodynamic aspects, toxicologic data as well as indications, dosage, age group for which it is registered, contraindications, interactions, precautions or warnings, adverse reactions, risks and precautions during pregnancy, lactation or within special populations, the measures to be taken in cases of overdose and other aspects, determined by the authority on the basis of the nature and scientific information available of the pharmaceutical product, with the aim of informing professionals legally qualified to prescribe or supply pharmaceutical products (Article 199c).

PATIENT INFORMATION LEAFLET (INFORMACIÓN AL PACIENTE)

The „Información al Paciente" is a document needed to inform the patient on a proprietary medicinal product. It contains the information concerning the authorised indication, warnings, contraindications, interactions with other products, precautions and other information as determined by the health authority in registry, to ensure its correct use. The brochure for pharmaceuticals direct sales, must provide in addition information about the usual dosage for use in particular and its use approved in the registry (Article 199d).

PHARMACOVIGILANCE OF ADVERSE REACTIONS (REACCIÓN ADVERSA A MEDICAMENTOS, RAM)

The pharmacovigilance system has to be established as follows: Health professionals have the duty to inform the Institute about all suspected adverse reactions which they are aware and which could have been caused by a pharmaceutical product. The same obligation shall lie by the Technical Director of the pharmaceutical company, which shall keep an up-to-date record of these events. In case of suspicion of a serious adverse reaction to medication, communication must be made within 72 hours (3 days) starting with the knowledge of the fact. Non serious cases must be communicated within a period of 30 days. A form (in .doc format) comparable to the CIOMS form, including a instruction to complete the form, is provided on the ANAMED website (Instituto de Salud Publica de Chile, date not available). The MAH has the duty to create, adopt and maintain a documented system to collect and treat any information about all suspected adverse reactions in a single file. He has to prepare and submit on a quarterly basis to the Institute of public health all information on suspected adverse reactions in the authorized forms, unless the Institute determines a shorter period by resolution. He further has to ensure that a prompt (within the time limits established by the Institute) and complete response to any request for additional information is given, if required by the Institute. The MAH further is obliged to keep up-to-date security information of the product and a continuous assessment of the risk-benefit ratio. The Institute on the other hand will analyze the information of pharmcovigilance and will if needed require necessary studies to evaluate the safety of a medical product, under the authorised conditions of use. It may also propose measures to minimize the risks associated with the use of proprietary medicinal products and to maintain an appropriate balance in the risk-benefit ratio (Article 216 – 220).

QUALITY COMPLAINTS (DENUNCIAS A LA CALIDAD)

In 2004 the Seccion Muestras Legales por Denucias a la Calidad was introduced into the Institute as a subdepartment of the Laboratorio Nacional de Control. If a complaint (no adverse reactions) has been detected it has to be sent to this section by a predefined formula (Instituto de Salud Publica de Chile, 2011), where the complaint is verified and evaluated (Seccion Muestras Legales por Denuncias a a Calidad, date not available).

INSPECTIONS OF STUDY CENTRES

The examination of centres contributing to biodisponsibility/bioequivalence studies according to the form F-BIOF-01 (Instituto de Salud Publica de Chile, date not available) can be inspected by the Institute. The inspection criteria are described in Resolution 727/05 (Ministerio de Salud de Chile, 2005) and the protocol of the visit is published in the "Acta para las visitas de Inspección a centros que realizan studios para demonstrar equivalencia terpéutica" I BIOF 01 for in vivo studies (Departamento Control Nacional Subdepartamento de Seguridad Sección Biofarmacia, 2008) and I BIOF 02 for in vitro studies (Departamento Control Nacional Subdepartamento de Seguridad Sección Biofarmacia, 2008).

STUDIES ON THERAPEUTICAL BIOEQUIVALENCE (EQUIVALENCIA TERAPÉUTICA)

Pharmaceutically equivalent are products with identical content of the same active principle, whereas therapeutically equivalents are products with the same mode of administration and the same effects with respect to efficacy and safety. (Ministerio de Salud de Chile, 2005)

For pharmaceutical products requiring the proof of therapeutic equivalence a list of pharmaceutical products that serve as reference are approved by Supreme Decree of the Ministry, issued as a proposition of the Institute. (Ministerio de Salud de Chile, 2012)

Also, by resolution of the Ministry standard technical criteria (labelling: (Ministerio de la Salud de Chile, 2012), norms: (Ministerio de Salud de Chile, 2005)) are adopted that establish the criteria necessary to proof therapeutic bioequivalence of pharmaceutical products. Furthermore rules and other procedures for the studies of bioavailability, as well as studies of therapeutic equivalence are established by a resolution of the Ministry, on the proposal of the Institute (Article 221). (Ministerio de Salud; Subsecretaria de Salud Publica de Chile, 2011).

The detailed description of the studies to proof bioequivalence (in vivo) are published in the Guía Téchnica G-Biof 01 (Instituto de Salud Publica de Chile, 2007). The studies have to be in conformity with the ethical principles of the Declaration of Helsinki, GLP, GMP and GCP. Further the studies require the approbation of the Comités de Evaluacion Ético Científico (CEEC) before they are submitted to the Institute. The documents needed for the submission to the CEEC are summarized in Annex 1. It is recommended that the investigator and the CEEC should be in close contact to each other during the different phases, especially during planning and initiating the study.

Studies consist of 3 phases: clinical, analytical and pharmacokinetical/statistical

For the clinical phase one reference site should be determined and a coordinator of the clinical phase should be introduced who is responsible for subject organisation, the administration, the samples needed (urine, blood...) and the observed adverse reactions, just to mention the most important. An internal monitor is responsible for guaranteeing the quality during the different phases of the study.

All analyses needed for the analytical phase should comply with GLP. The laboratory performing the analysis has to be quality certified for the analytical methods (SOP, audits...). All original documents (calculations, chromatograms...) have to be archived to document transparency.

All results from the pharmacokinetical/statistical phase should be performed by qualified persons. The calculations have to be specified in the study protocol. The results have to be presented in a written form. The minimal information needed are summarised in Annex 1. 4 forms for the correct submission of the study are provided by the Institute. From 01 for the request for approval of centers to conduct studies of Bioavailability/bioequivalence (Instituto de Salud Publica de Chile, date not available), Form 02 for the authorization of the protocol to conduct studies of bioavailablity/bioequivalence (Instituto de Salud Publica de Chile, date not available), Form 03 for the presentation of the study results (Instituto de Salud Publica de Chile, date not available) completed by Annex I to Form 03, a form for the tabulated presentation of the results (Instituto de Salud Publica de Chile, date not available).

To proof the inter-changeability the procedure of Bioexcensión (in vitro) has been established in Chile. The procedure is described in the Guía técnica G-BIOF 02 (Instituto de Salud Publica de Chile, 2007). The application for the bioextension is considered for

- Formulations with *in vivo* proof of biodisponsibility or –equivalence during the registration of a new pharmaceutical product
- Pharmaceutical products registered as “Similares”
- Changes after the approbation of a drug with therapeutic equivalence
- Formulations with similarity to other products, which has been proven in *in vivo* studies

The guideline describes in detail the application procedure, the methods recommended to determine the solubility, permeability and the kinetics of the release-dissolution *in vitro* and *in vivo* as well as how to present the application to the Institute including specifications to methods, validation, specificity and sensitivity, range, linearity, precision, robustness of the test and the influence of fitration. The results have to be included in annex II (Instituto de Salud Publica de Chile, date not available) form F-BIOF 06 (Instituto de Salud Publica de Chile, date not available) and presented together with the application forms F-BIOF 05 (Instituto de Salud Publica de Chile, date not available) and F-BIOF 04 (Instituto de Salud Publica de Chile, date not available). If the Institute approves a product as therapeutically equivalent it may publish the certificate “PRODUTO GENÈRICO INTERCAMBIABLE”.

PACKAGING MATERIAL

Packaging material for bioequivalent drugs have to be labelled in a defined manner which is described in detail in the brochure “Manual de Normas Gráficas” (Instituto de Salud Publica de Chile, date not available). An example for a generic product is shown in Figure 2.

Figure 2: Chilean Generica (ediciones especiales, 2012)

INTELLECTUAL PROPERTY RIGHTS (IPR)

Chile as a member of the WTO has to fulfil the TRIPS Agreement signed on January, 1st 1995, when it came into force. Additionally Chile signed the UCC Geneva (Universal Copyright Convention; September, 16st 1955) and WCT (World Intellectual Property Organisation Copyright Treaty; March, 6st 2002). In 2008 an intellectual property crimes unit, BRIDEPI, was established in Chile to protect the intellectual property rights (Dowling, 2010). But Chile still is not safe: The United States Trade Representative (USTR) observed positive steps taken in 2010 against copyright violation including the launch of a Ministerial-level interagency committee on IPR with a mandate to examine these issues (BRIDEPI), and the implementation of the new copyright legislation. But because of trademark law treaty Chile stays the fifth year on the US priority watch-list. „The USTR also urges Chile to provide adequate protection against unfair commercial use, as well as unauthorized disclosure, of undisclosed test or other data generated to obtain marketing approvals for pharmaceutical products, and to amend its Internet service provider liability regime to permit effective action against any act of infringement of copyright and related rights." (thepharmaletter, 2011).

