Animal Health market in the BRIC countries and comparison of its regulatory requirements for veterinary medicinal products with EU legislation

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List of Abbreviations

ACFTA	ASEAN-China Free Trade Agreement
AH	Animal Health
Anvisa	Agência Nacional de Vigilância Sanitária (Brazil)
API	Active Pharmaceutical Ingredient
art.	article
BE	Bioequivalence
BfT	Bundesverband für Tiergesundheit (Germany)
BRIC countries	abr. for Brazil, Russia, India and China
CDSCO	Central Drugs Standard Control Organisation (India)
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, Manufacturing and Control
CMS	Concerned Member State
CP	Centralised Procedure
CPP	Certificate of Pharmaceutical Product
CPV	Coordination of Veterinary Products (Brazil)
CVDE	Veterinary Drug Evaluation Center
CVMP	Committee for Medicinal Products for Veterinary Use
D&C Act and Rules	Drug and Cosmetic Act, 1940 and Drug and Cosmetic Rules, 1945 (India)
DCB	Brazilian Common Denomination
DCGI	Drug Controller General India
DCP	Decentralised Procedure
EC	European Commission
EEA	European Economic Area
e.g.	exempli gratia
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
etc.	et cetera
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
Fig.	Figure
GCP	Good Clinical Practice
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
IFAH	International Federation for Animal Health (Global organisation)
IFAH-Europe	International Federation for Animal Health (Europe)
IFPRI	International Food Policy Research Institute
INN	International Nonproprietary Name
IP	Intellectual Property
IVDC	China Institute of Veterinary Drug Control
LATAM	Latin American Countries
MA	marketing authorisation
MAPA	Ministry of Agriculture, Livestock and Supply (Brazil)
MOA	Ministry of Agriculture (China)
MRLs	maximum residue levels

MRP	Mutual Recognition Procedure
NCA	national competent authority
OiE	World Organisation for Animal Health
OTC	over the counter
PPP	Purchasing power parity
PamVet	Programa de Análise de Resíduos de Medicamentos Veterinários em Alimentos de Origem Animal (Brazil)
Ref.	Reference
r.h.	relative humidity
RMS	Reference Member State
SDA	Secretariat of Animal and Plant Health Inspection (Brazil)
SISCOMEX	Sistema Integrado de Comércio Exterior (Brazil)
TOPRA	Organisation for Professionals in Regulatory Affairs
TRIPS	Agreement on Trade Related Aspects of Intellectual Property Rights
UK	United Kingdom
US	United States (of America)
USA	United States of America
USDA	US Department of Agriculture
US FDA	Food and Drug Administration (USA)
VGNKI	Russian State Centre of Quality and Standardization of Animal Drugs and Feeds
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMPs	veterinary medicinal products
WHO	World Health Organisation

Short note to references

All references are listed according to a given number at the end of the thesis. Afterwards, legislation, guidelines and other legal texts are presented under separate headlines (Brazil, Russia, etc.) according to their national origin. With this structure, the reader has the option to see the relevant official texts from each of the presented countries at a glance.

1. Introduction

The key markets for veterinary pharmaceuticals, as for probably most of the European industries, are not exclusively localised inside the European Union (EU). Due to the globalisation and the liberalisation of markets, countries outside the EU and USA are becoming more and more attractive. On the one hand, there is an economic stagnation in the EU today (Ref. 1). On the other hand the economic potential of newly industrialised nations such as Brazil, Russia, India and China (abbreviated BRIC countries) is increasing rapidly at the same time (Ref. 2), and also the markets for veterinary medicinal products (VMPs) have the opportunity to benefit from the rapid growth of those emerging markets. (Ref. 3, Ref. 4, Ref. 5)

Major global market trends of the animal health (AH) sector are monitored by organisations, such as the International Federation for Animal Health (IFAH). That worldwide acting federation represents manufactures of veterinary medicines, vaccines and other AH products.

In its last global benchmarking survey from 2011, the IFAH points out that there is a slowing growth in the farm animal sector in Europe and the USA, accompanied by a much stronger growth in China, India and parts of South America. In addition, the IFAH observed a long-term growth in other emerging markets. (Ref. 5)

Today, European companies producing veterinary medicines register preferentially the main part of their products in several countries of the European Economic Area (EEA) via European procedures, such as the decentralised procedure (DCP), the mutual recognition procedure (MRP), or the centralised procedure (CP). The liberalisation of markets, the increasing global trade with livestock products and the growing demand for middle-class pursuits, such as companion animal bond in the developing countries, resulted in a rising demand for VMPs in countries such as Brazil, Russia, India and China.

In order to successfully register VMPs in the BRIC countries, it is essential to be familiar with their national law and the trends in the veterinary regulatory environment which will emerge in the near future. Unfortunately, today, the national regulatory law displays a high diversity, the comparableness to the EU legislation is limited and above all, all of the four BRIC countries have most recently tightened huge parts of their regulatory legislation. For those reasons, the successful authorisation and marketing of VMPs in the BRIC countries have been a great challenge for European companies in the past, and will be even more in the near future.

The aim of this thesis is to give the reader an overview on the AH market of the emerging countries, Brazil, Russia, India and China. Furthermore, similarities and differences between the pharmaceutical regulatory environment in the BRIC countries and the one in the EU are highlighted. The author would like to emphasise that, in many cases, public internet sources form the basis of the assumptions of this thesis. For this reason, only a part of “the big picture” can be demonstrated.

Current situation of changes in regulatory law in the BRIC countries

During the last decade, the registration requirements for VMPs in the BRIC countries have been tightened continuously.

Until 2010, in Russia the registration process of medicinal products had been faster compared to other emerging countries. Hence, the entry of a product previously marketed in the EU or US had been able to be executed in parallel or shortly later after in Russia, according to a pharmaceutical report of the Organisation for Professionals in Regulatory Affairs (TOPRA) about the Russian regulatory environment in 2011. (Ref. 6) However, that situation changed in April 2010, when Russia dramatically improved the standards for regulatory requirements with the introduction of its new Federal 'Law on Circulation of Medicines', which applies for veterinary and human medicines. In detail, the law introduced a wide range of changes that affected data requirements and procedures for clinical trial applications and marketing authorisations, as well as lifecycle management. (Ref. 6)

Above all, in the near future, a new law which is currently under revision will introduce new provisions for the registration of generics and definitions for different categories of medicines (originator, generic, biological product, biosimilars, combination product, etc.). (Ref. 7)

In Brazil, the pharmaceutical law (human and veterinary) was revised in the beginning of this year (2014). The changes will influence the complete Brazilian pharmaceutical environment by phasing out so-called "similar medicines". Latter are medicines with formulations identical to branded medicines, but without proven bioequivalence (BE). "Similar medicines" were introduced before 1996 (when Brazil did not recognize patents on pharmaceutical products), but are expired by 2014. That leaves a market of 2 billion US dollars per year to generics, phytotherapics and homeopathy (human and veterinary medicines). (Ref. 8)

In China the regulatory requirements and control mechanisms for pharmaceutical products were amended in order to improve the quality and safety of human medicines and VMPs, since there have been big concerns regarding active pharmaceutical ingredients (APIs) and traceability throughout the supply chain. This was triggered by scandals such as the worldwide contamination of various heparin products with over sulphated chondroitin sulphate, cases of contaminated glycerine originating in China and ending up in products as diverse as toothpaste, cough syrup and antihistamine tablets, and an alarming increase of reports about fake medicines. These amendments of the legislation upgraded the Good Manufacturing Practice (GMP) inspection standards by imposing more stringent technical requirements, quality control and validation procedures. (Ref. 9)

In India there is no separate regulatory framework for VMPs. It is implicated in the human medicine law the Drug and Cosmetic Act, 1940 and the Drug and Cosmetic Rules, 1945 (D&C Act and Rules). In 2003 a major change in import regulations occurred in the country. In detail, since this time stricter regulations for import licences are required for all types of medicines, according to the law "Notification GSR no. 604 (E)", which amends the D&C Act and Rules. (Ref. 10)

India is the only one of the four BRIC countries, which does not maintain a separate department for VMPs application assessment at the national competent authority (NCA). Resulting from that situation, national veterinarians and the pharmaceutical industry demanded an update of the current Indian pharmaceutical legislation which is published in "Confluence on Veterinary Regulatory Reforms in India" in 2012. (Ref. 11)

As a consequence of these diverse regulatory and organisational conditions, there is growing interest of the industry to harmonise the regulations for VMPs in the emerging countries. The

national governments are also interested in an access to safe and efficacious VMPs around the world.
Hence, the International Cooperation on Harmonisation of Technical Requirements for Registration of VMPs (VICH), a trilateral (EU-Japan-USA) programme (Ref. 12), has tried with strengthening efforts to harmonise requirements and to simplify processes in the BRIC countries during the last years (Ref. 13, Ref. 14) At their VICH outreach forum, a 2011 founded platform for non-VICH members, the organisation discusses the activities contributing to the VICH Guideline development process. Today, all four BRIC countries are members of the VICH outreach forum.

However these efforts are hampered by the local protectionism of the governments. Particularly today, there are more or less obvious tendencies of the national authorities to protect the local economy from the influence of foreign pharmaceutical industries.
For instance, Brazil' government has a specific industrial policy to promote the development of the national pharmaceutical industry in order to establish or expand regional industrial clusters. Since 2007, the Brazilian government has been strengthening its national production base of pharmaceutical products and medical equipment under the name "Health Industry Complex" (Complexo Industrial de Saúde). The main objectives of this policy were to reduce the annual foreign trade deficit on health-related goods from 7.1 billion to 4.4 billion US dollars, and to develop technology in order to produce 20 medicines considered strategic for the Brazilian healthcare system: both until 2013. (Ref. 8)

In Russia, there is also a national programme to support the domestic pharmaceutical industry. It encourages foreign manufacturers to localize their manufacturing operations inside the country. This tendency is currently very strong in Russia. Moreover, according to a market survey of Ernst & Young in 2012, 88 percent of the questioned pharmaceutical companies have the impression that an increase of the NCAs forced foreign companies to establish local production enterprises over the next five years. (Ref. 15)

Distribution of AH market shares

Together with the rapid economical growth of the BRIC countries during the last decades, the market share of VMPs has gained importance. In 2009, the global market share for Latin America was at 12% and for East Asia at 15% (including, among other countries, India, China and Russia). (Ref. 21) In the same study, the global market share for Europe was at 36%, for North America at 33% and for the rest of the world at 3%. (Ref. 21) Data provided by the IFAH supported this trend already in 2006. For example, in IFAH study, the AH market in Latin America represented an 11.6% share of the global volume of commercialised veterinary products commercialised, for a value of 1.870 million US $. (Ref. 22)

Unfortunately, a currently published report from IFAH in 2012 (Ref. 23), gives only limited information about the status of the BRIC countries in regard to the global market share. In that report, the authors divide the market share simply in three regions: Europe, America (North, Latin and South America) and Asia/Australia/Africa together in one calculation. Hence, the IFAH did not differentiate e.g. between developed and emerging countries. According to that report, Europe has 31% market share and therefore, if compared to the IFAH report from 2009, has lost 5% during the last four years. America has a market share of 47%, which is 2% more than in 2006, if both, the data for North America and Latin America would be added up. (However, it is not clear if that slight increase in market share is because of an increase of market share in Brazil or because of the fact that the above mentioned report did not include South America at all.) Asia, Australia and Africa have a market share of 22% (Ref. 23), but also here, no conclusions can be drawn in regard to the BRIC countries.

Generally, the AH market can be divided into three major product groups: pharmaceuticals, biologicals and medicinal feed additives. In 2012, the main product group of the VMPs was the pharmaceuticals with a market share of 62%. This product family includes antibiotics, anti-parasites and hormones. Having a market share of 26%, the second largest product group is the biologicals, of which the vaccines are the most popular representatives. Feed additives constitute the last product group with a 12% market share. (Ref. 24)

Currently, the worldwide biggest volume of sales belongs to the market segment of the anti-parasites. These VMPs are essential for the treatment of food producing animals in countries with intensive grassland farming, such as America, Australia and parts of Europe (Ref. 21)
In general, VMPs could be used for food producing animals and companion animals. In 2012, the global market share of VMPs was at 59% for food producing animals, and therefore comparatively higher than the market shares of 41% for companion animals. (Ref. 6)

In contrary to the human health industry, the development of the veterinary pharmaceutical market depends on the size and the price of animal populations, or on the price of the single animal. (Ref. 21) As a result, the impulses for the economic development of both market segments (food-producing and companion animals) are different: Economical aspects mostly drive the livestock husbandry and emotional values defined by the owner and/or economical considerations affect the keeping of pets.

2. The BRIC countries - a short presentation of economy, pharmaceutical market and their characteristics

The term BRIC countries were established by Goldman Sachs, a global investment banking company in 2001. In that year, Goldman Sachs published a paper titled 'Building Better Global Economic BRICs', which looked at the growth prospects of the four largest emerging economies that were culturally and geographically diverse. The main finding was that the BRIC countries would play an increasingly important role in the global economy in the subsequent decades. (Ref. 2)
Today, *"the BRICs are described as countries at the same stage of economic development, but not yet at the point where they would be considered more developed countries. The BRIC position argues that, since the four countries are "developing rapidly," their combined economies could eclipse the collective economies of the current richest countries of the world by 2050."* (Ref. 25)

In 2012, the IFAH noticed that the livestock production and global trade was changing due to the growing demand for livestock products in the developing countries. (Ref. 26) This was very obvious in countries with a huge economic growth rate such as the BRIC countries.
The International Food Policy Research Institute (IFPRI), an international agricultural research centre founded in 1975, points out that in the past, the developed world was a large supplier of meat and livestock for the developing world. Today, this situation is changing; the developing world rapidly increases the production and meets more of its growing domestic demand. (Ref. 27) As a result, traditional farming systems are becoming more and more industrialised; the percentage of livestock products such as meat, fresh milk and eggs produced in intensive production units is increasing rapidly in the countries of the developing world. *"Thus, with rising incomes, a smaller share of the food budget is spent on grains and other starchy staples and a larger share is spent on meat, milk, fish, fruits, vegetables, and processed and prepared foods."* (Ref. 27) Delgado et al. labelled this significant change in the consumption and production of livestock products as a 'Livestock Revolution'. (Ref. 28)

Today, countries such as Brazil, Russia, China and India show a rapid growth in livestock production and produce currently enough to meet their domestic demand, and continue to import more than they produce. The IFPRI anticipated that in the future many of the developing countries would follow the BRIC countries in terms of economic growth. (Ref. 27)
Consequently, the IFAH noticed that the demand of livestock products in the EU, USA and Japan could be met more and more by convenient products from the developing countries. (Ref. 26) This would be due to the liberalisation of markets and the implementation of clearer rules on technical trade barriers with respect to AH during recent decades.

At the same time, "*the importance of foodborne diseases, both in terms of human health and shocks to demand for specific food products,*" (Ref. 26) leads to a rising interest in high quality veterinary services, combined with adequate treatment with VMPs. Furthermore, in order to prevent the global spread of zoonoses like severe acute respiratory syndrome (SARS) and, more recently, influenza A (H1N1), developments in international law do increasingly incorporate food safety issues. (Ref. 26) This is a very crucial development, because such diseases had, to varying degrees, a huge impact on public health and economic in the past. (Ref. 29)

That situation is followed by a growing economical interest of the industry to prevent food producing animals from developing diseases of viral, bacterial, or parasitical origin. Furthermore, in intensive livestock units, the fertility of pigs and cattle is improved through application of hormones. In summary, an economic profitable livestock husbandry is only possible when effective management and adequate treatment with VMPs is applied.

2.1 Brazil

Brazil is the largest country in South America and shares boundaries with every South American country except Chile and Ecuador.

Population:	201 millions
country comparison to the world:	5.
GDP - per capita (PPP):	$12,100
country comparison to the world:	106.
Independence:	7 September 1822 (from Portugal)
Total area:	8,514,877 sq km
country comparison to the world:	5.
Capital:	Brasilia

Source: Ref. 30

Economy

Characterized by large and well-developed agricultural, mining, manufacturing, and service sectors, Brazil is the largest national economy among the Latin American countries (LATAM). The country also increases its presence in the world market. (Ref. 30) In addition, there is a general economic expansion, because the Brazilian economy was little affected by the last international recession and already resumed growth in 2009. (Ref. 8) Brazil is mostly trading with its neighbour countries and the United States. Brazil and the South American countries Argentina, Paraguay, Uruguay and Bolivia, have founded an economic association called MERCUSOR, or the “common market of the South”.

Pharmaceutical market

Today, the Brazilian AH market is considered as the second largest in the world immediately placed after the United States. “*Together with other Latin American countries, such as Mexico, Argentina and Colombia, the region represents an important source of revenue for global animal health companies. With European and other established markets presenting only limited growth perspectives, Brazil and Latin America are seen by most companies as important global growth drivers.”* (Ref. 31)

According to a publication about Brazil’s pharmaceutical industry (including the niche market for VMPs) from 2010, this sector is, among the major pharmaceutical markets, one of the fastest growing in the world. (Ref. 3)

Compared to other emerging markets, Brazil has an effective patent protection regime that is consistent with the rules of the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS). Furthermore, the existence of falsified medicines is relatively low in this country. (Ref. 3)

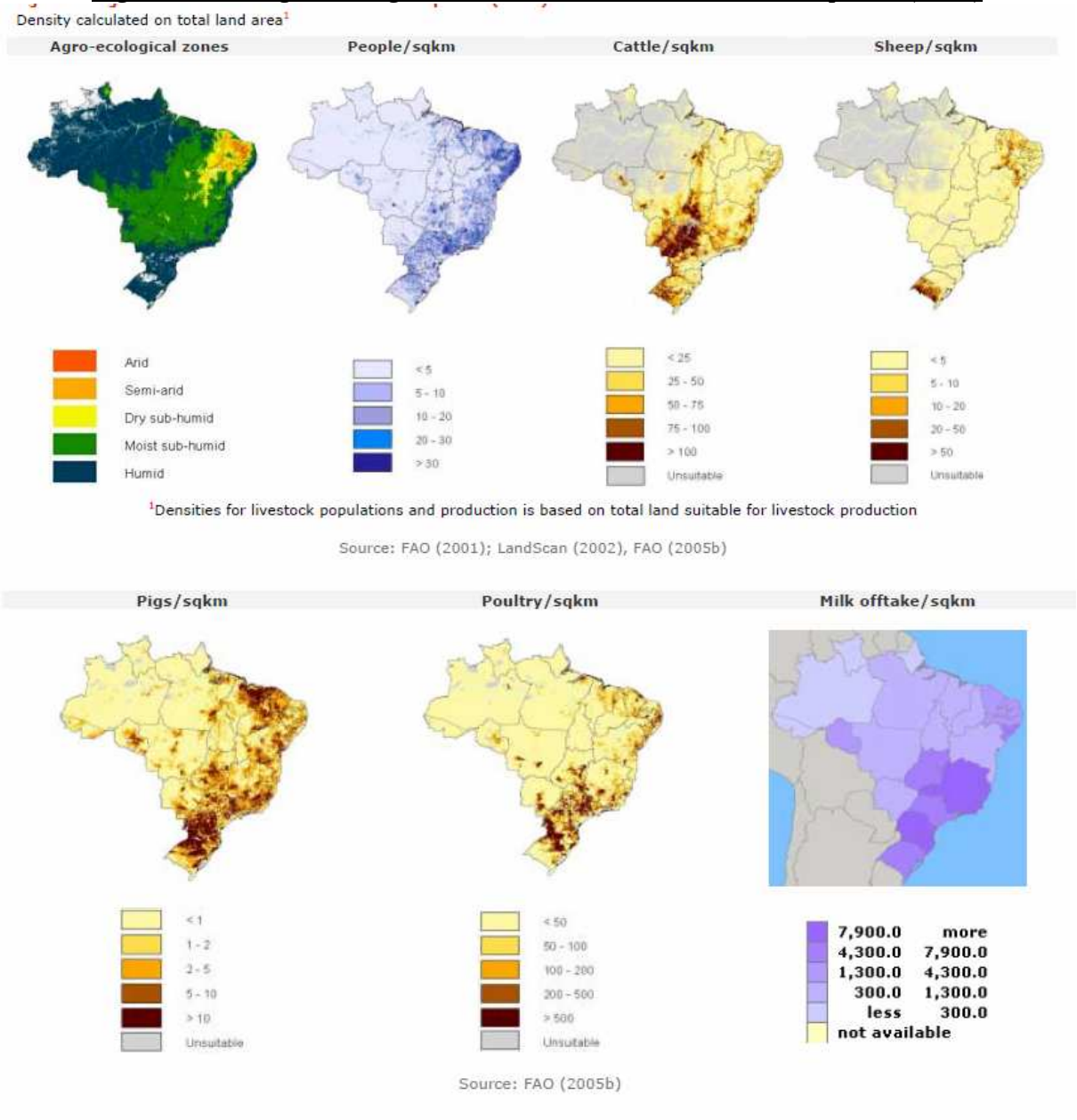
Moreover, the Brazilian pharmaceutical sector is a suitable example for foreign companies, which enter the market not only with human, but also with veterinary pharmaceutical products.

According to the above mentioned report, companies such as Novartis, Pfizer and Boehringer Ingelheim had a total market share (human and veterinary) of approximately 16% in Brazil in 2010 (Pfizer: 5%, Boehringer Ingelheim: 1%, Novartis: 10%). (Ref. 3)

Climatic conditions and densities of livestock populations

According to data of the Food and Agriculture Organisation (FAO) of the Untied Nations, most people, their companion animals and animal farming systems are located in the moist sub-humid zone of the country (see Fig. 5). To be able to market pharmaceutical products in such a climatic environment, medicines should be proven to be stable at 30°C/75% relative humidity (r.h.), i.e. climatic zone IVb stability testing, which is consistent with the guidelines of the World Health Organisation (WHO) (Ref. 32)

Fig. 1. Brazil: Agro-ecological zones and densities of livestock species (2000)



Source: Ref. 33

2.2 Russia

Russia's total area is 17 million km² and therefore the world's largest country. The Russian Federation stretches from North Asia to the Arctic Ocean and extends from Europe (the portion west of the Urals) to the North Pacific Ocean.

Population:	142,500 billions
country comparison to the world:	9.
GDP - per capita (PPP):	$18,000
country comparison to the world:	77.
Total area:	17,098,242 sq km
country comparison to the world:	1.
Capital:	Moscow

Source: Ref. 30

Economy

According to information of the world factbook, *"…Russia has undergone significant changes since the collapse of the Soviet Union, moving from a globally-isolated, centrally-planned economy to a more market-based and globally-integrated economy. Economic reforms in the 1990s privatized most industry. The protection of property rights is still weak and the private sector remains subject to heavy state interference."* (Ref. 30)

Pharmaceutical market

According to a market survey from Ernst & Young from 2012, Russia has undergone a massive reformation of the pharmaceutical industry (human and veterinary) since 2008. In 2012, there was and adoption of a number of highly important legislative acts as well as amendments and corrective adjustments to existing industry legislation. Ernst & Young points out that the Russian government has a strategy of developing the domestic pharmaceutical industry and supporting Russian manufacturers. (Ref. 15) Such a procedure will apparently lead to delays in the market entry of foreign companies.

Climatic conditions

The territory ranges from steppes in the south through humid continental climatic areas in most of European Russia; subarctic in Siberia to tundra climate in the polar north; winters vary from cool along the Black Sea coast to frigid in Siberia; summers vary from warm in the steppes to cool along the Arctic coast. (Ref. 30) Pharmaceutical products should be proven to be stable at the following conditions: 25°C / 60% r.h., i.e. climatic zone II stability testing. (Ref. 32)

2.3 India

The Republic of India has the second highest population in the world (1,220 billion); which converts to 16% of the world's population. The Indian peninsula is separated from the Asian mainland by the Himalayas, and dominates the South Asian subcontinent.

Population:	1,220 billions
country comparison to the world:	2.
GDP - per capita (PPP):	$3,900
country comparison to the world:	168.
Total area:	3,287,263 sq km
country comparison to the world:	7.
Independence:	15 August 1947 (from the United Kingdom)
Capital:	New Delhi

Source: Ref. 30

Economy – overview

"India is developing into an open-market economy, yet traces of its past autarkic policies remain. Economic liberalization measures, including industrial deregulation, privatization of state-owned enterprises, and reduced controls on foreign trade and investment, began in the early 1990s and have served to accelerate the country's growth, which averaged under 7% per year since 1997. India's diverse economy encompasses traditional village farming, modern agriculture, handicrafts, a wide range of modern industries, and a multitude of services." (Ref. 34)

Besides a strong economy, India has a huge middle class population, which had grown rapidly, from 25 million people in 1996 to 153 million people in 2010. If the economy continues to grow fast and literacy rates keep rising, approximately 34% is expected to join the middle class in the near future. (Ref. 35)

Pharmaceutical market

At the beginning of the last century, pharmaceuticals were completely imported from abroad; hence the Indian pharmaceutical market was practically non-existent. (Ref. 36) Some decades later, the demand for pharmaceuticals did rise significantly, which led to the necessity of having a comprehensive legislation. Due to this development, the Indian government passed the Drugs Act in 1940, valid for human and veterinary medicines. (Ref. 36)

Nowadays, the country is a major supplier of the world's generic medicines, but there are no specific national regulations for generic products. Because of their reasonable price, efficacy and safety, about 85% of medicines marketed in India are generic products (human and veterinary). (Ref. 37)

Moreover, the Indian AH market gains in importance. More and more companies are adapted to the special needs of the Indian veterinary environment and products for reasonable prices, such as herbal medicines, achieve an increasingly market share. Today, a huge growth is expected for the human and veterinary pharmaceutical market in the near future (Ref. 38, Ref. 35). These growth perspectives are "… *impossible for global Pharma companies to ignore, given that India will be one of the top 10 sales markets in the world by 2020.* […] *With considerable expertise in manufacturing of generics and vaccines, Indian companies have now also started significant research and development (R&D). India has the world's second biggest pool of English speakers and a strong system of higher education."* (Ref. 35)

An example is the Indian vaccine industry (for humans as well as for animals) that registered sales of 524 million $US from 2009 to 2010. The shares for veterinary vaccines alone was 107 million $US, which indicated a growth rate of 4.9% from 2008/2009 to 2009/2010. (Ref. 35)