PRICING AND REIMBURSEMENT

After the Pinochet government and a transition government the government of Patricio Alwyn (1990-1994) started to resolve the health sector problems. While maintaining the main structure of the decentralised health system with coexisting private and public sectors, the objectives were to increase equitiy and efficacy of the public system and to foster the participation of the Chilean community. The result of this initiative was first implemented between 1994 and 2000. The investments were financed by the state and through grants and loans from foreign democratic states (Marovac, 2001):

In Chile a private health and a public health sector exist, the later covers around 60% of the population (urban and rural poor, lower middle-class and retirees). The public sector is financed and administered by FONASA (Fondo Nacional de Salud) and delivered by SNSS (Sistema Nacional de Servicios de Salud) and the Department of Primary Care integrated in the Ministerio de la Salud.

The private sector covers about 25% of the Chilean population including the private health plans administered by ISAPRES (Institutiones de Salud Previsionales).

A third sector exists for army employees (10% of the population), which is separated from the public and the private sectors.

The Ministerio de la Salud guarantees every Chilean citizen free and equal access to health services and programs, the free choice between private and public health services, establishes national health policies, plans and norms (Códico Sanitario, (Chilean Government, 1968)) and supervises the organisations forming the public sector (Manuel, 2002):

SNSS: The Health Services are organised in a decentralised manner (28 regional Health Services) and are responsible for the coordination, management and development of the corresponding health care network, for the implementation of the integrated actions of promotion, protection and recovery of health, as well as rehabilitation and palliative care of the sick people.

FONASA: It is the public body responsible for granting care coverage, all people who are employed pay 7% of their monthly income in FONASA, those that lack own resources are funded by the State through a direct contribution. The resources come from general taxes and copayments (related to the income). FONASA finances SNSS on the bases of diagnosis. FONASA covers all medicines used for the diseases listed in GES (exAUGE) plan (Bibliotheca del Congresso National, 2011).

Public Health Institute: evaluates and registers pharmaceutical companies, monitors diseases, issues drugs, medicines, cosmetics and devices for medical use, (authorization, quality, importation), among others.

CENABAST: It aims to provide drugs and clinical inputs to the establishments of the national system of health services, municipal health facilities and others belonging to the public sector, such as the hospitals of the armed forces or universities.

Superintendencia de Salud: It is an organisation that has as main functions to oversee and control ISAPRES and FONASA and to ensure the fulfilment of the obligations of the law, as well as to monitor that all public and private health providers are accredited and certified (Ministerio de la Salud de Chile, 2012).

ISAPRES: provides different health plans to members, however it has to cover in all plans preventive medicine exams, sickness pay insurance and protection for pregnant women and children (<6 years). The funds of ISAPRES come from mandatory and voluntary contributions of the members (Manuel, 2002).

In summary the Chilean health care system is well developed most of the expenses are out-of-pocket and the expenditure per capita are relatively high. Nevertheless the prices of medicines are rather low.

STARTING BUSINESS

On the basis of a score consisting of “number of procedures”, “time needed”, “costs” and the “paid-in minimum capital requirement” Chile ranks on number 1 (The World Bank and International Finance Corporation, 2012):

In 2011 Chile introduced an online system for registration and since 2012 the government provides an immediate temporary operating licence to new companies. Therefore operations can immediately start without former inspections by tax authority.

Therefore starting a business in Chile is fast, easy and financially feasible even for SME.

COSTS OF REGISTRATION, MARKETING AUTHORIZATION, DISTRIBUTION, MARKETING AND IMPORT

Process	$
Simplified Application for Registration of Pharmaceuticals	213.000
Authorisation for Bioequivalence/Bioextension Studies (protocol)	453.449
Import (Custom's Agent)	depending on product value

Table 9: Costs for Registration, Marketing Authorization, Studies and Import in Chile

(Instituto de Salud Publica de Chile, 2012)

Especially the authorization or change of laboratories involved in bioequivalence or bioextension studies is very expensive ($ 300.000 - $500.000) depending on their function (clinical, analytical...). Variations of the labelling, packaging or modifications of the process have different values and are processed separately. The Secretariat does not charge any activities on marketing or distribution.

OUT-LICENSING

The entrance to the Mexican pharmaceutical market is hampered by the presence of global players and a developed wholesaler market. SME need to have a strong and matching partner to get a chance in this strongly competitive market. Out-licensing seems to be an appropriate approach. The SME can further focus on the home countries and the development of other products, while the partner is responsible for pharmaceutical licensing and marketing of the products in Latin American countries.

Several points should be considered prior to the start of an out-licensing process:

How to find the right partner? – Sending offers to large partners will not be very successful, because foreign and small companies are one amongst others. Often it is more appropriate to find a mid-sized partner. This can be supported by AHK in the country of interest. (AHK, 2010; Lachman, et al., 2005)

How to attract the right partner? – It is important to customize information, to find synergistic points, to sum up the benefits for the potential partners and to outline the product's value. Therefore all data (preclinical, clinical as well as market data) should be grouped in a short and understandable brochure. (Lachman, et al., 2005)

How to communicate? – The out-licensing process is complex. To save time fast communication of data and information is required. Web-based technology offers a wide-range of contact management programs, which are useful to have actual information at all partner's offices independent on local time. (Lachman, et al., 2005) A consultant for negotiating, reviewing and drafting of the agreements should be hired.

How to offer the product? – Often the foreign market has different needs as the home markets have. Therefore the possibility of delivering bulk ware is a good alternative to meet the market's needs. (Lachman, et al., 2005)

How to set up agreements of objectives? – In cooperation with the local partner forecasts expected for the first three years should be set up in sales and volume. Actual statistical data,

experiences from the past and influencing factors for the future development should be included in these negotiations.

How to guarantee high quality partnership? – Before the agreement is signed (latest point) both partners should be audited by each other or an independent consultant. The main points to be examined should be the company (structure, organisational chart, relationship to other companies, subsidiaries, suppliers), the companies quality assurance system (policies, standard operation procedures, guidelines) and the relevant certificates and registrations needed for the partnership. In the agreement an audit scheme (once a year, twice a year) should be defined.

How to distribute work and responsibility? In the agreement between the partners the responsibilities should be clearly defined. Small companies will transfer large parts of the pharmaceutical value chain to a partner, for example the cost intensive clinical studies to bigger and more experienced partners, whereas medium sized companies will give up only the responsibility for registration and marketing. Pharmacovigilance should be under the responsibility of the producer because the information on safety, efficacy and quality should be collected in one department to get insights in the product risk-benefit-balance.

MEXICO – MARKET ACCESS BY OUT-LICENSING

Conform to Art. 17 et seq. of the "Ley General de Salud", the Mexican General Health Law (Estados Unidos Mexicanos - Secretaria de Salud, 2003), the "Secretaría de Salud" (Secretary of Health) transferred all authority on medical registration, control and promotion to the "Comisión Federal para la Protección contra Riesgos Sanitarios" (COFEPRIS), established in 2001.

COFEPRIS is a decentralized technical, administrative and operational autonomous body. The Federal Commissioner is appointed by the President of the Republic on the proposal of the Secretary of health. The Secretary of Health supervises COFEPRIS (COFEPRIS, 2012). The eCTD is accepted in Mexico and both, the European as well as the US American standards for submission are deemed legally valid.

DRUG REGULATION PROCESS

The drug regulation process in Mexico is ruled by the "Reglamento de Insumos para la Salud" (Estados Unidos Mexicanos, 1998).

Besides this regulation guidelines and formats exist to standardize the processes: Each part is described in a process defined by a "Homoclave: COFEPRIA-XX-YYY" and a description. Corresponding to the "homoclave", EXCEL-sheets exist as forms to complete (Annex II). Related documents are listed to add to the requests.

Title 1 of the regulation lists definitions in general. In Title 2, chapter I the conditions for drugs, scientific investigation, production and the national government as the head of the national competent authority are reviewed concerning quality, labelling, packaging as well as prescription and the handling of hallucinogenic or psychotropic agents. In the following chapters biologics and hemoderivatives (II, Art. 43), hallucinogenic and psychotropic agents (III, Art. 44-80), vitamins (IV, Art. 81-82), homeopatics (V, Art. 83-85), herbal medicines (VI, Art. 86-71), generics (VII, Art. 72-80), biotechnological products (VIII, Art. 81), others (IX, Art. 82-87) are defined and classified. Here the focus is set onto generics: Generics are interchangeable drugs (intercambiables, Art. 72). The products are defined as generics by the "Consejo de

Salubridad General y la Secretaría" (Art. 73) and published as interchangesble medicines periodically in the "Diario Oficial de la Federación" (Art 74). The criteria for the definition as generic/interchangeable drug are listed in Art. 75: They have a current registration or the active substance and the pharmaceutical form is equal in concentration and potency to a patented drug with the same way of administration, they are published by the "Consejo de Salubridad General y la Secretaría" as interchangeable ("Catalogo de Medicamentos Genéricos Intercambiables"), the bioequivalence is proven by a study in comparison to an innovative product or a reference. The Catalogo is too the basis for the pharmacist to choose a drug, if the INN was used for the prescription of a drug (Art. 78). The "Consejo de Salubridad General y la Secretaría" invites the manufacturer of pharmaceutical products to produce generic drugs (Art. 80). Title 3 focuses on herbal medicines.