Table 1. Increased vaccine sales in India, 2009- 2010

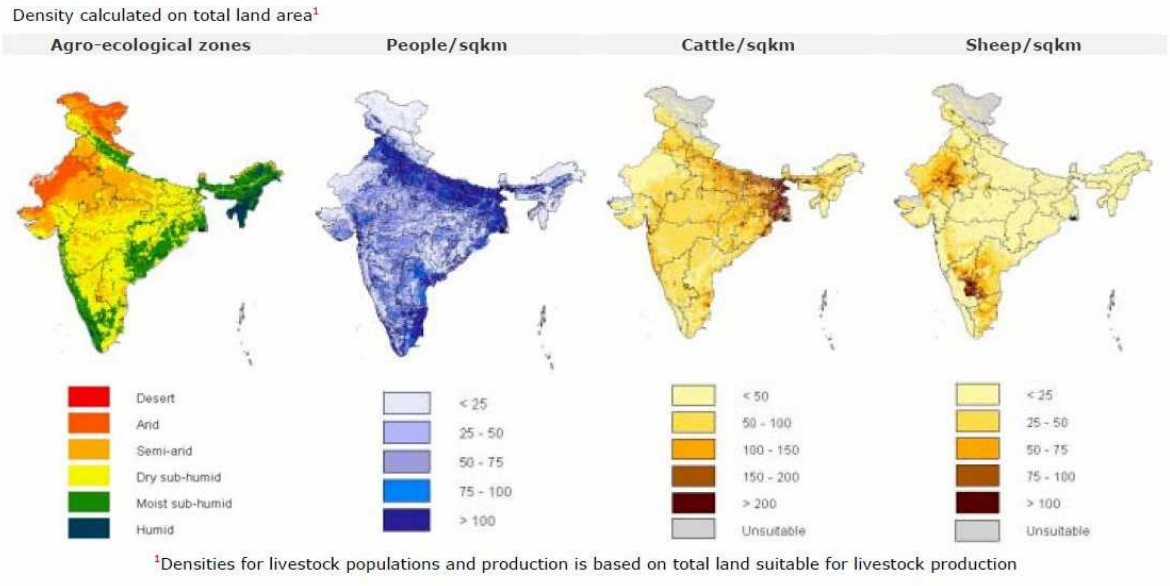
		2008-09 (US$ millions)	2009-10 (US$ millions)	Growth rate
Human Vaccines	Export	155	179	15.5%
	Domestic	215	238	10.7%
	Total	370	417	12.7%
Animal Vaccines	Total	102	107	4.9%

Source: Ref. 35

Climatic conditions

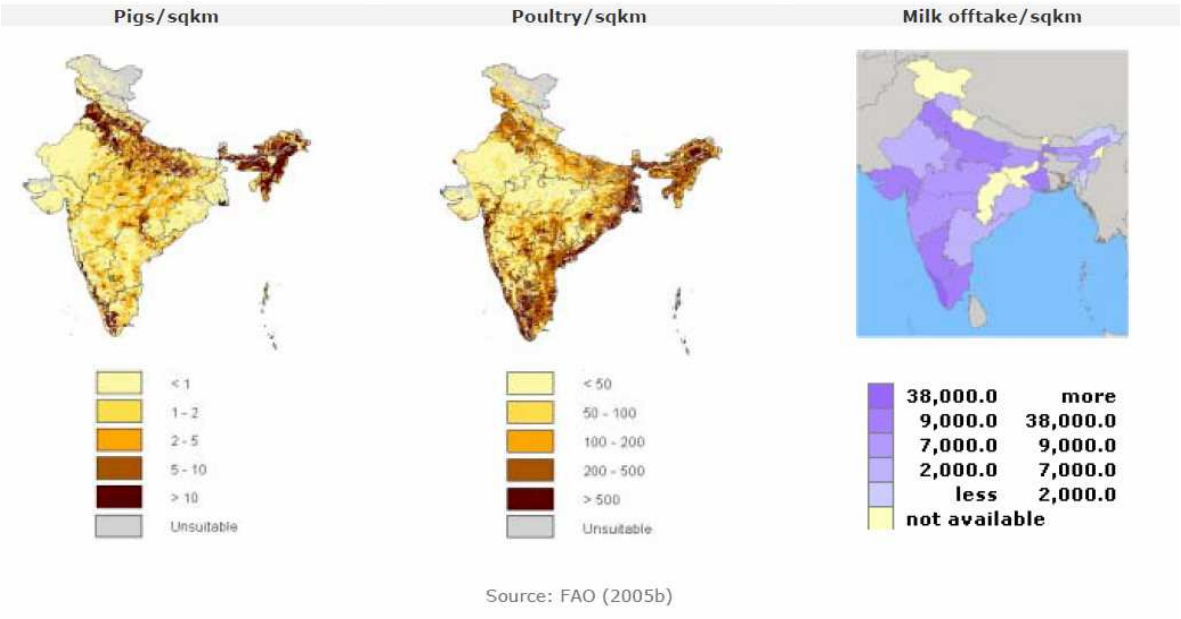
Generally speaking, India has a tropical monsoon climate. Although the majority of the northern part of India is located beyond the tropical zone, the entire country has a tropical climate, which is marked by relatively high temperatures and dry winters. Most of the livestock can be found in the dry to moist sub-humid climatic zone. According to the WHO stability guideline No. 953, pharmaceuticals must be proven to be stable at the following conditions: 30 °C/70% r.h., i.e. climatic zone IV stability testing. (Ref. 32) For details, please see table 5.

Fig. 2a. India: Agro-ecological zones and densities of livestock species (2000)



Source: Ref. 39

Fig. 2b. India: Agro-ecological zones and densities of livestock species (2000)



Source: Ref. 39

2.4 China

China borders Eastern Asia in the West and has coastline that extends from North Korea to Vietnam, along the East China Sea, Korea Bay, the Yellow Sea, and the South China Sea.

Population:	1,349 billions
country comparison to the world:	1.
GDP - per capita (PPP):	$9,300
country comparison to the world:	124.
Total area:	9,596,961 sq km
country comparison to the world:	4.
Capital:	Beijing

source: Ref. 30

Economy – overview

China's human pharmaceutical market is expected to become the largest in the world by 2050. This is due to a rapidly growing economy and urban middle class sector (520 million people predicted to be of upper middle class status by 2025). (Ref. 40) The ASEAN-China Free Trade Agreement (ACFTA) is a trade bloc consisting of the ten ASEAN member states and the People's Republic of China. The ACFTA came into effect in January 2010. This organisation is now recognised as the largest regional emerging market in the world, as it was valued with €7.5 trillion of trade in 2010 (Ref. 40)

Today, *"china is the world's third largest economy […] with large potential markets for goods, equipment and expertise, and so it offers many opportunities and challenges. The country is shifting away from resource-intensive manufacturing, resulting in major industrial upgrading in many industrial sectors."* (Ref. 9)

Pharmaceutical market

The AH industry in China included 1,800 companies in 2011. A majority of the produced medicines were live and inactivated vaccines. In that year, 270 billion doses live vaccines and 60 billion millilitre inactivated vaccines were produced. Furthermore, China`s industry produces the complete spectrum of veterinary medicines, such as antimicrobial, anti-parasites, disinfectants, antipyretic-analgesic and anti-inflammatory medicines. (Ref. 41)

With attention to the Chinese regulatory environment, the IFAH Europe noticed a strong local protectionism in China in its last benchmarking report from 2011: *"…There is a 2-speed system between local and foreign companies; and China also accepts quality standards from local companies that in some cases are so low that they damage their own industry."* (Ref. 4)

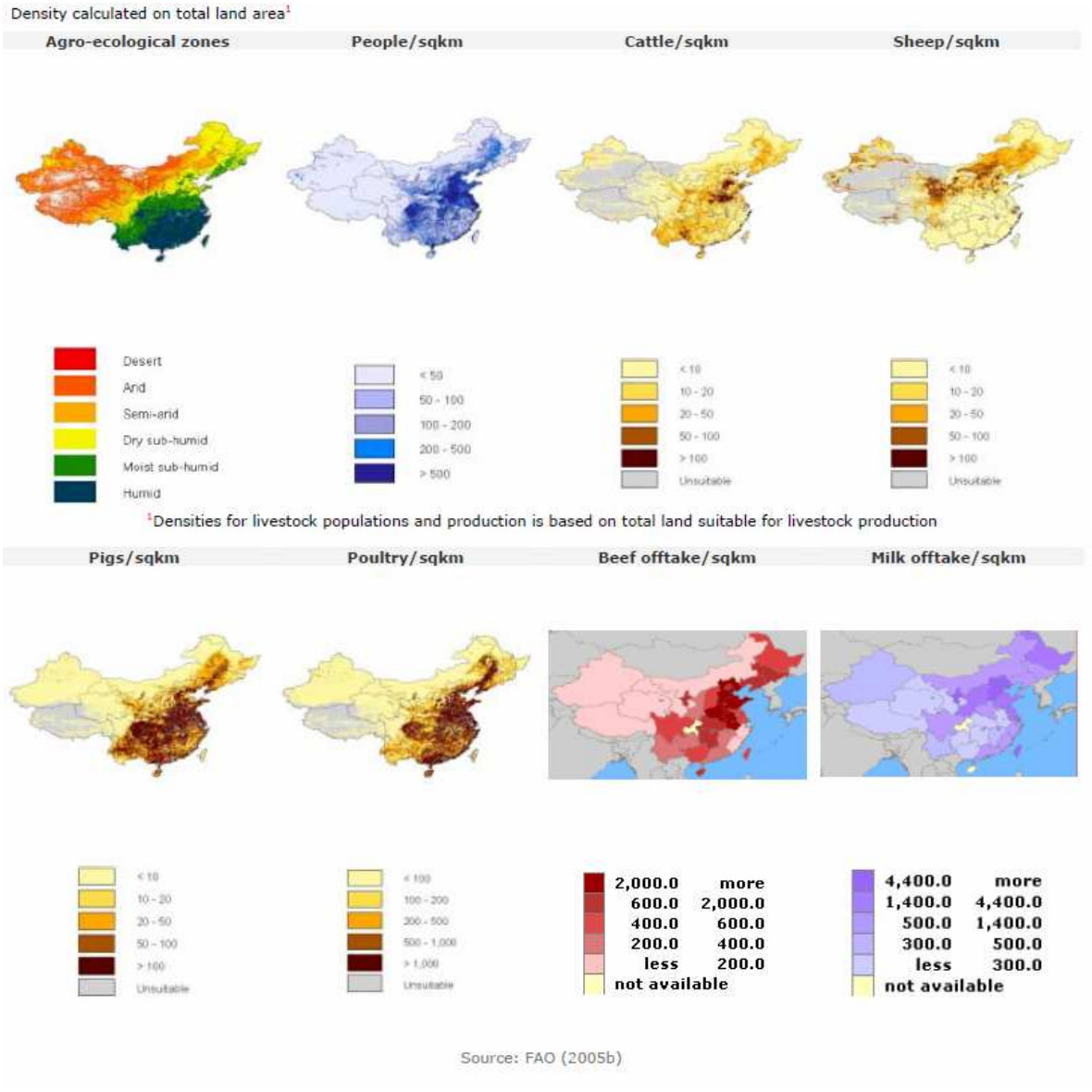
Moreover, the IFAH Europe is concerned about intellectual property (IP) protection issues. Currently, questions are raised on how much detail has to be revealed to meet the requirements of the NCAs. As an illustration, one interviewee of the IFAH report noted that the authorities make every effort to be approachable; a frequent comment sounds like this: *"…for biologicals, the Chinese authorities request details and demand strains; this produces a strong internal debate on how to deal with the situation but, as China is the number 2 or 3 market in the world, it is impossible to stay out of it – we need to be sure of the market, but also get into it in a way we don't regret later."* (Ref. 4)

In addition, there have been concerns about the quality of certain APIs of Chinese origin in many countries. In particular, an instance of heparin contamination of an API could be tracked back to China and resulted in recall of the final product in 2008. As a consequence, in inspection standards were upgraded 2009, with the goal having more rigid and robust technical requirements. (Ref. 42)

Climatic conditions

The FAO data indicates that most of the people, their companion animals and animal farming systems are located in the moist sub-humid and humid zone of the country (see Fig. 6). Therefore, pharmaceutical products should be proven to be stable at the following conditions: 30 °C/65% r.h. , i.e. climatic zone IVa stability testing. (Ref. 32)

Fig. 3. China: Agro-ecological zones and densities of livestock species (2000)



Source: Ref. 43

3. Animal husbandry

3.1 Livestock and poultry

In April 2013, three of the four BRIC countries are leading the list of the ten countries with the world's largest cattle population. (Ref. 44) The world leader in cattle production was India (327 million animals), followed by Brazil (203 millions) and China (104 millions). In 2013, Russia was the world's 9th largest cattle producer, counting 19 million animals. The estimated total global cattle population was 1.027 billions in October 2013. Compared to the population in 2009, the number of animals remained relatively stable with an increase of only 0.4% during these years. In detail, there was an increase of animals in two of the four BRIC countries (India with +5.3 % and Brazil with +11.9%) between 2009 and 2013. Russia and China reduced their population by -8.3% and -1.5%, respectively during the same time period of four years. (Ref. 44)
Similar to Russia and China, the EU and the US market reduced their cattle population by -5.4% and -4.1%, respectively, during the last five years. Yet, the EU market ranks 5th in the international comparison.

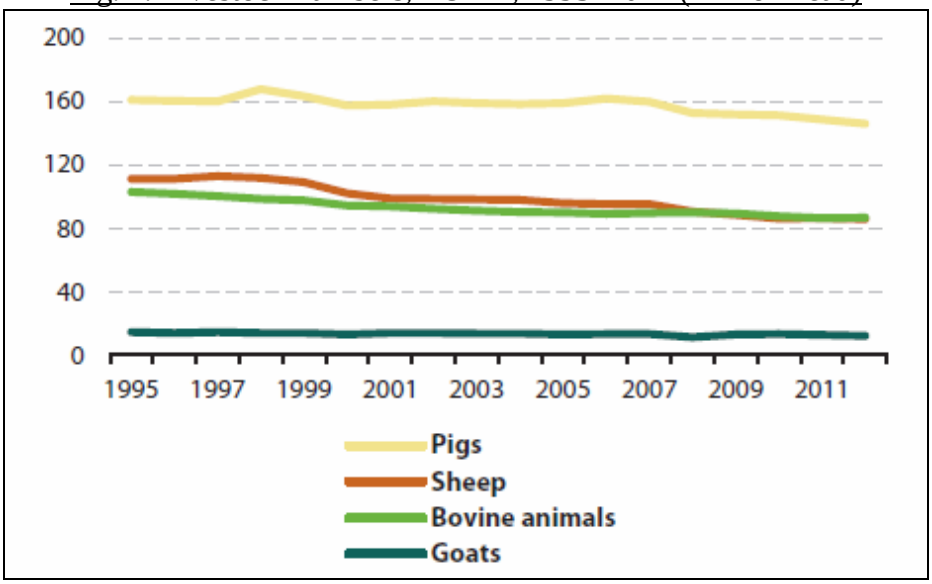
The importance of livestock husbandry in the BRIC countries is also emphasized by the fact that three of the four BRIC countries appeared in the 2013 top ten list of the global pig population in the above-mentioned USDA report. (Ref. 44)
China leads the list, having a pig population of 466 million animals in 2013. The increase since 2009 remains relatively low (+0.8%), compared to countries such as Brazil that showed and increase of +13.7% during the same period. Russia, number five on the list, has increased its pig population by +6.6% to 17 million animals in 2013. The USDA report does not provide any data for India. However, a publication of the Indian department of animal husbandry, dairying and fisheries (Ref. 45), mentions a massive decline in the pig population by -17.7% between the years 2003 and 2007 (from 13.5 to 11.1 millions). For this reason, the author assumes that the current production of pork only plays a minor role in the Indian livestock husbandry.
In contrast to BRIC countries, the pig population of the EU and the US declined by -3.1% and -3.0%, respectively. Nevertheless, the EU ranks second and the US third on the USDA list of the world pig population.

Moreover, there has been a rapid increase in the demand of poultry meat in the BRIC countries and many other developing countries during the last three decades. For example, the average consumption of poultry meat in the Latin American Countries (LATAM) and the Caribbean rose from 7.97 to 22.57 kilograms/capita/year between the years 1980 and 2007. This is an increase of +64.7%. During the same time period, the increase in the demand of poultry meat in the developed countries (USA, Canada, EU, Japan, and Australia) was +48.7% and therefore comparatively moderate. (Ref. 27)

The European Commission has recently published the decline in livestock population across the EU countries. (Ref. 46) The authors described the current trends as follows:
"Since the early 1980s, there has been a steady downward trend in the number of livestock on agricultural holdings across the EU. Indeed, estimates of pig and sheep populations for the EU‑27 in 2012 point to new lows (see Figure 5, below)*; there were 15.1 million fewer pigs when compared with 1995 (an overall decline of 9.4 %) and 25.3 million fewer sheep (an overall decline of 22.8 %). There were also an estimated 16.1 million fewer cattle in 2012 than 1995 (although the number of cattle was marginally higher in 2012 than a year earlier) and there were 2.2 million fewer goats."* (Ref. 46)

Presumably, this decrease is caused by the decline in the human population among the EU member states. According to a publication of the European Commission, the number of humans in the age of 15 to 64 years will drop by 48 million until 2050. (Ref. 47)

Fig. 4. Livestock numbers, EU‑27, 1995–2012 (million head)



Source: Ref. 46

3.2 Companion animals

As mentioned before, the economic boom of the BRIC countries is accompanied by an increase in the middle-class pursuits such as companion animal bond. (Ref. 4) Regarding the keeping of dogs as pets, the percentage of animals in Brazilian domestic homes rose from 2007 to 2012 by +14.3% to a total number of 35.7 millions. (Ref. 48) Hence, Brazil is listed as having the world's second largest pet dog population in 2012. (Ref. 49) The only country with a considerably higher amount of pet dogs is the US, keeping 75.8 millions dogs as companions.

The cause of this development is an increasing number of Brazilian couples, which had been childless for a longer time period. At the same time, demographic trends are boosting pet ownership, especially with regards to smaller housing units in the cities, as more Brazilians are now living alone. Furthermore, there is a highly visible trend to a rapidly urbanization of the middle class and to higher salaries for workers. (Ref. 50)
In Russia, the increase in the dog population was +28.0% between 2007 and 2012, and therefore higher than in Brazil. (Ref. 50) This development results in a situation where Russia, keeping 15 million pet dogs, has the world's fourth biggest pet dog population in 2012. (Ref. 48) The author assumes that the above described socio-economic conditions in Brazil could also be found in Russia; even more because the gross domestic product (GDP) - per capita (PPP) also has a comparatively high standard among the BRIC countries (India: $12,100; Russia: $18,000 GDP - per capita (PPP)).

India had one of the world's lowest rates of dog ownership, only counting four dogs per 1,000 people. This situation changed quickly between 2007 and 2012, according to a market research of Euromonitor. (Ref. 50) During this time period of 5 years, India had shown an increase of 58% of the total number of pups. This is the fastest growth rate among the 53 countries surveyed by Euromonitor in this study. (Ref. 48)

In China, the total pet number has reached approximately 100 million; according to a report of the World Organisation for Animal Health (OiE) in 2012. (Ref. 51) Yet, Euromonitor predicted for 2013 a solid growth of the population of dogs, cats and other pets in China. This would be due an increasing number of households with childless couples. (Ref. 50)

Over the last decade, the Chinese government has adopted regulations for dog management in big cities. Today, it is only allowed to have one dog in each family. In addition, it is illegal "to keep strong, large or aggressive dogs." (Ref. 51) The author assumes that such regulations were implemented because of the constant growing dog population in big urban centres. Otherwise, there must be an extremely low rate of dog owners in rural regions, because entire China only has a rate of two dogs per 100 people. Within Asia, it is only Malaysia that has a lower rate of dogs: 1.2 dogs per 100 people. (Ref. 48)
A 2012 publication of the IFAH-Europe revealed that the EU had over 196 million pets of which 60 million were dogs. (Ref. 52) Compared to the top ten countries worldwide with the largest dog population, the EU was ranked second, only exceeded by the US having 75.8 million pet dogs.

In particular, the largest pet dog population inside the EU was observed in France with 7.4 million dogs, although the country shows a decrease by -6.9% between 2007 and 2012. The EU average country has 2.8 million dogs and a decline of -0.1%. Presumably, that decrease is caused by the same reason as mentioned above for decline in EU livestock: a decline in the human population among the EU member states. (Ref. 47)
The downward trend in the human population in the EU is a long-term development, and the pet-owner-ratio does not work if there is a decreasing number of a potential owner. In this respect, the author supposes that the above mentioned decline in the pet dog population could be seen as an indicator for the development of the complete pet population in the EU.

Table 2: Changes in dog population (2007-2012), selected countries

		Percent change in the number of dogs since 2007	Total dogs in 2012 (millions)
Top 5	India	**+58.1%**	10.2
	Philippines	+38.3	11.6
	Venezuela	+29.8	3.1
	Russia	+28.0	15.0
	Argentina	+20.1	9.2
Bottom 5	Greece	-2.9	0.7
	Romania	-4.2	4.1
	Japan	-4.3	12.0
	France	-6.9	7.4
	Switzerland	**-9.8**	0.4
Other Countries	Brazil	+14.3	35.7
	China	+2.3	27.4
	US	+2.2	75.8
	EU Average	-0.1	2.8

Source: Ref. 50

4. Competent veterinary authorities and regulatory legislation in the BRIC countries and the European Union

4.1 Organisation and responsibilities of competent authorities

In this chapter, the author presents the structure and function of the national competent authorities (NCAs) responsible for the evaluation and registration of VMPs in the BRIC countries. For comparative reasons, the organisation and function of the EMA will be briefly discussed.

In general, the organisation of the NCAs, responsible for evaluation and supervision of veterinary medicine, varies from country to country. According to a publication of the Indian Veterinary Journal in 2012 (Ref. 11), the agencies could be divided in two groups, based on how the control of veterinary medicines is organized:

- NCAs in countries, where the veterinary medicine control is part of a "single agency" system that regulates human medicines under supervision of the national Ministry of Health, and
- NCAs in countries where a separate agency regulates the veterinary medicines under the supervision of the national Ministry of Agriculture.

Regarding the system for evaluation and supervision of veterinary medicine in the BRIC countries, a "single agency" system is observed in India. In that country, only one department assures the evaluation of human and veterinary medicines: the Central Drugs Standard Control Organisation (CDSCO), a subdivision of the Ministry of Health and Family Welfare of India.
According to that overall classification, the NCAs of Brazil, Russia and China work as separate agencies under the control of the local Ministry of Agriculture. Hence, the Brazilian Ministry of Agriculture, Livestock and Supply (MAPA), the Russian Federal Service for Veterinary and Phytosanitary Surveillance (Rosselkhoznadzor) and the Chinese Ministry of Agriculture (MOA) have their main focus on agricultural issues, such as livestock disease prevention and food safety.

If the EMA, which acts as a supranational authority of the EU, was to be described according to the above-mentioned groups, the authority could be characterized as a "single agency" system. Since November 2009, the EMA has been part of the general directorate for health and consumer affairs (abr. DG SANCO) of the European Commission (EC) and for this reason; the EMA could be interpreted as a "European Ministry of Health". Before November 2009, the EMA had been part of the general directorate for enterprise and industry (abr. DG ENTR), but then was transferred to DG SANCO in order to increase the protection of patients and safety of medicines throughout the EU. (Ref. 54) The EMA's management board is made up of representatives from each of the 28 EU Member States, the EC, and the European Parliament, of patients', doctors' and veterinarians' organisations. In addition, Iceland, Liechtenstein and Norway have an observer status. The management board has a supervisory role with e.g. the appointment of the executive director and the monitoring of the EMA's performance. The EMA's duty is the protection and promotion of public and animal health, fulfilled by the evaluation and supervision of medicines for human and veterinary use. (Ref. 18) On national level, the European NCAs are structured in various ways. Each country has its own organisational system (single or separate agencies).

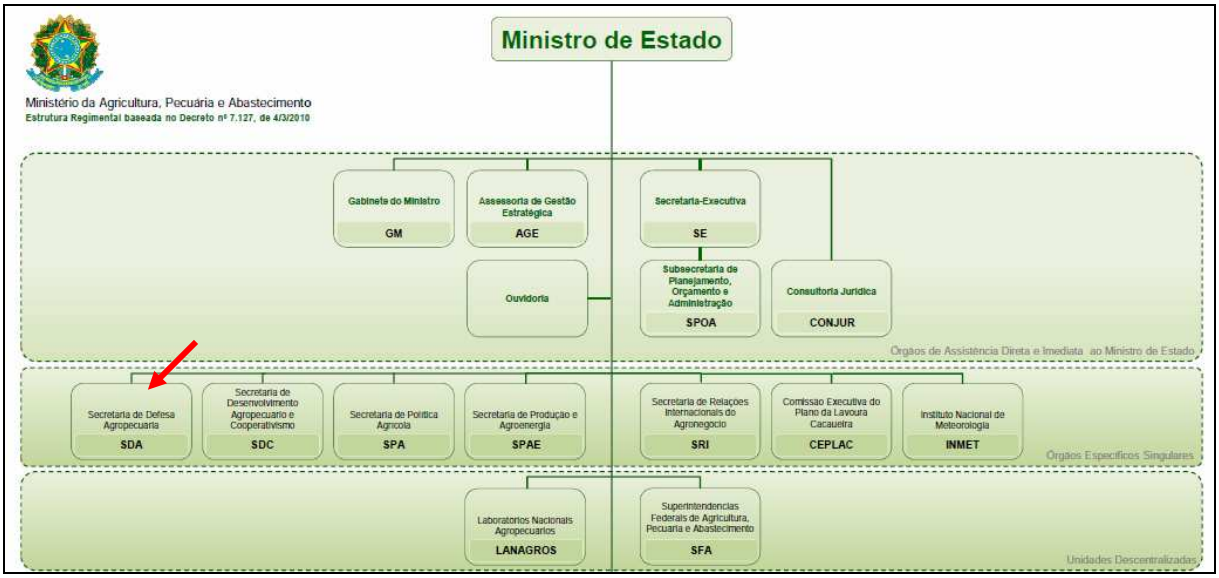
Table 3. Overview about the national competent authorities of the BRIC countries and the supranational agency of the EU

Country/ EU	Competent Authority	Web Page	Language of the Web Page	Address
Brazil	Coordination of Veterinary Products (CPV) / Livestock Inputs Inspection Department (DFIP), Secretariat of Animal and Plant Health Inspection (SDA), Ministry of Agriculture, Livestock and Supply (MAPA)	http://www.agricultura.gov.br/animal/produtos-veterinarios	Portuguese only	Ministério da Agricultura, Pecuária e Abastecimento. Secretaria de Defesa Agropecuária Departamento de Fiscalização de Insumos Pecuários - DFIP Coordenação de Fiscalização de Produtos de Uso Veterinário - CPV Esplanada dos Ministérios - Bloco D, Anexo A, 4º andar, Sala 449 - A CEP – 70.043-900 – Brasília-DF.
Russia	Rosselkhoznadzor / Import. Export. Transit Federal Service for Veterinary and Phytosanitary Surveillance	http://www.fsvps.ru/fsvps/main.html?_language=en	Russian only	107139, Moscow, Orlikov per., 1/11, Russia
India	Central Drugs Standard Control Organization (CDSCO) Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India	http://cdsco.nic.in/index.html	English	Central Drugs Standard Control Organization Directorate General of Health Services Ministry of Health and Family Welfare Government of India FDA Bhavan, ITO, Kotla Road, New Delhi -110002, India
China	China Institute of Veterinary Drug Control (IVDC)/ Center for Veterinary Drug Evaluation (CVDE), Bureau of Veterinary Service, Ministry of Agriculture (MOA)	http://www.ivdc.gov.cn/English/	Chinese and English	Veterinary Desk Address: Administrative Examination and Approval Office Ministry of Agriculture No.11 Nongzhanguan Nanli, Chaoyang District, Beijing, China Postcode: 100125
European Union	Veterinary Medicines Devision, European Medicines Agency (EMA)	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/veterinary_medicines_regulatory.jsp&mid=WC0b01ac058001ff8a	English	European Medicines Agency, 7 Westferry Circus, Canary Wharf, London E14 4HB, United Kingdom

4.1.1 Brazil

In Brazil, the office responsible for evaluation and registration of VMPs is called "Coordination of Veterinary Products" (CPV). The CPV is a subdivision of the Secretariat of Animal and Plant Health Inspection (SDA) of the Ministry of Agriculture, Livestock and Supply (MAPA). The MAPA is a federal department. Despite the evaluation of veterinary medicines, the responsibility of the MAPA is to formulate and implement policies for agribusiness development. The policies include the aspects of market, technological, organizational and environmental care for the consumers.
Furthermore, the Livestock Inputs Inspection Department, another subdivision of the SDA, promotes food security in terms of control of residues and contaminates in animal products. For details please see organisation chart of the MAPA below. (Fig. 5; arrow highlights the division of SDA)

Fig. 5. Organisation chart of the Ministry of Agriculture, Livestock and Supply (MAPA)



Source: Ref. 54

The CPV evaluates and authorises the complete range of products for veterinary use, defined by the Brazilian law 467/1969, article 1, paragraph 1.