Title 4, Art 99-130, defines the roles of the counties, the pharmacies and drug stores and the manufacturer, who is responsible for the supervision of the manufacturing process and the compliance to GMP and title 5 (Art. 131-152) import and export procedures in general.

The procedure for the request for registration of a drug (Insumo para Salud) is laid down in Title 6 (article 153-192). The process follows the official format COFEPRIS-05-001 (COFEPRIS, date not available): All data on the product, the manufacturer, import conditions, etc., have to be transferred to an EXCEL-sheet ("Autorizaciones, Certificados y Visitas") which is provided in the process description. The completed form (original and one copy) has to be submitted to COFEPRIS and the fees have to be paid (preferentially by electronic invoice). Documents to be included in the case of a juristic person are original and copy of the incorporation agreement or notary's power that credits the legal representative, and for juristic as well as for physical persons a copy of the official identification of the legal representative or authorized persons and the "Registro Federal de Contribyentes" (social security number).

Between 10 days (if the applicant complies with the requested information) the authority decides on the request and an alphanumerical number is granted (SSA). The registration takes place as follows:

I. In the case of medicinal products containing active ingredients and with therapeutic indications already registered in Mexico, the registration shall be issued within a maximum period of 40 days. If the applicant presents favourable data issued by a third party acknowledged by the Secretariat, the record will be awarded within a maximum of 20 days.
II. In the case of medicinal products whose active ingredients are not registered in the United States of Mexico, but are registered and sold freely in the country of origin the granting will be issued within a maximum period of 60 days. When the applicant presents favourable data published by a third party acknowledged by the Secretariat, that the drug meets the conditions and complies with good manufacturing practices or an international organization acknowledged by the Secretariat recommends the approval of the drug, the secretariat will give the record within a maximum of 20 days.
III. In the case of medicines with new molecules, the resolution must be issued within a maximum period of 90 days (Art. 166).

Day	Action
0	Submission of request for authorization, payment of the corresponding tariff (Table 11: Costs for Registration, Marketing Authorization, Import, Distribution and Marketing in Mexico Table 11, electronical submission is possible.
1	Start of procedure Submission is recorded: „the time and date of presentation are noted“ „a reference number for the entry and future tracking is given“ Upon payment of the fees the procedure starts.
1-10	The COFEPRIS reviews the application
10	Decision is made on the application and the licence is granted, an identification number (SSA, alphanumerical) is given and registration starts.
30-50	Registration of products with active substances already registered in Mexico
30-70	Registration of products with active substances registered and commercialized in the home country of the registrant
100	Registration of new products

Table 10: Timeline for authorization in Mexico

The documents needed for registration are (a) the technical information including analytical data on identity and purity of the components, stability data of the finished product corresponding to given norms (Estados Unidos Mexicanos - Secretaria de Salud, 2006) and the proof of therapeutic efficacy and safety, (b) the prescription information, and (c) the labelling (Estados Unidos Mexicanos - Secretaria de Salud, 2000) (Art. 167). For products manufactured in a foreign country the marketing authorization certificate of the country of origin, the proof of GMP and the contact data of the licensing partner (if there exists no subsidiary of the manufacturer in Mexico) has to be added to the documents for registration (Art. 170).

Persons other than the MAH may only develop the registered product with the authorization of the MAH, and in the same conditions under which the product was authorized for sale and under the following requirements:

I. The site where the product is manufactured has a license or a notice of operation, as laid down in this regulation;
II. The MAH has at all times and without any restrictions, the possibility to monitor the conditions of manufacturing of the product and to establish, if appropriate, improvements or adjustments that it considered necessary, to ensure that the manufacturing is done under the same conditions in which it was authorized, and
III. that the name and address of either the manufacturer and the MAH are printed on the label of the product, if the manufacturing process is carried out continuously for more than three hundred sixty days. (Art. 183)

VARIATIONS

Every change in the manufacturing process (variation) and in distribution has to be declared to the competent authority (Art. 176, 185 ff.). The process for variations is ruled by article 185 ff., “Reglamento de Insumos para la Salud” and described by COFEPRIS-05-002 (COFEPRIS, date not available). An EXCEL-sheet provided by COFEPRIS has to be used for the request.

To obtain the authorization of variations to the conditions of registration of any pharmaceutical product, it has to follow by application in the official format including labelling and, if needed, prescribing information and the following:

I. stability tests in accordance with the relevant standard for changes in the processes of manufacturing, material of primary packaging, expiration date, and additives or excipients (3 lots, climatic zone II);
II. written technical justification, that endorses the need or desirability of change in primary packaging;
III. certificates of additives and excipients, and their references to changes of these ingredients;
IV. specifications for the active substance, the excipients and the finished product signed by company's QA for process changes and the control methods of manufacturing and packaging;
V. As mentioned in article 176 of the regulation national and foreign manufacturing variability has to be submitted to the Secretaria. (Art. 186)

The Secretaria will answer requests for variations of the registration of any medicinal product in accordance with the following time limits:

I. within 45 days, in the case of modifications that involve changes in the production process;
II. within 30 days, if modifications concerns
    a. the time of expiration; the additives, without change in the pharmaceutical form;
    b. the primary packaging;
    c. the change of national to foreign manufacturing, without modifications in the production process;
    d. the change of foreign national manufacturing, without modification in the production process;
III. In 20 days, when modifications concerns to:
    a. The name or domicile of the MAH without changes in the production process;
    b. the trade name of the medicine;
    c. the name or domicile of the foreign manufacturer, without change in the production process;
    d. the presentation and content of the packaging;
    e. the secondary packaging, and
    f. the conditions of sale and supply to the public, without changes of therapeutic indication and of formulation.

If the Secretaria does not respond in the indicated time the request will be understood proceeding. If more than one type of modification is submitted, the maximum time interval for responding has to be expected. If the request for an amendment to granted registration is submitted including a certification issued by a third party authorized by the Secretaria, a granting within a period of fifteen days is possible (Art. 186).

For changes in the prescription information an interval of 20 days is needed (Art. 187). All requests must be submitted in a written form and according to the official formats (Art. 190).

IMPORT

The import of drugs with the aim to commercialize them is ruled in Title 5, Chapter 1, Art. 131-149: All imported drugs have first to be registered by the competent authority. "Homoclave COFEPRIS-01-002-B" with its related EXCEL-sheet describes the process. Needed documents are receipt which indicates the number of products free of charge, the airport, port or city

where the products are imported, a fact sheet indicating the use and the mode of administration and a list of supplements, if applicable.

Different permissions for import and the procedures to submit are described in chapter IV Art. 193-205.

PRODUCTION AND MANUFACTURING

Production and manufacturing has to be performed according to Norma NOM-059-SSA1-2006 of the Mexican Government, based on and partially identical to the international guidelines in Good Manufacturing Practices (Estados Unidos Mexicanos - Secretaria de Salud, 2008). It is not necessary to own a production site in Mexican territory (Avena, 2012)

PHARMACOVIGILANCE

The Mexican Pharmacovigilance System and its implementation are ruled by "Reglamento de Insumos para la Salud, Art. 38" (Estados Unidos Mexicanos, 1998) and described in detail in the Guideline "NOM-220-SSA1-2002, Instalación y operación de la farmacovigilancia" (Estados Unidos Mexicanos - Secretaria de Salud, 2004) This guideline is based on and partially identical to

- ICH-E2E. Pharmacovigilance Planning. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use, 2003.
- ICH-E2A. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use, 1994.
- ICH-E6. Good Clinical Practice: Consolidated Guidance. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use, 1996

All adverse reactions which have been observed during medical treatment, during clinical studies and studies on intensive pharmacovigilance and during campaigns of vaccination have to be reported to the Centro Nacional de Farmacovigilancia (CNFV). For the reporting official formats have to be used which are offered by the CNFV (COFEPRIS, date not available). Serious or lethal adverse reactions have to be reported within 7 days after their identification, within 5 days if it is more than one case or immediately if more than 3 identical cases have been observed. Non serious adverse reactions have to be reported within 30 days after their identification. The MAH has to investigate and validate the observed adverse reactions and to archive all related information. The CNFV has to be informed on cumulative adverse reactions by periodic reports (every 6 month after first authorization; yearly for the first 3 years of authorization, then every five years).

INSPECTIONS

Inspections are only planned for national manufacturers. In the case of importation of bulk ware it is only necessary to prove by certificates that the manufacturing process is in concordance with the GMP guidelines. (Estados Unidos Mexicanos - Secretaria de Salud, 2001)

BIOEQUIVALENCE

The studies to prove bioequivalence (interchangeability) are ruled by the Guideline NOM-177-SSA1-1998, which describes sample characteristics, the evaluation criteria, the in-vivo testing in human beings, the analytical procedures and the authorized third parties involved in the

study. The appendices A (protocol of the study), B (statistical analysis) and C (normalised processes) of this Guideline summarize the required documents and results They are listed in Annex II.

Interchangeable generic drugs are defined as equal to the proprietary medicinal product, containing the same drug or active substance and pharmaceutical form, concentration or power, which uses the same route of administration, , shows equal or comparable specifications, is compliant with the pharmacopoeias and the required analytical test. It is proven that the profiles of dissolution, bioavailability and other parameters are equivalent to the innovative drug or the reference product registered in the catalog of interchangeable generic drugs (COFEPRIS, 2009), and is identified by its generic name (Estados Unidos Mexicanos - Secretaria de Salud, 1999).

The study for the proof of bioequivalence is devided in three parts:

(1) Evaluation of a dissolution profile, (2) proof of bioequivalence in humans and (3) the chemical analysis (climatic zone II).

The dissolution profile has to be documented from the drug and the reference product (shelf life 1 year minimum, one lot each, three series, twelve measuring points of each product). Prior to testing parameters for validation have to be tested: linearity and precision (for the system), linearity, accuracy, precision, stability and specificity (for the method). The report of this part of the study has to include: a description of the drugs used (INN, generic name, pharmaceutical formula, dose, lot numbers, expiry date and date of fabrication), the test systems used (material and methods, dilution media, agitation conditions, temperature, times, volumes...) and the method of dissolution including the results of content verification, validation and chemical analysis.

The study of bioequivalence in humans has to be done according to the General Mexican Drug Law and the international GCP guidelines. The protocol of the study has to be revised and approved by the general coordinator or principal investigator, approved by the ethic committee of the responsible institute, where the study takes place and compliant to the protocol formula published in Appendix A of the Guideline (Estados Unidos Mexicanos - Secretaria de Salud, 1999). Local research ethical committees at hospitals are responsible for the ethical evaluation of the study protocols (Bioethical Knowledge Center, 2012). In a study on the presence of Mexican Ethics Committees 101 active committees could be identified, established between 1985 and 2006. Their main duties are ethical problems/dilemmas related to clinical practice and research projects like clinical studies (Valdez-Martínez E, 2008). All clinical studies have to be approved by the national ethics committee, the investigational review board (IRB) and the national Ministry of Health. “Moreover, in order to protect the rights of certain vulnerable subject groups, there are specific laws regarding clinical trial protocols for human subjects in selected communities, including women, children, elderly, handicapped, and indigenous populations” (Virk, 2009). The institutions involved in the approval process work in accordance to the ICH guidelines and GCP: “Although Mexico has a complicated and redundant system for the approval of clinical research protocols and the importation of study drugs, attempts have been made in the last year to update both the system and its efficiency. At this point, approval times of new research protocols are similar to those in the United States, and certainly better than in the majority of Latin American countries” (Castellanos, et al., 2002).

The subjects to be included in the study should be healthy without sensitivity against the tested drug, between 18 and 55 years old and with a body weight ±10% of ideal weight. The minimal clinical test profile should include general urine, blood analysis, hepatic transaminases, hepatitis B, HIV, thorax radiography and electrocardiogram, which has to be performed in clinical laboratories compliant with GCP. Further investigations have to be justified in the protocol.

The subjects should not have any history of drug addiction or abuse of alcohol, coffee or caffeine containing beverages nor should they use concomitant drugs. An informed consent, and a documentation of the voluntary participation has to be signed by the subjects.

The study has to be performed according to the current legislation, compliant with GCP guidelines and following the study protocol. Adverse reactions occurring during the study should be registered by formats provided by the Secretaria. Parameters to be determined are: plasmatic concentration AUC $_{0\rightarrow t}$, AUC $_{0\rightarrow\infty}$ and C_{max} and urinary elimination rates if necessary, including the calculation methods, the biostatistica analysis and the data on specificity, precision and reproducibility of the methods used.

The chemical analysis includes the validation of testing in the biological matrix concerning precision (range, recovery) accuracy, stability, limits of quantification and detection, selectivity and tolerance.

An overview of the documents required for the application is listed in the Annex II Mexico.

PACKAGING

Primary and secondary packaging material is ruled by Reglamento de Insumuos para Salud – Seccion Segonda (Estados Unidos Mexicanos, 1998). The etiquettes should contain the generic name, the brand name, except in the case of the interchangeable generic drugs, active ingredients, name and address of the manufacturer and, if appropriate, of the distributor, storage conditions, expiry date, batch number, dosage and route of administration, precautions, including its use/risk during pregnancy, warnings, symbol that identifies it as generic interchangeable drug, and indications according to the international nomenclature accepted.

In the case of branded generic product, the INN must be printed in a proportion not smaller than one third of the brand name and in the same typeface, or if not possible in “Helvetica” font.

Figure 3: Packaging material for generic drugs in Mexico

A: active substance, B: concentration, C: content and pharmaceutical form: tablet, capsules, dragees, solutions etc. D: Logo „Generic“ E: Logo „manufacturer, distributor“ (nteraded de todo, 2012)

The interchangeable, generic drugs are differentiated and identified by the logo “GI”, which has to be printed on the packaging material in the colors red, yellow and blue.

Figure 4: Logo "Generic" - colors allowed

INTELLECTUAL PROPERTY RIGHTS

The intellectual property rights are ruled by the “Ley de la Propiedad Industrial” (Estados Unidos Mexicanos, 2012; Estados Unidos Mexicanos (SICE), 2012) a law based on the TRIPS-Agreement and the conditions laid down in the NAFTA-Agreement: The law constates that a person who creates an invention, a utility model or an industrial design has the right to exclusively exploit it for his benefit by himself or by someone authorized by him. (Artículo 9) Patents apply to inventions, registrations to utility models and industrial designs. A physical person or a corporation can be given a patent or registration. (Artículo 10). The patent or registration holder is protected by this law due to inspections and sanctions (Artículo 213 ff.).

PRICING AND REIMBURSEMENT

The Mexican Medical system consists of three levels of health care covering nearly all Mexican people:

The open system: it delivers primary care services to the poorer segments of the Mexican society that are people who are unemployed, self-employed or engaged in the informal economy. About 33 million people belong to this group. They are covered mainly by the Ministry of Health (Estados Unidos Mexicanos - Secretaria de Salud, 2012), the Insituto Mexicano del Seguro Social (IMSS, 2012), the Mexico City government (Departamento del Distrito Federal, 2012), the Red Cross organisation and some state, municipal and university organisations.

The premium based system: this system is funded by employer and employees. 37 million people contribute to this system. They can use the services of the Insituto Mexicano del Seguro Social (IMSS, 2012), the Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE, 2012) and some employers (Petroleos Mexicanos, Secretaria de la Defensa Nacional, Secretaria de Marina) who provide their own health care units.

The private system: This is only used by middle and upper class Mexican population (20 million people). This system is covered by direct payment (out of pocket), private insurance companies, employees of banks and executives of large corporations (private insurances).

The “Acuerdo que establece las reglas de operacion para la fijacion o modificacion de precios de los medicamentos y sus materias primas” describes tree types of medicines:

- Basic medicines: basic drugs for the use in the public and private sector

- Essential medicines: basic drugs of importance for public health
- Common medicines: which are not included in one of the former groups

Prices should be calculated on the following factors: primary costs, manufacturing costs, total costs, purchase price and retail price. (Estados Unidos Mexicanos - Secretaría de Salubridad y Asistencia, 1984)

STARTING BUSINESS

To find a suitable partner for a successful access to the Mexican market is one big challenge for a SME. The AHK Mexico provides a range of services such as lists of business partners, pre-market and import-checks, individual identification of business partners by a profile provided by the SME including the organisation of visits in Mexico (AHK-Mexico, 2010). Both partners the local distributor, in most cases the bigger partner, and the foreign supplier (SME) should work closely together to be effective during the process of registration. Support for contact to authorized clinical centres and laboratories, regional ethic committees, the competent authority on the level of language, relationships and special knowledge of the market has to be provided by the local partner, whereas product and scientific knowledge (PK, PD, Toxicology, safety, efficacy, risk-benefit-ratio...) has to be brought up by the SME. Therefore it is very important to develop a relationship of deep confidence between the partners.

COSTS OF REGISTRATION, MARKETING AUTHORIZATION, DISTRIBUTION, MARKETING AND IMPORT

Process	$
Registration of a generic drug	60.100
Licence for distribution of pharmaceutical products	22.949
Permit for importation	3.952
Permit for marketing authorization (Analysis, authorization and authorization for third parties)	6.702
Permits for publication	
Television and internet,	38.163
Cinema, video...	5.311
Radio	3.724
Press	1.258
Catalogues, brochures...	867
External announcements	6.709

Table 11: Costs for Registration, Marketing Authorization, Import, Distribution and Marketing in Mexico

(COFEPRIS, 2012)

RESUMEE

Every Latin American Country has its own specialities in terms of socioeconomics and infrastructure, market characteristics as well as in its regulatory processes and reimbursement/pricing conditions.