In detail, the scope of duties of the CPV includes any *"… chemical, biological, biotechnological medicine or preparation, applied individually or collectively, directly or mixed with food, for the prevention, diagnosis, cure or treatment of animal diseases, including additives, supplies promoters, enhancers of livestock, medicines, vaccines, antiseptics, disinfectants or use environmental equipment, pesticides and all products used in animals or their habitat, protect, restore or modify their bodily functions and physiological as well as products for beautifying the animals."* (Ref. 54)
In addition, the MAPA inspects and registers manufacturing sites of the veterinary industry that are located in Brazil.

4.1.2 Russia

In Russia, two different authorities are involved in the evaluation and registration of VMPs, namely the Federal Service for Veterinary and Phytosanitary Surveillance (Rosselkhoznadzor) and the Federal State Institution "Russian State Centre of Quality and Standardization of Animal Drugs and Feeds" (VGNKI). Latter is a subordinated institute of Rosselkhoznadzor.
Rosselkhoznadzor examines, approves, and registers veterinary medicines and pesticides for utilization in Russia. It regulates product registration procedures and the use of officially registered pesticides.

According to the Russian law N 404, 07. November 2011, Rosselkhoznadzor issues "*…permits to import into, export from and also to transit through the territory of the Russian Federation animals, products of animal origin, medicinal (pharmaceutical) products for veterinary use, feed and feed additives for animals …, sets deadlines and sets sequence of administrative procedures (activities) carried out at the request of the applicant, and sets the interaction between structural units of the Service, its officials, interaction the Service with applicants authorized by the veterinary authorities of subjects of the Russian Federation, Federal Customs Service of the Russian Federation in the field of reference, the veterinary services of foreign states in the provision of public services.*".

In addition, Rosselkhoznadzor is responsible for protecting the population from animal infectious diseases and is under the control of the Ministry of Agriculture of the Russian Federation.

However, Rosselkhoznadzor only provides limited information for people who are not familiar with the Russian language.
There is a registry (as of May 2011) for registered VMPs that are accessible for interested parties under http://www.fsvps.ru/fsvps/laws/1278.html. Unfortunately, the document is only available in Russian language.
The catalogue contains the brand name, name of registrant, date of registration, and expiration date for each product. Chemical agents that are not listed in this catalogue are illegal to use in Russia, and their residues are not allowed in or on imported foodstuffs.

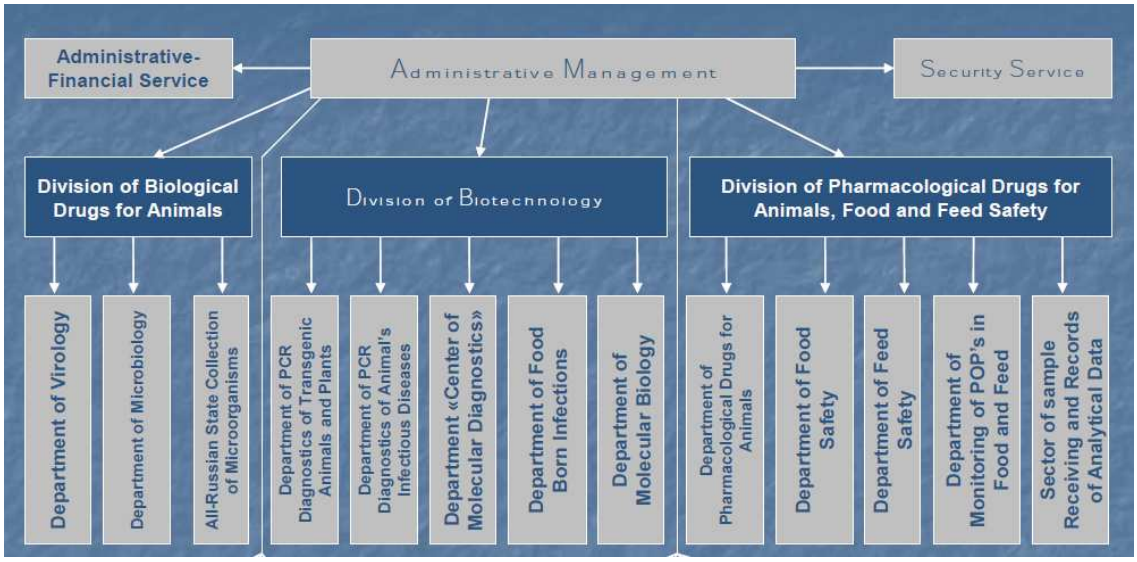
Despite the administrative scope of Rosselkhoznadzor, the duties of the VGNKI include quality and risk assessment of VMPs. Specialists of the VGNKI, who evaluate documentation of applications for a MA, are located in three different divisions of the authority; namely

- the division for biological drugs for animals,
- the division of biotechnology, and
- the division of pharmacological drugs for animals, food and feed.

For details, please see organisation chart of the VGNKI below (Fig. 6).

According to a self-presentation of the VGNKI on its homepage (Ref. 55), the VGNKI is Europe's largest centre for certification of veterinary medicines, feed and feed additives. Furthermore, VGNKI is an official centre of the OiE, an intergovernmental organisation responsible for improving animal health worldwide. Its responsibilities include food safety and diagnosis and control of animal diseases in Eastern Europe, Central Asia and the Caucasus. The Institute is accredited by the State Standard of the Russian Federation as a certification body of veterinary medicines and feed and testing centre on those types of products.

Fig. 6. Structure of the Russian State Centre of Quality and Standardization of Animal Drugs and Feeds (VGNKI)

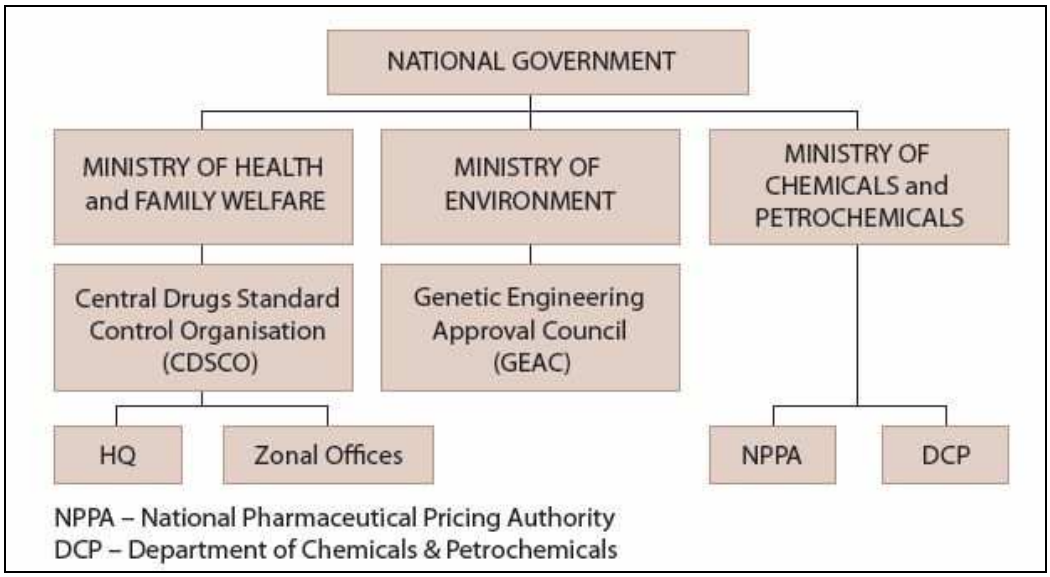


Source: Ref. 55

4.1.3 India

In India, the NCA responsible for human and veterinary medicines is the Central Drug Standards Control Organization (CDSCO), a subdivision of the Drug Controller General India (DCGI). According to a report of TOPRA about the Indian pharmaceutical environment in 2010, the "*.. medical regulatory structure is divided between national and state authorities. There are also 35 state-level Food and Drug Administrations, one for each of India's states and territories. The DCGI registers all imported drugs, new drugs, biologicals and drugs in selected categories. It also has responsibility for medical devices, clinical trials and quality standards. The state FDAs register all other products, accredit manufacturing plants, and conduct the bulk of quality monitoring and inspections.*" (Ref. 36)

Fig. 7. Organisation of India's pharmaceutical regulatory system



Source: Ref. 36

The CDSCO does not have a separate Veterinary Division or Veterinary Medicine Control Authority. In addition, the Indian Drug and Cosmetic Act, 1940 and Rules, 1945 is valid for both human and veterinary medicines. In the case of an evaluation of pharmaceutical VMPs, veterinarians or special trained personal review the applications.

The D&C Act and Rules distinguishes between the evaluation of pharmaceutical and biological VMPs. According to part II "The central drugs laboratory" of the D&C Act and Rules the evaluation of veterinary biologicals (anti-sera, vaccines, toxoids and diagnostic antigens) should be carried out at a separate laboratory, namely the Indian Veterinary Research Institute. (Ref. 56)
Moreover, *"…for the purpose of examination of Anti-sera, Toxoid and Vaccines and Diagnostic Antigens for Veterinary use, the person appointed shall be a person who is a graduate in Veterinary Science, or general science, or medicine or pharmacy and has had not less than five years' experience in the standardization of biological products or person holding a post-graduate degree in Veterinary Science, or general science, or medicine or pharmacy or pharmaceutical chemistry with an experience of not less than three years in the standardization of biological products."* according to part V 1, 244. "Qualifications of Government Analyst", of D&C Act and Rules.

4.1.4 China

In China, the organisation for evaluation and approval of applications for VMPs is comparable to its neighbour country Russia. Also, two different agencies are involved in the evaluation and registration of VMPs, namely the Institute of Veterinary Drug Control (IVDC) and the Veterinary Bureau of the Chinese Ministry of Agriculture (MOA).

In particular, the IVDC is responsible for the assessment of veterinary medicines, quality supervision and inspection of veterinary medicines and appliances. That national institute and one of its subdivisions, namely the Veterinary Drug Evaluation Center (CVDE), share following duties: monitoring of veterinary medicines residues, collection of veterinary cultures, drafting and revising national standards of veterinary medicines, as well as preparation and calibration of the national standards and reference materials of veterinary medicines. (Ref. 41) The IVDC is a national veterinary technical support institution, which is directly affiliated to the MOA.

The Veterinary Bureau of the MOA comprises of six divisions: the Division of Veterinary Drug and Appliances, the Division of Animal Disease Prevention, the Division of Animal Disease Inspection and Supervision, the Division of Veterinarian Administration, the Division of Science, Technology and International Cooperation, and the Division of General Affairs. (Ref. 41)
The Veterinary Bureau differentiates between veterinary medicines and veterinary biologics. Medicines include pharmaceuticals, antibiotics, herb medicines (traditional Chinese medicine) and disinfectants. Biologics include vaccines, toxoids, antisera and diagnostic kits. Furthermore, the Veterinary Bureau is responsible for veterinary medicinal devices. (Ref. 41)

4.1.5 European Union

The European Medicines Agency (EMA), located in London, UK, is a centralised scientific agency. The EMA is responsible for the scientific evaluation of applications for marketing authorisations (MAs) for human and veterinary medicines; processed in a centralised procedure. Moreover the EMA sets maximum residue limits (MRLs) for residues of VMPs legally accepted in foodstuffs. (Ref. 18) Such kind of procedure allows the applicant to simultaneously market their product in all of the currently 28 EU member states plus Norway, Iceland and Liechtenstein.
The agency was set up in 1995 in an attempt to harmonise (but not replace) the work of existing national medicine regulatory bodies. The establishment of such an agency was possible with funding from the EU and the pharmaceutical industry, as well as with indirect subsidy from member states.

The EMA has seven scientific committees that carry out the scientific evaluation of applications from pharmaceutical companies. The core scientific advisory committees of the EMA are the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Medicinal Products for Veterinary Use (CVMP). All committees are mostly comprised of members nominated by the EU member states. The assessment of veterinary medicinal products occurs in accordance with the EU legislation, particularly with Directive 2001/82/EC and Regulation (EC) No 726/2004. (Ref. 18)

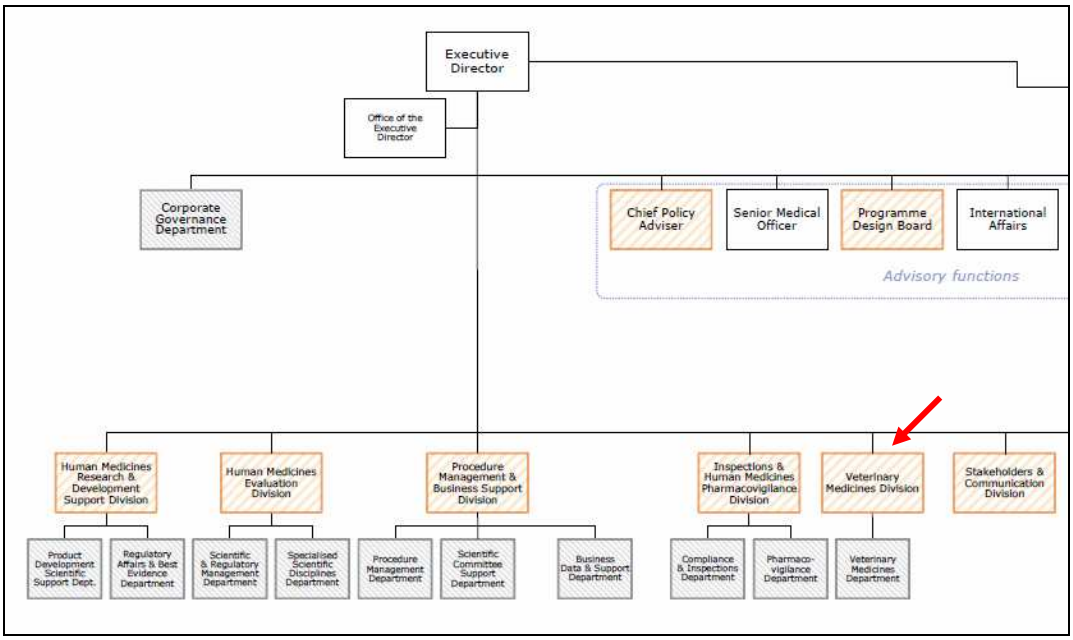
In the EU, a directive is a supranational legislative act and addressed directly to each EU-member state. The content of a directive must be implemented in the national law of each EU member state within a defined period of time. In addition, a regulation is a supranational law, is directly binding, "breaks" national law and is addressed to each person of the EU.

On the one hand the EMA, a fairly new agency, wants to reduce the huge amount of costs that pharmaceutical companies face when they have to obtain separate approvals from each member state. On the other hand, the EMA pursues the goal to eliminate the protectionist tendencies of states unwilling to approve new medicines that might compete with those already produced by domestic pharmaceutical companies.

The EMA is divided into separate departments and divisions, whereof one is responsible for all activities related to veterinary medicines and is demonstrated by the graphic below (Fig. 8).

The scope of the Veterinary Medicines Division is *"…the provision of advice during the development of products, the authorisation process itself and post authorisation activities such as variations to authorisations and pharmacovigilance, as well as all aspects of public health related to the use of veterinary medicines, particularly the establishment of maximum residue levels (MRLs) for the presence of residues of veterinary medicines in foodstuffs of animal origin."* (Ref. 18)
Moreover, *"the Division acts as the source of advice from the Agency on veterinary topics to European Union institutions, the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) and international organisations such as the World Organisation for Animal Health (OIE) and Codex Alimentarius."* (Ref. 18)

Fig. 8. EMA, agency structure 2013. Veterinary Medicines Division: see arrow



Source: Ref. 18

4.2 Laws and regulations

In this chapter, key legislation for new, generic and, if applicable, similar veterinary medicines of the BRIC countries and requirements for import of VMPs into those nations are presented in comparison to EU law. Furthermore, main aspects of changes of regulatory legislation that were amended and/or introduced recently or which will be in force in the near are discussed. Web pages publishing recent changes in law are shown to facilitate the efforts of a foreign RA manager to follow the current regulatory legislation in each of the presented countries.

In general, national legislation concerning human and veterinary medicine can usually be distinguished from laws specifically addressed to VMPs (see table 4). In cases where it is not clear if there is a specific veterinary legislation, the author presents the relevant human laws.

Table 4. Key legislation for veterinary medicines in the BRIC countries and the EU

Country/ EU	Laws	Scope	Effective date	Contents
Brazil	Decreto N° 467	veterinary medicine	13. February 1969	Indicates the surveillance of products for veterinary use and manufacturing establishments
	Decreto N° 5.053	veterinary medicine	22. April 2004	Regulation of products for veterinary use and manufacturing establishments or distributors
Russia	Law N 61 “On circulation of medicinal products”	human and veterinary medicine	31. March 2010	The scope of the law covers research and development, clinical trials, assessment of efficacy, quality and benefit–risk ratios, marketing authorisation, manufacturing, distribution, retail, and import and export of pharmaceutical and biological products.
India	Drug and Cosmetic Act, 1940 & Drug and Cosmetic Rules, 1945	human and veterinary medicine	1940 / 1945	Regulatory aspects related to the manufacture, sale, import, export and clinical research of medicines and cosmetics.
China	State Council regulation "Regulations on Administration of Animal Drugs"	veterinary medicine	11. January 2004	Specific provisions on animal drug producers, control over medicines in veterinary medical institutions, new animal drug approval, management of drug import and export, and supervision, trademark and advertisement of animal medicines.
European Union	Directive 2001/82/EC	veterinary medicine	06. November 2001	Controls on the manufacture, authorisation, marketing, distribution and post-authorisation surveillance of veterinary medicines applicable in all EU member states.
	Regulation (EC) No 726/2004	human and veterinary medicine	31.03.2004	Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

4.2.1 Brazil

In general, the Brazilian veterinary legislation is separated from the law for human pharmaceutical products. It is only available in the national language, Portuguese. Two decrees constitute the key law for veterinary regulatory issues:

Decreto No. 467 (effective since: 22.04.1969)
characterises the surveillance of VMPs and manufacturing establishments, and
Decreto No. 5.053 (effective since: 22.04.2004).
specific regulation for VMPs, distributors and manufacturing establishments.

a) New VMPs

Legal basis: Decreto No. 5.053, chapter VI (registration of VMPs) and chapter IX (exemptions from registration).
As a general rule, a product not yet approved for marketing in Brazil is considered as a new product. Exceptions are (among others):

- Products with synthetic or semi-synthetic active ingredients, isolated or in association;
- A product that results from:
  - A modification of the pharmacokinetic properties;
  - Withdrawal of an active ingredient of a product already registered;
  - New salts, isomers: although the corresponding molecular entity has been already approved for registration.

Prior to the actual registration process, there is a phase of pre-registration. This step allows the MAPA to validate if the manufacturer and the importer are capable of manufacturing and controlling the quality of the medicinal product for which the marketing authorization is applied. (Ref. 57)

b) Generic and similar VMPs

Over the last years, Brazilian law has experienced significant changes in regard to generic products. Since the introduction of law No. 12689/2012 in October 2012 (Lei Ordinária 12689/2012), which updated Decreto No. 467, there has not been any regulation for generic products for veterinary use in Brazil. Solely the so-called similar or "me-too" products, which do not need a proof of bioequivalence (BE), have been previously described by Decreto No. 467, article 36. Since October 2012, companies have the option to register similar and generic products.
Both types of medicines could be differentiated by the requirements for registration. (Ref. 58)

I. Similar or "me-too" medicines

Similar medicines were introduced before 1996, when Brazil did not recognize patents on pharmaceutical products. However, they must be phased out by 2014. (Ref. 3) Similar medicines contain identical formulations to branded medicines, but do not have proven BE, as in the case of generics.
Further requirements for registration are:

- owner's trade name or the trademark,
- identical API as the reference product,
- identical pharmaceutical concentration and form,
- excipients can either be identical or non-identical,
- follows the specifications of the pharmacopoeia are followed and relevant quality standards are met.

II. Generic VMPs

In Brazil, generic medicines for veterinary use were introduced most recently, in October 2012, after law No. 12689/2012 had came into force. For registration, this group of VMPs must demonstrate BE to the reference product.

Further requirements for registration are:

- product design by the Brazilian Common Denomination (DCB), or in case of its absence, by the International Nonproprietary Name (INN),
- identical API as the reference product,
- identical pharmaceutical concentration and form,
- identical administration, dosage and therapeutical indication. (Ref. 58)

As a rule, similar and generic VMPs can only be produced after the expiration of the patent of the reference product. This is to prevent interference with the rights of the patent owner, either concerning the product or a process.

In addition, companies applying for the registration of a generic product would have to submit their own safety and efficacy studies, as long as the data exclusivity of the reference product (for the use of clinical trails and related dossiers) lasts. The maximum term of protection of undisclosed information is 10 years. This refers to law no. 10,603 of 17 December 2002, which protects data exclusivity for veterinary and agrochemical products. (Ref. 59)

c) Import requirements

Legal basis: Decreto No. 5.053, chapter IX (exemptions from registration) article 30:

Within three years, imported VMPs shall also be fully developed and produced in Brazil itself. Exceptions are possible in case it is duly proven that the entity class veterinary medicine can not manufactured on national territory.

Applications for MA include that the foreign company has:

- a business partnership with a local service provider or manufacturer; or
- a business agreement with a trade representative company; or
- an establishment of a local sales office, to develop an own distribution chain. (Ref. 3)

Legislation:

- INSTRUÇÃO NORMATIVA SDA N° 6, 28.03.2012
  - Defines the criteria in order to grant the renewal of licences for imported veterinary products
- INSTRUÇÃO NORMATIVA SDA Nº 29, 14.09. 2010, section II, article 18-23
  - Establishes procedures for the import of products intended for animal feed and veterinary use in order to ensure the safety and traceability of their marketing in Brazil

Among other requirements for import operations, a company has to be registered with the Brazilian foreign trade system SISCOMEX. SISCOMEX (Sistema Integrado de Comércio Exterior) is an instrument that integrates the activities of licensing, follow up and control of foreign trade operations using a computerized flow of information. (INSTRUÇÃO NORMATIVA SDA Nº 29; 14.09.2010, section II, article 18-23) In addition, the importer needs an import licence and a shipping authorisation.

d) Recent changes in legislation

In addition to the above mentioned changes in law for generic and similar VMPs, the regulatory requirements for prescription only medicines will be tightened at the beginning of January 2014, according to law no. 25 from 25. November 2012. (Instrução Normativa nº 25, 08.11.2012) In its annex 1, the law specifies a group of substances "of special control". The following substances belong to that group: narcotics, psycotrophic substances and their raw material, retinoide, anti-retrovirals and hormones such as steroids and beta-adrenoceptor agonists. (Instrução Normativa nº 25, 08.11.2012)

e) Publication of current law

Typically, the MAPA publishes the relevant legislation for veterinary medicinal products in Portuguese for download on its homepage http://www.agricultura.gov.br/animal/produtos-veterinarios. (Ref. 54) If a new regulation shall come into force, the MAPA initially publishes the proposed regulation for public consultation on its web page. Any interested party can submit comments and suggestions within a certain time. After the end of that public consultation, the new regulation will be published. With this, the regulation comes into force. (Ref. 60)

4.2.2 Russia

In Russia, the key legislation for veterinary medicines comprises the federal law N 61-FZ of 12-Apr-2010 on the Circulation of Medicines. The law is valid for both human and veterinary medicines. The law represents *"... the basic legislative document for the Russian pharmaceutical market. This Law provides main principles of the state regulations on pharmaceutical products research and development, clinical trials, manufacturing, marketing authorization, wholesale and retail sales, drug preparation (by pharmacies), state control of medicines efficacy, effectiveness and quality, as well as medicines import/export."* according to a regulatory summary about Russia published by IDRAC, a global regulatory database from ThomsonReuters. (Ref. 61)

In general, a company can register in four different categories of VMPs (Fed. law no. 61, Art. 13):
1) original medicinal products;
2) reproduced medicinal products (generic products);
3) new combinations of medicinal products;
4) previously registered medicinal products but manufactured in other dosage forms.

a) New VMPs

The content of application is formally identical for all medicines, according to the Federal Law N 61-FZ. In addition, subordinate acts regulate the registration process.
Namely, these acts are:

- Ministerial Order N 1413n of 23-Nov-2011: on Approval of the Guideline on the Format and Content of the Registration Dossier of a Medicinal Product
- Ministerial Order N 759n of 26-Aug-2010: on Procedure of the Submission of Medicinal Product Dossier Documentation for the Registration Purpose
- Ministerial Order N 760n of 26-Aug-2010: on the Adoption of an Application Form for a Variation to a Registration Dossier of a Registered Medicinal Product
- Federal Law N 271-FZ of 11-Oct-2010: Amending Federal Law N 61-FZ of 12-Apr-2010
- Federal Law N 3-FZ of 8-Jan-1998: on Narcotics and Psychotropic Substances, as amended
-

All documents and data should be submitted in Russian language or have a certified translation into Russian. The format and structure of dossier for registration process doesn't follow the VICH format, since the country has its own requirements.

In addition, clinical studies performed in Russia are needed. The federal law N 61-FZ introduced new requirements for local clinical data in support of all new applications, including generics, new indications and line extensions (human and veterinary). There were no agreements on recognition of clinical data signed between Russian and other national authorities. The sole exception is, if a BE study is not feasible and the products have been established for medical use in Russia for more than 20 years. (Ref. 6)

b) Generic VMPs

In the Federal Law N 61-FZ, "reproduced medicinal products" (generic products) are not subject to an abridged registration procedure. As mentioned above, the application content is the same for all medicines, including generics. However, the documentation on pre-clinical, toxicological and clinical tests of generics differs from that of original medicines. (Ref. 7)

However, generics are reviewed according to an accelerated procedure. In detail, expedited expert assessment does follow a procedure according to the Federal Law N 61-FZ , art. 26. Hence clinical studies and findings of a bioequivalence study for a VMP are examined within sixty workdays. (Ref. 7) Bioequivalence studies should be performed in compliance with the regulations approved by an authorised federal executive power body (Federal Law N 61-FZ, art. 12). As a rule, data obtained from clinical trials of medicinal products which have been already published, as well as documents containing results on bioequivalence studies or therapeutic equivalence should be submitted. An accelerated procedure is not applicable for biological products and products registered in Russia for the first time.

c) Import requirements

Legislation:

- Federal Law N 61-FZ of 12-Apr-2010 on the Circulation of Medicines, as amended
  - basic principals concerning the import of medicines
- Decree of the Government of the Decree N 771 of 29-Sep-2010 on the Procedure of Import of medicines for medical use into the Russian Federation
  - requirements for the content of import applications to various authorities.