Because of their limited financial and human resources SMEs are hindered to enter the Latin American market as a whole. Therefore this guide is attributed to the access to only two selected countries. One process designed as an out-licensing process (Mexico) and the other as a foundation of a subsidiary (Chile).

Both processes fit to the condition of a fictive European SME with generics in its portfolio:

- The socioeconomic situation in Chile and Mexico is acceptable for the planned business.
- The infrastructure in both countries is well developed and allows access to pharmaceutical products to a high number of patients.
- The markets are profitable and show opportunities for a business in these countries
- Trade with both countries is facilitated by the existence of Free Trade Areements with the EU and the support by the AHK especially for small enterprises.

The most challenging part of course is the registration of the products by the competent authorities. All Latin American countries are very much interested in harmonization of the regulatory processes, so the acceptance of the CTD (and the eCTD in Mexico) is a big advantage. Chile especially accepts the European standards, whereas Mexico accepts the US-standard as well. Therefore a European Marketing Authorization is a good starting point for SMEs.

Despite that each country has its own specialities in specifications (analysis, stability...) and study design. They are ruled by a variety of regulations, guidelines and supported by formats and norms. These documents are only provided in Spanish language and all correspondence has to be made in Spanish. Therefore the assistance of a professional translator – probably because of confidential information within the staff - is mandatory.

The Chilean competent authority provides all needed documents, guidelines, regulations and forms covering the process of registration and marketing authorization on its homepage ANAMED (http://www.ispch.cl/anamed). Correspondence with the authority – if made in Spanish language – is fast and competent: An email, sent to the "OIRS – Oficina de Informaciones, Reclamos y Sugerencias" (http://www.ispch.cl/oirs/index.htm) on tariffs for marketing authorization was immediately acknowledged by a registration number and answered within one working day. For safety reasons a registration, free of charge, is needed.

The Mexican competent authority COFEPRIS offers a good overview of needed documents and provides EXCEL-based forms to submit, but the basic documents for detailed information (guidelines, regulations and norms) are more hidden (http://www.salud.gob.mx/unidades/cdi/nomssa.html). Therefore basic information is not easy to find. This – in addition to the market situation – makes it reasonable to enter the Mexican market with a partner, experienced in the regulatory framework of the Mexican government.

The submission and approval of the study protocol for the proof of bioequivalence is easier and less redundant in Chile compared to Mexico (3 institutions have to decide on the approval of the study protocol).

Both countries recommend authorized national and international centres for the clinical and analytical performance of the tests needed.

Despite that the specifications and the measurements needed are more specified in Mexico (3 lots for stability data, indigen/latino inclusion in study group) and mainly follow the FDA-standards.

In Chile two studies are needed to get the granting "generic interchangeable drug", while in Mexico only one study is recommended.

	Chile	Mexico
Ethical approval	Comité de Evaluación Ético Científico (CEEC)	Local Research Ethical Committee Investigational Review Board Ministery of Health
Bioequivalence (in vivo)	Clinical Analytical PK/Statistical	Analytical PK Dissolution profile
Bioextension (in vitro)	Solubility Permeability Kinetics	

Table 12: Comparison of Bioequivalence Study Requirements in Chile and Mexico

The costs for the marketing authorization in Chile are higher than in Mexico, but in addition costs for marketing arise in Mexico and import costs are on a higher level compared to Chile. Therefore in the case of out-licensing the profit will be reduced due to the profit sharing with the partner.

Comparable are the regulations of drug production, inspections and packaging. Both countries recommend a specific design of the packaging material for generic drugs.

The monitoring of the safety and efficacy after marketing approval is comparable in both countries. Chile additionally demands, besides adverse events, the reporting of complaints to an authorized institution.

The guide presented here will only serve as a possible way for SME to enter the Latin American market. After all it is a strategic decision for every SME which country and strategy it will choose first to enter the Latin American market. If there is limited experience with the Spanish/Portugese market the decision should be to go together with a partner experienced in Latin American countries, who knows the cultural differences, the regulatory body and the local market. This decision includes further opportunities in other countries, where the partner is or will be active. In the case of a block buster this strategy would be adequate.

The decision for founding a subsidiary is more risky but more profitable, too. It allows a slow but controlled growth and gathering knowhow and image. But further expansion will be very limited. This way is the best to choose if you have a niche product with high interest in the country you plan to enter.

The final decision is up to the SME. Therefore a close cooperation of the different departments - Manufacturing, Clinical Department, Regulatory Affairs, Pharmacovigilance and Quality as well as the Legal Department/attorney – should be initiated to develop a company and product specific regulatory strategy for the entrance into the Latin American World.

FIGURES AND TABLES

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LIST OF ABBREVIATIONS

AHK	Chamber of Commerce (German)
ANAMED	Agencia Nacional de Medicamentos (CA Chile)
APEC	Asian-Pacific Economic Cooperation
ASEAN	Association of South East Asian Nations
ASINFAR	Columbian National Association of Local Laboratories
AUC	Area Under the Curve
BRIDEPI	Intellectual Property Crimes Unit (Chile)
CA	Competent Authority
CAN	Andean Community
CEEC	Ethics Committee (Chile)
CENABAST	Institute of the Health Ministry for the supply
CIOMS	Council for International Organization of Medical Sciences
CNFV	National Centre of Pharmacovigilance (Mexico)
COFEPRIS	Comision Federal para la Proteccion contra Riesgos Sanitarios (CA Mexico)
(e)CTD	(electronical) Common Technical Document
D.S.	Decreto “Codico Sanitario”
EAC	East African Community
EMA	European Medical Agency (Europe)
FDA	Food and Drug Agency (United States of America)
FOB	Free On Board
FONASA	Chilean Health Insurance
FTA	Free Trade Agreement
GCC	Cooperation Council for the Arab States of the Gulf
GCG	Global Cooperation Group
GCP	Good Clinical Practices
GDP	Gross Domestic Product

GES (ex AUGE)	Chilean Health Plan
GI	interchangeable generic drug (Mexico)
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
ICH	International Committee of Harmonization
IMSS	Institute of Social Security (Mexico
INN	International Non-proprietary Name
ISP	Instituto de la Salud Publica de Chile
ISSSTE	Institute of Health and Social Services(Mexico)
IPR	Intellectual Property Rights
ISAPRES	Chilean Health Insurance
KI	Key Indicator
LLC	Limited Liability Company
M&A	Merger and Acquisition
MAH	Marketing Authorization Holder
MNC	Multi-National Company
NAFTA	North American Free Trade Agreement
OECD	Organisation for Economic Co-operation and Development
OTC	Over-The-Counter
PAHO	Pan American Health Organisation
PANDRH	Pan American Network for Drug Regulatory Harmonization
PD	Pharmacodynamic
PK	Pharmcokinetics
RA	Regulatory Affairs
RAM	Adverse Reaction (Chile)
RHI	Regional Harmonization Initiative
SADC	South African Development Community
SEREMI	Secretarias Regionales Ministeriales de Salud

SIS	Peruvian Health Insurance
SME	Small and Medium-sized Enterprise
SmPC	Summary of Product Characteristics
SNSS	National System of Health Care (Chile)
SOP	Standard Operation Procedures
SSA	alphanumerical registration number (Mexico)
TRIPS	Trade Related aspects of Intellectual Property rightS
UCC	Universal Copyright Convention
USTR	United States Trade Representative
WCT	World Intellectual Property Organisation Copyright Treaty
WTO	World Trade Organisation

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ANNEX 1 CHILE

DOCUMENTS FOR COMITÉS DE EVALUACIÓN ÉTICO CIENTÍFICO (CEEC)

1. Study protocol
2. Form of informed consent
3. Written information for the subjects for informed consent
4. Including criteria for subjects
5. Payments to the subjects
6. Information on the product (characteristics, effects, results of other studies)
7. CV and other documentation of the researchers to demonstrate their qualification
8. Other information which the CEEC considers to be necessary
9. All information should be provided in Spanish language.

DOCUMENTS OF BIOEQUIVALENCE STUDIES

1. Table of content
2. Title of the study
3. Name and address of the investigators
4. Signatures of the main investigator and the other authorised investigators
5. Sites of the study and the associated sites
6. Time period when the different phases of the study have been performed
7. Names and lot numbers of the products compared
8. Declaration that the compared products are comparable and that they are commercially available
9. Results of the assays and pharmaceutical characteristics (physical description, dimensions, average weight)
10. The complete protocol including the inclusion and exclusion criteria
11. Possible changes within the protocol
12. Documentation that the study has been approved by an CEEC and that it is in comformity to GCP and GLP.
13. Demographic data of the subjects
14. Names and addresses of the subjects
15. Details and justifications of the changes within the protocol
16. Details of the analytical methods, complete validated data, quality control data, criteria to accept or reject the results of the assays.
17. Representative chromatograms
18. Diagrams with deviations
19. Detailed calculations of the pharmacokinetical parameters
20. Documentation of the statistical analysis
    a. Randomization scheme
    b. Plasma concentration and sample time for studied product and reference product
    c. AUC $_{0\rightarrow t}$, AUC $_{0\rightarrow\infty}$, C_{max}, T_{max}, K_e and $t_{1/2}$ for the studied product and the reference product
    d. Logarithmically transformed measurement for the demonstration of bioequivalence
    e. Analysis of variance for AUC $_{0\rightarrow t}$, AUC $_{0\rightarrow\infty}$, C_{max}
    f. Inter- and intraindividual variability and total variability if possible
    g. Confidence intervals for AUC $_{0\rightarrow t}$, AUC $_{0\rightarrow\infty}$, C_{max}
    h. Geometrical and arithmetical average value of AUC $_{0\rightarrow t}$, AUC $_{0\rightarrow\infty}$, C_{max}
    i. Partial AUC if necessary

j. AUC $_{0\rightarrow t}$, AUC $_{0\rightarrow\infty}$, C_{max}, grade of stabilty (C_{max}-C_{min} /C_{prom}) and percentage of stability if measured.
k. Additional adequate information can be added.

DOCUMENTS FOR MARKETING AUTHORISATION

1. Name and address of the applicant and its legal representative
2. Name of the technical director or designee
3. Name of the product
    a. Trade name or generic name (INN) or otherwise pharmacopoeial or chemical name
    b. Pharmaceutical form
    c. Unit dose per pharmaceutical form
    d. Route of administration
4. Class or therapeutic group and further indicating the anatomical-therapeutic classification
5. Manufacturing process including
    a. Domestic manufacture for those products manufactured in a legally and technically qualified pharmaceutical laboratory, whether mad by their own premises or by third parties or
    b. Imported products, including
        i. Imported finished products, manufactured abroad
        ii. Imported semi-finished products
        iii. Bulk-ware
        iv. Imported intermediate products for further processing
6. Identification of the licensor under the name that appears on the license, if the procedure is done on use of license
7. Name and address of the producer establishment, if it is produced in the country or in a foreign country
8. Presentation of the product, describing the contents of the different containers: sales to the public, clinical packaging and/or medical samples if appropriate; including those elements or devices for its administration if included.
9. Physical description of the packaging material, indicating its or the devices' type if necessary for its administration.
10. Documents in Spanish language or duly translated documents under the firm's legal representative, signed by the company or the technical director, if appropriate, consisting of the following in the case of products imported or manufactured in the country:
    a. For imported finished products
        i. Certificate of health registry or certificate of the pharmaceutical product, or certificate of an approval or official certification of WHO issued by the health authority of the country of origin which credits by signature that the producer or distributor meets the conditions required by the health legislation of their country; that the product is registered in country of origin in accordance with the current regulations, including its authorized formula; and that the product is not subject to any restrictive regime or control.
        ii. Manufacturing agreement signed between the applicant and a pharmaceutical laboratory of foreign production.
        iii. Legalized and granted license.

iv. Legalized license, granted by the competent health authority of the country where the producer is located, stating that the foreign manufacturer is duly authorized in their country; that it complies with good manufacturing practices, according to the WHO recommendations, listing areas of production or types of products it is authorized to manufacture and other accreditations additionally to those mentioned in article i.
v. Import convention authorized by a notary or duly legalized.
vi. Manufacturing and/or distribution agreement authorized by notary, attaching the authorization of each company.
vii. Convention on quality control of the authorized pharmaceutical company for the Institute, authorized by a public notary.

In the case of imported pharmaceutical products finished, semi-finished, bulk or intermediate products it is recommended that the applicant certifies the compliance with good manufacturing practices of the manufacturer.

Technical information

1. Clinical and pharmacological monography in Spanish language, signed by the technical Director or designee
2. Labelling of the product in Spanish language
3. SmPC
4. PIL

Pharmaceutical Quality

1. Composition of the pharmaceutical product
    a. Declaration of qualitative and quantitative analysis of one of the active component
    b. Declaration of qualitative and quantitative analysis of one of the excipients
    c. Declaration of qualitative analysis of any excipient used and eliminated during the production process
    d. The active component calculated on the bases of number or volume or biological activity
    e. The active compounds and excipients declared as INN
    f. Pigments and colorants with generic names
2. For the active component:
    a. Description of the method used for quality control
    b. Declaration of supplier and manufacturer of the active principles, attaching a certifiate of analysis with all the parameters that characterize the active ingredient.
    c. Origin of the primary reference standard including analysis certificate including its origin, power, traceability and other relevant tests for characterization.
    d. Spectrogram or chromatogram of the active principle and the standard for any technical method, if appropriate.
    e. Condition of storage of the active principle as raw material.
3. Technical specifications and methods of control of all excipients, adjusting to the requirements referred to in the Pharmacopoeia or official texts in force in Chile or monographs if it was not indicated in these texts.
4. Analytical methods, in Spanish, signed by the professional technician making the request and the head of the department of quality control.

a. The analytical methodology should be comprehensive, characterising the pharmaceutical product and it must include all necessary controls to ensure the quality of the product, depending of the elaborate pharmaceutical form.
b. The analytical methodology of all pharmaceutical products must include the following methods: General testing: sensory description (appearance, size, shape, colour, smell, between others); selective identification to the active compound, valuation, power or activity of the active ingredient, the determination of impurities if appropriate and description of the type and material of packaging material, both primary and secondary.
c. Specific tests according to pharmaceutical form will be established according to the additional technical rules issued, existing by the Institute.
d. The methodology shall submit their validation in all cases if it is not described in acknowledged pharmacopoeias.

5. Special tests
    a. For pharmaceutical forms with modified release such as retarded, enteric, prolonged or others the conditions have to be declared and proved by pharmacokinetic studies (dissolution or diffusion studies).
    b. Bioequivalence studies and bioavailability studies have tob e performed for pharmaceutical products with well known mode of action.
6. Summary that includes the analytical parameters and criteria of acceptance essential for the product validation, the finished product specifications, that the proprietary medicinal product must comply with during storage life.
7. Proposition of the storage life, the storage conditions and packaging, both for the proprietary medicinal product for the reconstituted product, if appropriate, demonstrated by studies of stability that correspond with the following details:
    a. Stability data: studied formula, responsible persons for study of stability conditions of temperature, humidity, material of container and studied series (minimum 3 series or pilot lots), also including the program design and the analytical procedures used and the product specifications of the finished product; all above according to the guide of stability of pharmaceutical products, adopted as a technical standard by Supreme Decree of the Ministry, acting on a proposal of the Institute.
    b. When the product requires dilution prior to its administration, studies of stability for the formulation, the solvent (if is) (included in the presentation) and the reconstituted product have to be provided. In the case that the required diluents are not included in the package, but recommending the solvents studies of stability concerning the formulation and the reconstituted product has to be provided, too.
    c. If the product should be diluted prior to its immediate use, it must attach the study of compatibility with thinners corresponding, exempting it from the requirement established in the previous letter.
    d. In the case of an active principle that cannot be incorporated in a formula of another approved proprietary medicinal product in the country, the results of forced degradation studies and stress test have to be provided, under the same conditions and in addition to the requested in paragraph 2.

8. Technical information relating to the manufacturing, quality control and physico-chemical data, have to be summed in a table added by a flow diagram of the process indicating where flow-checks are carried out.

ANNEX 2 MEXICO

DOCUMENTS OF BIOEQUIVALENCE STUDIES

1. Title page of study protocol
    a. Title of the protocol
    b. Name of the pharmaceutical product
    c. Identification number (if available)
    d. Author of the protocol
    e. Name of the sponsor
    f. Name of Quality Assurance Officer
    g. Name of investigator
    h. Site where the study is performed
    i. Address of the site
    j. Date of the protocol
    k. Signature of the investigator and the sponsor or representative
2. Table of Content
3. Introduction
4. Objective
5. Experimental Design of the Study
    a. Type of the study
    b. Number of subjects
    c. Tested drug and reference drug
    d. Duration of Treatment
    e. Laboratory Studies
    f. Biological fluids examined
    g. Samples (frequence...)
6. Selection of Subjects
7. Clinical Design of the Study
8. Statistical Analysis (According to Appendix B of the Guideline)
    a. Introduction
    b. Descriptive Statistics
        i. AUC and Cmax tabulated for each subject
        ii. Difference between probe and reference
        iii. The quotient of probe and reference
        iv. Log (base 10) of the quotient of probe and reference
        v. Figures
    c. Statistical Models
        i. Sequence of administration
        ii. Interindividual variability
        iii. Period of administration
        iv. Treatment
        v. Experimental Error
        vi. Interpretation (The subjects chosen for the study must be allocated randomly to the study sequences. Variances associated with the two treatments, as well as the two sequences of management must be equal or at least comparable.)
    d. Pharmakokinetic
        i. $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow \infty}$
        ii. C_{max}
        iii. Logarithmic transformation
    e. Variance Analysis

f. Sequential Effects
g. Criteria for Equivalence (the range of 80 to 120% for the ratio of the averages of the products is sufficient as a criterion of equivalence. This corresponds to a range of ± 20% for the relative difference between the averages of products. When the data are transformed to the logarithms, using AUC and C_{max} the criterion of equivalence uses a range of 80-125%)

9. Adverse Events
10. Criteria for Discontinuation
11. Administration
12. Source Data Management
13. Informed Consent
14. Exclusion Criteria
15. Documentation
16. Timeline of the Study
17. References and Bibliography

DOCUMENTS FOR THE REQUEST FOR MARKETING AUTHORIZATION

The printouts on the following pages are provided by COFEPRIS as EXCEL-Sheets to complete and to submit together with mentioned documents for the request to the competent authority (COFEPRIS, date not available).