For the registration of imported of VMPs into the Russian Federation, the NCA Rosselkhoznadzor requires a Certificate of Pharmaceutical Product (CPP). A CPP is also required, for changes in chemistry, manufacturing and in the control part of the documentation (CMC) of the product (i.e. change of manufacturing site, of pharmaceutical formulation / composition). In case a CPP is not available, a GMP certificate, a free sales certificate (FSC) and a manufacturing license can be submitted. (Ref. 62)

d) Recent changes in legislation

A TOPRA review about Russian regulatory legislation in 2011 (Ref. 6), states that the regulatory environment has changed dramatically since Russia's new federal law "on circulation of medicinal products" came into force in April 2010. In general, the introduction of this law "*…brought a wide range of changes affecting data requirements and procedures for clinical trial applications and marketing authorisations as well as lifecycle management."*(Ref. 6) Furthermore, the review stresses that, before law No. 61 came into force, *"…Russia was one of the few emerging markets where registration requirements allowed market entry in parallel or shortly after the EU and US."* (Ref. 6)

Some of the main changes of the Federal Law N 61-FZ are listed below:

- mandatory local registration of a clinical study for newly registered (including generics) or modified medicines,
- new timelines and fees for clinical trial applications and MAs,
- product labelling requirements,
- manufacturing licensing, and
- importation licences.

The law affected the majority of existing procedural guidelines and required development and adoption of new guidelines. The procedural changes were introduced by a number of decrees issued shortly after Federal Law N 61-FZ had come into force.

Furthermore, substantial changes of the Federal Law N 61-FZ are expected at the beginning of 2014, according to a draft law of the Russian Federation. (Ref. 7)
In detail, the new law introduces for the first time definitions of biological medicinal product, comparator, biosimilar, interchangeable medicinal product, and clarifies some existing

definitions (e.g. reproduced medicine (or generic), bioequivalence study, etc.). It also introduces new provisions with regard to the registration of generics as well as differentiations between categories of medicines (originator, generic, biological product, biosimilars, combination product, etc.). At the moment, the draft law is under expert consultations within the national government. (Ref. 7)

e) Publication of current law

For a foreign RA manger how is unfamiliar with the Russian language, it is not easy to find information about the current Russian legislation. The homepage of the ministry of agriculture (www.mcx.ru) as well as the homepage of the NCA Roszdravnadzor (www.fsvps.ru/fsvp) provides only limited access to the current legislation. However, the internet platform IDRAC from ThomsonReuters (Ref. 19) publishes regulatory summaries about the Russian regulatory legislation in short time intervals. Moreover, English translations of the relevant laws are available on this platform, too.

4.2.3 India

In India, there is no separate law for veterinary medicines, as both, human and veterinary medicines are regulated by the Drug and Cosmetic Act, 1940 and the Drug and Cosmetic Rules, 1945 (D&C Act and Rules).

In general, the D&C Act and Rules has listed the medicines in schedules. Schedules H and X list prescription-only medicines. All medicinal products that are not included in the list of 'prescription-only medicines' are considered as non-prescription medicines (OTC, or over the counter). However, there is no legal recognition of the expression 'OTC medicines'. (Ref. 36)
Aside from the general classification into 'prescription-only medicines' and 'OTC medicines', a separate schedule for the production of vaccines for veterinary use (of bacterial and viral origin) can be found. Schedule F(1), part I(A) provides the requirements for bacterial vaccines and Part I(B) concerns for viral vaccines.
Since India is a former colony of the British Empire, the Indian regulatory legislation is orientated towards the British law and is subjected to specific requirements. For instance, the current edition of the British Veterinary Pharmacopoeia is applicable to all veterinary medicines, which are not specified in Schedule F(1). (D&C Act and Rules)

a) New VMPs

Any medicine, including generics, which has been marketed for less than four years in India, would be considered as a "new medicine" and has to follow the same procedure as a new medicine submission and approval.

b) Generic VMPs

Generic products refer to medicines that have been granted marketing authorization by Drug Controller General of India (DCGI) under the Drugs and Cosmetics Act, 1940 and have been sold in the Indian market for years (at least more than four years) with no national patent protection. Those medicines are bioequivalent to branded medicines in their pharmacokinetic and pharmacodynamic properties. (Ref. 37)
Generics can be registered if the clinical efficacy and safety is equal to those of reference medicinal products. Bioavailability and bioequivalence studies are mandatory by regulations to ensure therapeutic equivalence between a pharmaceutically equivalent test product and the reference product. Several in vivo and in vitro methods are used to measure product quality.
For bioavailability and bioequivalence studies CDSCO has laid down specific guidelines (Ref. 63), which should be complied in conjunction with schedule Y of the Drugs and Cosmetics Act, 1940 and Good Clinical Pratice (GCP) guidelines issued by CDSCO.
In India, DCGI's permission is not required for products whose generic versions are already available for more than four years. (Ref. 37)

c) Import requirements

An import licence and a registration certificate from the pharmaceutical manufacturer located outside the country, are required by the Ministry of Health and Family Welfare in India. The foreign manufacturer has to apply to the DCGI to obtain a registration certificate. The manufacturer must have a legal Indian presence or an authorised signatory residing in India to complete the procedure. (D&C Act and Rules)
Import licences are required for all types of medicines and are valid for three years. (Ref. 36)
The applicant for an import licence can be a pharmaceutical manufacturer in India, a manufacturer's authorised agent in India (as specified in the registration certificate), or an importer selling medicines in India. (D&C Act and Rules)

Applications should be made using form 40 of the D&C Act and Rules. Information and undertakings are specified in schedule D(I) and schedule D(II). (Ref. 36)

Legal basis:

- D&C Act and Rules
  - Chapter III-Sections 8 to 15
  - Part IV-Rules 21 to 43B
  - Part X-A – Rules 122–A to 122-E
  - Application and Licence Forms-Forms 8, 8A, 9,10, 10A, 11, 11A, 12 , 12A, 12B, 40 and 41, Form 44;
- Schedules D, D (I) and D (II).
- Customs Act, 1962,
- Foreign Trade Act, 1992,
- Indian Customs Tariff Act, 1975. (Ref. 10)

d) Recent changes in legislation

At the moment, guidelines for bioavailability and bioequivalence are under revision by CDSCO. Latter NCA intends to release contemporary requirements which would be in line with the current scientific knowledge on the subject. (Ref. 37).

Moreover, Indian veterinarians and the pharmaceutical industry urgently need an update of the current legislation for VMPs. In detail, India has currently no complete guideline for veterinary medicines and chemicals such as medicine, immune-biological and feed additives. For instance, the D&C Act and Rules does not include specifications for feed supplements at the moment; and there are currently no standardised pharmacovigilance, traceability and recall mechanism for veterinary medicines and chemicals. For those reasons, Indian veterinarians postulated a list of required changes in the Indian regulatory environment at a conference on "Veterinary Regulatory Reform: Current Status and the road ahead" in October 2012. (Ref. 11):

a) The construction of complete guidelines for veterinary medicines and chemicals such as medicines, immune-biologicals and feed additives.

b) A standardisation of the pharmacovigilance system, traceability and recall mechanism for veterinary medicines and chemicals along with livestock products.

c) Harmonization of standards (maximum residue limits, acceptable daily intake, risk management plans) considering a more and more globalising economy.

Furthermore, the participants of the above mentioned conference point out that India needs a much more effective institution for veterinary medicine regulation at central and state level.
At central level:

- *"Participation of veterinarians in drug consultative committee will be mandatory for the veterinary drugs and formulations with core professionals.*
- *New drug approval committees must include veterinarians for the veterinary drugs and formulations.*
- *A veterinary pharmacopoeia is immediately required covering all veterinary medicine, immune-biological and chemicals used as feed additives, supplements and disinfectants etc."* (Ref. 11)

At state level:

- *"Veterinarians should be appointed as Veterinary Drug Officers/Inspectors for veterinary related drugs and chemicals."* (Ref. 11)

In addition, a major change in import regulations occurred in India, in 2003. According to Notification GSR no. 604 (E) dated 24.08.2001 (D&C Act and Rules), implemented in 2003, an import licence will be required for all types of medicines. Prior to distributing a VMP by a foreign company in India, import licence and certification registrations are required by the Ministry of Health and Family Welfare. The new law requires that foreign manufacturing sites must be registered.
The amendments of Notification GSR no. 604 (E) in 2003 had been overdue for the longest, because of the following reasons:

- Before Notification GSR no. 604 (E) came into force, an imported medicine should be of "standard quality", but there were rare provisions to ascertain this aspect. As a consequence, various medicines were available to Indian distributors at a discount when a substantial percentage of the life period of these medicines was expired.
- There had been any data about the status of the pharmaceutical manufacturer whose medicines were being imported into India. As a result, the manufacturer's compliance with GMP, nature and competency of the manufacturing and testing facilities, and other related information had not been available.
- Many medicines of dubious quality with unauthenticated claims had been imported to India, prior to the year 2003. (Ref. 10)

e) Publication of current law

A presentation of the current Indian law can be found at the homepage of the Central Drugs Standard Control Organization (http://cdsco.nic.in/index.html) and on the web page of the Indian health services (http://indianhealthservices.in/dnc_act.php).

4.2.4 China

According to a self-presentation of the MOA in 2013, *"China now has a relatively well-established legislation of animal drug laws, regulations, technical standards and norms, relatively full-fledged drug control system and a rather complete production chain where GMP management is fully adopted."* (Ref. 41)

Today, the Chinese NCAs are looking at established and proven regulatory systems (eg, Europe and the US), according to TOPRA's assessment of the Chinese pharmaceutical environment in 2010. (Ref. 9)
However, the above mentioned report from TOPRA points out that it is undoubtedly necessary for China to adapt the existing regulatory legislation to its very specific national situation in the coming years.

a) New VMPs
The Chinese MOA distinguishes between:

a) pharmaceuticals and herbal medicines, and
b) biologicals.

Legal basis for point a):

1. Regulations on Administration of Veterinary Drugs (Order No. 404 of the State Council)
2. Measures for Registration of Veterinary Drugs (Order No. 44 of the Ministry of Agriculture of the People's Republic of China)
3. Announcement No. 442 of the Ministry of Agriculture of the People's Republic of China

Legal basis for point b):

1. Regulations on Administration of Veterinary Drugs (Order No. 404 of the State Council)

b) Generic VMPs
Today, China has only a few regulations for human generic products, but the term "generic product" is commonly used inside the country, according to the regulatory legislation platform IDRAC (which gives only information for human medicines). In detail, the China's Food and Drug Administration has published guidelines for bioavailability and bioequivalence study of the medicinal products for human bodies in 2005. In addition, chapter 5 of the order no. 28: regulations on medicine registration administration, from 2007, governs the application of generics in China. (Ref. 64)

Regarding VMP legislation, the author has not found any regulation for generic and/or similar products in China. Thus, special regulations for generic VMPs in China may not exist at the moment.

For human medicines, the term generic product refers to a medicine that has been granted MA and been sold in the Chinese market for years without having patent protection in China. (Ref. 64) Moreover, the term "essentially similar product" is defined for human medicines. If two pharmaceuticals have the same amount of APIs that qualify for the same quality criteria, have the same pharmaceutical form, and have proven bioequivalence, they can be regarded as "essentially similar products". (Ref. 64)

In general, the following requirements for registration of a generic human medicine should be meet:

- No violation of the patent rights of the reference medicinal product (RMP)
- Specifications should be comparable to or beyond those of the RMP
- Clinical efficacy and safety data should be comparable to those of RMP and should comply with Chinese specific guidelines. (Ref. 64)

The author assumes that, as long as there are no specific regulations for generic VMPs, the provisions for human medicines maybe applicable for a generic application in the country.

c) Import requirements

For import, the Chinese MOA distinguishes between:

a) pharmaceuticals and herbal medicines, and
b) biologicals.

Legal basis for point a):

1. Regulations on Administration of Veterinary Drugs (Order No. 404 of the State Council)
2. Measures for Registration of Veterinary Drugs (Order No. 44 of the Ministry of Agriculture of the People's Republic of China)
3. Announcement No. 442 of the Ministry of Agriculture of the People's Republic of China

Legal basis for point b):

1. Regulations on Administration of Veterinary Drugs (Order No. 404 of the State Council)
2. Administrative Measures for Imported Animal drugs (Order No. 2 of the Ministry of Agriculture of the People's Republic of China)

In general, the applicant for an import licence must have Chinese nationality or, if the applicant is foreign, a Chinese legal representative must be authorised. (Ref. 40)
In addition, clinical trials and verification tests must be conducted in designated agencies (by MOA) within the territory of China. (Ref. 65)
At the end of the registration process, a "Certificate for Imported Veterinary Drugs" is issued for each new medicine. Revised specifications, instructions and labels for those medicines are included and enter into force on the day of their issuance.

In addition to the above mentioned procedures for VMPs import, the MOA distinguishes between two different types of imported feed and feed additives. For both types of imported products do exist different requirements and authorisation procedures.