Cofepris
Comisión Federal para la Protección contra Riesgos Sanitarios

Comisión Federal para la Protección contra Riesgos Sanitarios

AUTORIZACIONES, CERTIFICADOS Y VISITAS

SALUD

No. DE INGRESO (USO EXCLUSIVO DE LA COFEPRIS)	NO. RUPA

ANTES DE LLENAR ESTE FORMATO LEA CUIDADOSAMENTE EL INSTRUCTIVO, LA GUÍA Y EL LISTADO DE DOCUMENTOS ANEXOS.
LLENAR CON LETRA DE MOLDE LEGIBLE O A MÁQUINA O A COMPUTADORA.

1 SOLICITUD DE:

		ALTA O NUEVO	MODIFICACIÓN	PRÓRROGA	OTROS
LICENCIA	☐	○	○		
PERMISO	☐	○	○		
PERMISO DE IMPORTACIÓN O EXPORTACIÓN	☐	1a VEZ ○ SUBSECUENTE ○	○	○	
REGISTRO	☐	○	○	○	REVOCACIÓN ○
AUTORIZACIÓN	☐	○	SÓLO PARA PROTOCOLOS ○	SÓLO PARA TERCERO AUTORIZADO ○	
CERTIFICADO	☐	○	○		
VISITA DE VERIFICACIÓN	☐	○			

HOMOCLAVE DEL TRÁMITE:	NOMBRE DEL TRÁMITE:

MODALIDAD DEL TRÁMITE:

2 MODIFICACIÓN DE: (sólo en caso de haber seleccionado este campo en la sección 1)

NÚMERO DE DOCUMENTO A MODIFICAR:

DICE / CONDICIÓN AUTORIZADA	DEBE DECIR / CONDICIÓN SOLICITADA

SI EL ESPACIO ES INSUFICIENTE PODRÁ AMPLIAR EL CAMPO.

3 DATOS DEL PROPIETARIO :

NOMBRE DEL PROPIETARIO (PERSONA FÍSICA) O RAZÓN SOCIAL (PERSONA MORAL)			R.F.C.
			C.U.R.P. (DATO OPCIONAL)
CALLE, NÚMERO EXTERIOR Y NÚMERO O LETRA INTERIOR		COLONIA	DELEGACIÓN O MUNICIPIO
LOCALIDAD		CÓDIGO POSTAL	ENTIDAD FEDERATIVA
ENTRE CALLE	Y CALLE	TELÉFONO	FAX

4 DATOS DEL ESTABLECIMIENTO:

RAZÓN SOCIAL O DENOMINACIÓN DEL ESTABLECIMIENTO			R.F.C.
CALLE, NÚMERO EXTERIOR Y NÚMERO O LETRA INTERIOR		COLONIA	DELEGACIÓN O MUNICIPIO
LOCALIDAD		CÓDIGO POSTAL	ENTIDAD FEDERATIVA
ENTRE CALLE	Y CALLE	TELÉFONO	FAX

No. DE LICENCIA SANITARIA O INDIQUE SI PRESENTÓ AVISO DE FUNCIONAMIENTO	R.F.C. DEL RESPONSABLE SANITARIO

CLAVE (SCIAN)	DESCRIPCIÓN DEL SCIAN

HORARIO:	D	L	M	M	J	V	S	DE		A		FECHA DE INICIO DE OPERACIONES (a)	DIA	MES	AÑO
	D	L	M	M	J	V	S	DE		A					

(a) SOLO PARA EL ALTA DE LICENCIA SANITARIA.

INDIQUE NOMBRE COMPLETO , C.U.R.P. Y CORREO ELECTRÓNICO		
REPRESENTANTE LEGAL		
NOMBRE COMPLETO	C.U.R.P. **(DATO OPCIONAL)**	CORREO ELECTRÓNICO
PERSONA AUTORIZADA		
NOMBRE COMPLETO	C.U.R.P. **(DATO OPCIONAL)**	CORREO ELECTRÓNICO

5 DATOS DEL PRODUCTO:

Consultar instructivo de llenado.	**PRODUCTO**	**PRODUCTO**
1) NOMBRE DE LA CLASIFICACIÓN DEL PRODUCTO O SERVICIO		
2) ESPECIFICAR		
3) DENOMINACIÓN ESPECÍFICA DEL PRODUCTO		
4) NOMBRE (MARCA COMERCIAL) O DENOMINACIÓN DISTINTIVA		
5) DENOMINACIÓN COMÚN INTERNACIONAL (DCI) O DENOMINACIÓN GENÉRICA O NOMBRE CIENTÍFICO O IDENTIFICADOR ÚNICO DE LA CODE		
6) FORMA FARMACEÚTICA O FORMA FÍSICA		
7) TIPO DE PRODUCTO		
8) FRACCIÓN ARANCELARIA		
9) CANTIDAD DE LOTES		
10) UNIDAD DE MEDIDA		
11) CANTIDAD O VOLUMEN TOTAL		
12) NÚMERO DE PIEZAS A FABRICAR		
13) Kg. o g. POR LOTE		
14) No. DE PERMISO SANITARIO DE IMPORTACIÓN O EXPORTACIÓN O CLAVE ALFANUMÉRICA		
15) No. REGISTRO SANITARIO		
16) No. DE ACTA		
17) PRESENTACIÓN		
18) USO ESPECÍFICO O PROCESO	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
19) CLAVE DEL(OS) LOTE(S)		

20) INDICACIONES DE USO		
21) CONCENTRACIÓN		
22) INDICACIONES TERAPÉUTICAS		
23) FECHA DE FABRICACIÓN		
24) FECHA DE CADUCIDAD		
25) TEMPERATURA DE ALMACENAMIENTO		
26) TEMPERATURA DE TRANSPORTE		
27) MEDIO DE TRANSPORTE O ADUANA DE ENTRADA		
28) IDENTIFICACIÓN DE CONTENEDORES		
29) ENVASE PRIMARIO		
30) ENVASE SECUNDARIO		
31) TIPO DE EMBALAJE Y No. DE UNIDADES DE EMBALAJE		
32) No. DE PARTIDA		
33) CLAVE DEL CUADRO BÁSICO O CATÁLOGO DEL SECTOR SALUD (CBSS)		
34) PRESENTACIÓN DESTINADA A	EXPORTACIÓN ☐ GENÉRICO ☐ SECTOR SALUD ☐ VENTA ☐	EXPORTACIÓN ☐ GENÉRICO ☐ SECTOR SALUD ☐ VENTA ☐
35) FABRICACIÓN DEL PRODUCTO	NACIONAL ☐ EXTRANJERO ☐	NACIONAL ☐ EXTRANJERO ☐
36) UNIDAD DE MEDIDA DE APLICACIÓN DE LA TIGIE (UMT)		
37) CANTIDAD DE UNIDAD DE MEDIDA DE APLICACIÓN DE LA TIGIE		
38) TIPO DE ORGANISMO GENÉTICAMENTE MODIFICADO (OGM) SÓLO UN PRODUCTO POR SOLICITUD		
39) NÚMERO DE PROGRAMA IMMEX (SOLO PARA EMPRESAS QUE ESTÉN DENTRO DEL PROGRAMA PARA LA INDUSTRIA MANUFACTURERA, MAQUILADORA Y DE SERVICIOS DE EXPORTACIÓN		

NOTA: REPRODUCIR ESTE RECUADRO, TANTAS VECES COMO SEA NECESARIO CONFORME A LO ESTABLECIDO EN CADA TIPO DE TRAMITE.

6 INFORMACIÓN PARA CERTIFICADOS:

USO DEL CERTIFICADO (PARA EXPORTACIÓN, REGISTRO, PRÓRROGA Y OTROS)	PAÍS DESTINO
ESPECIFICAR CARACTERÍSTICAS	

7 PROTOCOLO DE INVESTIGACIÓN:

NUEVO ☐ MODIFICACIÓN O ENMIENDA ☐

TÍTULO DEL PROTOCOLO
VÍA DE ADMINISTRACIÓN (Medicamentos o Dispositivos Médicos)
NOMBRE DEL INVESTIGADOR PRINCIPAL
NOMBRE(S) DE LA(S) INSTITUCIÓN(ES) DONDE SE REALIZARÁ LA INVESTIGACIÓN

DATOS DE CON QUIEN EFECTUA LA OPERACIÓN:

8A PARA REGISTRO (MAQUILA):

NOMBRE DEL MAQUILADOR NACIONAL O EXTRANJERO (PERSONA FÍSICA) O RAZÓN SOCIAL (PERSONA MORAL)			R.F.C. (a)
CALLE Y NÚMERO	COLONIA		DELEGACIÓN O MUNICIPIO
LOCALIDAD	CÓDIGO POSTAL	ENTIDAD FEDERATIVA	
ETAPA DEL PROCESO DE FABRICACIÓN		No. DE LICENCIA SANITARIA O AVISO DE FUNCIONAMIENTO	
NOMBRE DEL RESPONSABLE SANITARIO			R.F.C. DEL RESPONSABLE SANITARIO
TELÉFONO Y FAX	CORREO ELECTRÓNICO		

8B FABRICACIÓN, DISTRIBUCIÓN O ALMACENAMIENTO DE PRODUCTOS IMPORTADOS O NACIONALES:

NOMBRE DEL FABRICANTE EN EL EXTRANJERO PARA PRODUCTOS DE IMPORTACIÓN (PERSONA FÍSICA) O RAZÓN SOCIAL (PERSONA MORAL)			
CALLE Y NÚMERO	COLONIA O EQUIVALENTE		LOCALIDAD O EQUIVALENTE
PAÍS	CÓDIGO POSTAL	ESTADO	
NOMBRE DEL PROVEEDOR O DISTRIBUIDOR (PARA INSUMOS PARA LA SALUD)			R.F.C. (a)
CALLE Y NÚMERO	COLONIA O EQUIVALENTE		DELEGACIÓN O MUNICIPIO (a)
LOCALIDAD O EQUIVALENTE	CÓDIGO POSTAL (a)	ENTIDAD FEDERATIVA (a)	
NOMBRE DEL ESTABLECIMIENTO QUE ACONDICIONARÁ O ALMACENARÁ LOS INSUMOS PARA LA SALUD (PERSONA FÍSICA) O RAZÓN SOCIAL (PERSONA MORAL)			R.F.C. (a)
CALLE Y NÚMERO	COLONIA O EQUIVALENTE		DELEGACIÓN O MUNICIPIO (a)
LOCALIDAD O EQUIVALENTE	CÓDIGO POSTAL	ENTIDAD FEDERATIVA (a)	

NOTA: EN CASO DE SER MÁS DE UN FABRICANTE O DISTRIBUIDOR, REPRODUCIR EL APARTADO 8 B) EN UNA HOJA ANEXA, CUANTAS VECES SEA NECESARIO.

8C IMPORTACIÓN / EXPORTACIÓN / REGISTRO:

REGIMEN DE IMPORTACIÓN: (SOLO PARA IMPORTACIÓN) TEMPORAL ☐ DEFINITIVA ☐ DEPÓSITO FISCAL ☐

NOMBRE DEL FABRICANTE			R.F.C. (a)
CALLE Y NÚMERO	COLONIA		DELEGACIÓN O MUNICIPIO (a)
LOCALIDAD O EQUIVALENTE	CÓDIGO POSTAL	ENTIDAD FEDERATIVA O PAÍS	
NOMBRE DEL PROVEEDOR O DISTRIBUIDOR			R.F.C. (a)
CALLE Y NÚMERO	COLONIA O EQUIVALENTE		DELEGACIÓN O MUNICIPIO (a)
LOCALIDAD O EQUIVALENTE	CÓDIGO POSTAL	ENTIDAD FEDERATIVA O PAÍS	
NOMBRE DEL DESTINATARIO (destino final)			R.F.C.
CALLE Y NÚMERO	COLONIA O EQUIVALENTE		DELEGACIÓN O MUNICIPIO (a)
LOCALIDAD O EQUIVALENTE	CÓDIGO POSTAL	ENTIDAD FEDERATIVA O PAÍS	
NOMBRE DEL FACTURADOR (b)			R.F.C.
CALLE Y NÚMERO	COLONIA O EQUIVALENTE		DELEGACIÓN O MUNICIPIO
LOCALIDAD O EQUIVALENTE	CÓDIGO POSTAL	ENTIDAD FEDERATIVA O PAÍS	

PAÍS DE ORIGEN	PAÍS DE PROCEDENCIA
PAÍS DE DESTINO	ADUANA DE ENTRADA O SALIDA (Especifique sólo una)

(a) SÓLO CUANDO EL ESTABLECIMIENTO SEA NACIONAL.
(b) SÓLO PARA INSUMOS PARA LA SALUD.

9 DATOS DE PUBLICIDAD:

MEDIO PUBLICITARIO

AGENCIA (Nombre o razón social)

DOMICILIO DE LA AGENCIA (CALLE, No Y LETRA, COLONIA, LOCALIDAD, C.P., TELÉFONO, CORREO ELECTRÓNICO)

NÚMERO DE PRODUCTOS O TIPO DE SERVICIO	DURACIÓN O TAMAÑO

NOTA: SE DEBERÁ PRESENTAR UNA SOLICITUD POR CADA PROYECTO Y MEDIO PUBLICITARIO

10 AUTORIZACIÓN DE TERCEROS:

NUEVO ☐ PRÓRROGA ☐

A) LABORATORIO DE PRUEBA

ANÁLISIS DE ALIMENTOS, BEBIDAS Y SUPLEMENTOS ALIMENTICIOS Y PRODUCTOS DE PERFUMERÍA Y BELLEZA ☐

ANÁLISIS DE MEDICAMENTOS Y DISPOSITIVOS MÉDICOS ☐

ANÁLISIS DE PLAGUICIDAS, FERTILIZANTES Y NUTRIENTES VEGETALES ☐

☐ OTRO (ESPECIFIQUE) _____

B) PRUEBAS DE INTERCAMBIABILIDAD PARA MEDICAMENTOS GENÉRICOS INTERCAMBIABLES

UNIDAD CLÍNICA PARA REALIZAR ESTUDIOS DE BIODISPONIBILIDAD Y/O BIOEQUIVALENCIA ☐

UNIDAD ANALÍTICA PARA REALIZAR ESTUDIOS DE BIODISPONIBILIDAD Y/O BIOEQUIVALENCIA ☐

UNIDAD ANALÍTICA PARA ESTUDIOS DE PERFILES DE DISOLUCIÓN ☐

C) UNIDADES DE VERIFICACIÓN.

VERIFICACIÓN DE ESTABLECIMIENTOS ☐ OTRO ☐

MUESTREO ☐ (ESPECIFIQUE) _____

DECLARO BAJO PROTESTA DECIR VERDAD QUE CUMPLO CON LOS REQUISITOS Y NORMATIVIDAD APLICABLE, SIN QUE ME EXIMAN DE QUE LA AUTORIDAD SANITARIA VERIFIQUE SU CUMPLIMIENTO, ESTO SIN PERJUICIO DE LAS SANCIONES EN QUE PUEDO INCURRIR POR FALSEDAD DE DECLARACIONES DADAS A UNA AUTORIDAD, Y ACEPTO QUE LA NOTIFICACIÓN DE ESTE TRÁMITE SE REALICE A TRAVÉS DEL CENTRO INTEGRAL DE SERVICIOS U OFICINAS EN LOS ESTADOS CORRESPONDIENTES AL SISTEMA FEDERAL SANITARIO.(Artículo 35 fracción II de la Ley Federal de Procedimiento Administrativo)

LOS DATOS O ANEXOS PUEDEN CONTENER INFORMACIÓN CONFIDENCIAL, ¿ESTÁ DE ACUERDO EN HACERLOS PÚBLICOS? SI ☐ NO ☐

_____

NOMBRE Y FIRMA DEL PROPIETARIO, O REPRESENTANTE LEGAL O RESPONSABLE SANITARIO

PARA CUALQUIER ACLARACIÓN, DUDA Y/O COMENTARIO CON RESPECTO A ESTE TRÁMITE, SÍRVASE LLAMAR AL SISTEMA DE ATENCIÓN TELEFÓNICA A LA CIUDADANÍA (SACTEL) A LOS TELÉFONOS 2000-2000 EN EL D.F. Y ÁREA METROPOLITANA, DEL INTERIOR DE LA REPÚBLICA SIN COSTO PARA EL USUARIO AL 01-800-112-0584 O DESDE ESTADOS UNIDOS Y CANADÁ AL 1-800-475-2393. O A LOS TELÉFONOS DE LA COFEPRIS EN EL D.F. DE CUALQUIER PARTE DEL PAÍS MARQUE SIN COSTO EL 01-800-033-5050 Y EN CASO DE REQUERIR EL NÚMERO DE INGRESO Y/O SEGUIMIENTO DE SU TRÁMITE ENVIADO AL ÁREA DE TRAMITACIÓN FORÁNEA MARQUE SIN COSTO AL 01-800-420-4224.