Type one:
The products were previously approved by MOA, and therefore the requirements for import include only quality aspects.
Type two:
The products are not listed as previously approved, and therefore, feeding studies and safety data in addition to quality tests are mandatory. (Ref. 65)

d) Recent changes in legislation

Over the past few decades, China has seen large changes in regard to its human healthcare system, its regulated healthcare industry and its governing institutions. For instance, since fake medicine scandals had become a major political issue in the western part of the world, China introduced Good Clinical Practice and Good Laboratory Practice based on international guidelines. Furthermore, the goal is to increase the GMP inspection standards by imposing more stringent technical requirements, quality control and validation procedures. (Ref. 9) Also, the veterinary legislation has been updated during the last years and the regulations are still under development. (Ref. 9)

Concerning VMP control, the MOA has increased the quality control of vaccines against major animal diseases, and the review and approval of VMPs and GMP in 2011. Since then, the MOA examines medicine quality through random inspection and rectified the Chinese medicine market. In this regard, the MOA plans to implement a so-called "Good Sales Practice for Animal drugs". In addition, the Chinese Veterinary Pharmacopoeia 2010 had officially taken effect in July 2011. (Ref. 41）

The quality standards for VMPs were also tightened. In 2010, three laws were issued in this regard:

- Inspection and Acceptance Measures for Quality Management Standards in Production of Animal Drugs (issued: 09.01.2010),
- Norms for the Business Operation and Quality Management of Animal Drugs (issued: 03.01.2010)
- Administrative Measures for Labels and Instructions of Animal Drugs (issued: 03.01.2010)

e) Publication of current law

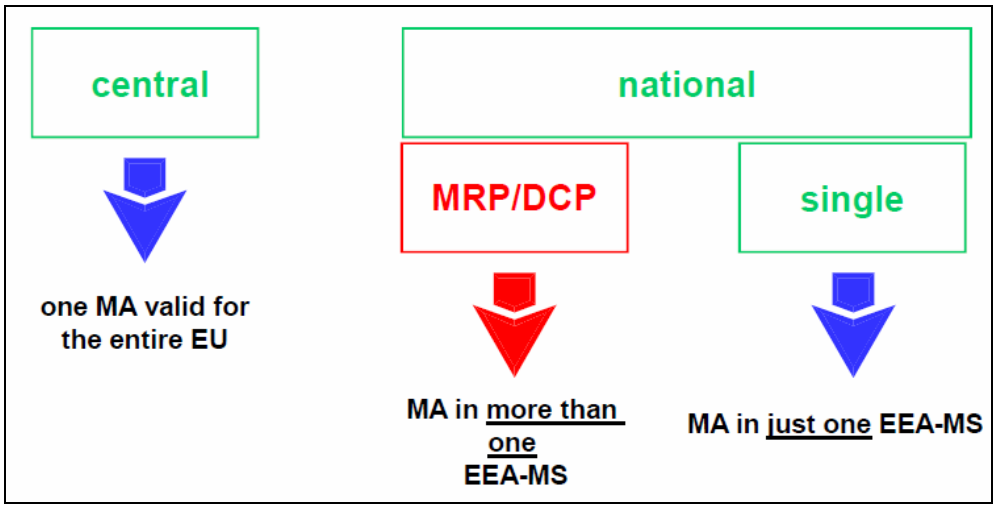
In general, the IVDC publishes novel registrations and renewals for veterinary medicines on its web page:
http://www.ivdc.gov.cn/English/RegulatoryInformation/Legislation/201009/t20100903_34368.htm (Ref. 66)

4.2.5 European Union

Since the 1960s, a large body of legislation has developed, including progressive harmonisation of requirements for the granting of MAs, and has been implemented across the European Economic Area (EEA).
In principle, Directive 2001/82/EC, lastly amended by Directive 2004/28/EC, and Regulation (EC) No 726/2004 laid down the requirements and procedures for obtaining a MA, as well as the rules for the constant supervision of products after their authorisation. Moreover, these laws lay down harmonised provisions in related areas such as the manufacturing, wholesaling or advertising.
As a rule, a directive is a legislative instrument that is binding for the EU countries to which it is addressed. It defines the results to be attained, but leaves it to the country to determine the form and methods. A directive is valid as soon as it was transformed into national law. In the case of regulations of VMPs, the deadline for the implementation of Directive 2004/28/EC into national law was the October 30, 2005.
Moreover, a regulation is an instrument of general scope that is binding in its entirety and directly applicable in all EU countries. They are directly applicable, so that they do not need transposal into the EU countries' domestic law and directly confer rights or impose obligations. Hence, a regulation breaks national law, because it is directly binding.

Since the mid-90s, there have been two Community authorisation procedures in place by which a MA in the EU can be obtained; the Mutual Recognition Procedure (MRP) and the Centralised Procedure (CP). Both procedures are supported by the EMA that is in charge of providing the NCAs with scientific advice on VMPs.
In detail, the CP is optional for most novel veterinary medicinal products, but is subject to agreement by the Committee for Medicinal Products for Veterinary Use (CVMP). The CP consists of a single application which, when approved, grants MAs for all markets within the EU.
The MRP is to be used if the aim is to register in more than one Member State, and if the VMP in question has already received a MA in any of the MS at the time of application. The MRP is based on the idea that a national authorisation approved in one EU Member State, which then becomes the Reference Member State (RMS), should be mutually recognized in other EU countries. These other MSs that are also involved in the procedure are called Concerned Member States (CMS). The complete procedure is based on the assumption that the evaluation criteria in the EU member states are sufficiently harmonized and are of the same standard.
Since the implementation of Directive 2004/28/EC into national law in October 2005, a new Community authorisation procedure came into force: the Decentralised Procedure (DCP). This procedure is applicable in cases where an authorisation does not yet exist in any of the MS. Identical dossiers are submitted in all MSs where a MA is sought. A RMS, selected by the applicant, will prepare draft assessment documents and send them to the CMS. They, in turn, will either approve the assessment or the application will continue into arbitration procedures. In an effort to minimize disagreements and to facilitate the application for MAs in as many MSs as possible, the DCP involves CMS at an earlier stage of the evaluation than under the MRP. (Ref. 67) At the end of each of the three different procedures, there is a national phase in which the summary of product characteristics and all concerned texts for label, package leaflet and box will be translated into the national language of each MS. After this step is completed, the MS provides the applicant with a valid national MA.
In parallel, the application for a MA in only one MS (national procedure) is also still possible. In that case, the application should be based on the national regulatory requirements of the MS in question.

Fig. 9. Different ways for applications for MA in the EEA



Source: Ref. 68

a) New VMPs

In the EU, self-standing applications (new products) are distinguished from applications based on a reference medicinal products (generic products).

Legal basis (for DCP, MRP, national application):

Article 13(a), Directive 2001/82/EC – well established use (bibliographic application)

Article 13(b), Directive 2001/82/EC – new combination of known active substances

Article 13(c), Directive 2001/82/EC – informed consent

Similarly, there is the possibility for a MA by the Community via the CP (Article 3(2), Regulation (EC) No 726/2004), if:

a) the medicinal product contains a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community; or

b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation in accordance with this Regulation is in the interest of patients or animal health at Community level.

c) Immunological VMPs for the treatment of animal diseases that are subject to Community prophylactic measures.

b) Generic VMPs

Legal basis:

Article 13(1), Directive 2001/82/EC – generic product,

Article 13(3), Directive 2001/82/EC – generic product with additional data (e.g. new strength),

Article 13(4), Directive 2001/82/EC – biosimilar medicinal product, and

Article 3(3), Regulation (EC) No 726/2004 - generic product (CP).

Article 13(1), Directive 2001/82/EC: A generic medicine is the same as a medicine which has already been authorised to be marketed in the EU (the reference product). A generic medicine contains the same active substance(s) as the reference medicine and is used at the same dose(s) to treat the same disease(s) as the reference product. The generic product must be bioequivalent to the reference product. Certain changes e.g., change of pharmaceutical form may be permitted if it is supported by the appropriate non-clinical/clinical data as a “hybrid” application.

For an application of a generic product, conduction of a successful bioequivalence studies are mandatory. The concrete requirements are listed in the "Guideline on the conduct of bioequivalence studies for veterinary medicinal products".
In addition, studies on environmental risk assessment (ERA) could be required by a European NCA in a few cases, due to safety reasons. This the case, when the original product was authorised at a previous time point when no ERA study had been required for the application, but the relevant legislation had been updated during the meantime, the applicant for a generic product then could be forced by the NCA to provide sufficient results of an ERA.
In general, the applicant can apply for MA via CP, DCP, MRP or national procedure.

c) Import requirements (Importation from third countries (non-EEA countries)
Legal basis: Directive 2003/94/EC; article 4
Directive 2001/83/EC, title IV (manufacture and imports)

Manufacture of batches of medicinal products in third countries must be carried out in accordance with the marketing authorisations held in the Community/Member States. The manufacturer must be authorised according to the laws of the country concerned and must follow GMP standards at least equivalent to those of the EC.

d) Recent changes in legislation
New variation regulation (EC) No 1234/2008:
In January 2010 previous regulations were replaced by a single regulation to provide a simpler and more flexible legal framework. This regulation relates to products authorised under EU procedures, but amending legislation published in 2012 extended the provisions to purely national authorisations from August 2013. The outcome should be a fully harmonised European system for regulatory changes.

Moreover, an update Directive 2001/82/EC is expected for the next future, because the last amendment was put in place about ten years ago and since that time, important deficiencies of the directive have become obvious. In particular, the industry was concerned about ineffective data protection clauses and the failure of the legislation to deliver a true single market in the EU for VMPs. The insufficient and uneven availability of VMPs across the EU is also a key driver for changes of the current legislation. (Ref. 69)

Key proposals from the industry include (among others) the following points:

- Improved data protection Today: (8+2)+1+1+1 years, provides a maximum of 13 years if three additional food-producing species are added to the first product. Proposal: (8+2)+3+3+3+3 years, giving a maximum of 22 years if four additional major innovations are added to the first product.
- Simplification of registration procedures: The current system of different procedures (CP, DCP, MRP and national) should be replaced by a single regulatory procedure using the best aspects of the centralised and decentralised procedures. This procedure would be based on a single data dossier (in English) and a single scientific assessment, and would result in a single decision for marketing authorisation in the EU (also named as 1-1-1 concept). (Ref. 69)

e) Publication of current law

The European Commission publishes the complete EU legislation in the area of VMPs on its homepage: http://ec.europa.eu/health/documents/eudralex/vol-5/index_en.htm (Ref. 70) in volume 5 of "The Rules Governing Medicinal Products in the European Union". Furthermore, numerous guidelines of regulatory and scientific nature have additionally been adopted under the name Notice to Applicants to facilitate the interpretation of the veterinary medicines legislation and its uniform application across the EU,:

- Volume 6: Detailed explanation of the MA procedures and other regulatory guidance intended for applicants
- Volume 7: Scientific guidance on the quality, safety and efficacy
- Volume 4: Specific guidance on the legal requirements for GMP
- Volume 8: Specific guidance on the legal requirements for maximum residue limits
- Volume 9: Specific guidance on the legal requirements for Pharmacovigilance

5. General challenges for marketing authorisation applications in the BRIC countries

In this chapter, the author provides the reader with a short overview about the national requirements for registration of foreign VMPs in the BRIC countries. In general, the indicated review times are highly variable and unpredictable, depending on local agency resources, reviewer's perspective, number of rounds of questions from agency and speed of answers from applicant and if deadline to reply is specified by the NCA.

In general, for a MA submission it is recommended to submit a dossier in accordance with the following structure:

Part 1: Administrative and legal information
Part 2: Quality information
Part 3: Safety (Pharmaceutical and toxicological studies)
Part 4: Efficacy (Clinical studies)

In addition, a Summary of Product Characteristics (SPC) and information on labelling and package inserts should be added.

5.1 Brazil

Table 5. Brazil: General regulatory requirements and considerations

Requirements / Considerations	Brazil
Time limit for VMP licence	Decreto No. 467, article 3: 10 years, for local produced VMPs. Imported VMPs: Same validity as the certificate issued in the country of origin, max. 3 years.
Renewal	Decreto No. 5.053, chapter IX, article 30: Local products must be renewed every 10 years. Submission: 120 days prior to end of its validity. Decreto No. 467, article 3: 45 days after entry of renewal application, the applicant receive a provisional licence, valid for 1 year.
Variations	Various requirements e.g.: Decreto No 5.053: chapter I, article 17, chapter XIV, Annex I, point 6. ATO Nº 4 (24.04.2007): Categories of changes. In general 2 types of variations (type A and B)
Data protection periods for new products	Law 10.603/02: - *Protection for original products:* 5 years – starts with registration or until the first release of the information in any country, whichever occurs first, with a minimum of 1 year of protection guaranteed. - *New data required after grant of registration (for products mentioned in the items above):* The remainder of the term of protection granted for the data in the corresponding registration or 1 year from the presentation of the new data, whichever occurs last.
Manufacturing licence	Manufacturing licence is needed, shall be renewed annually.* [1]
CPP	Not needed for submission but it is required for local approval.*[1] Approvals of reference agency (EMA/US Food and Drug Administration (FDA)) In many cases, local registration process can still be perceived as a "validation" of those from reference agencies. The EMA and the US FDA are still "the" main reference authorities not only for local approval but also for issues such as labelling. In order to prove a reference agency's approval, Brazil relies on the CPP from the US FDA or country of origin, as applicable.*[1]
Labelling requirements	In Portuguese as per local regulations. Mock-ups required for submission.* [1]
MRL	Brazil maintains a national MRL list and defers to Codex Alimentarius when there is no national MRL established.[2] National residue limits for bovine milk are published by Anvisa (Agência Nacional de Vigilância Sanitária) under the name PAMVet (Programa de Análise de Resíduos de Medicamentos Veterinários em Alimentos de Origem Animal) [3]
Review time	12–18 months (Questions might come ~5–6 months after submission). [*1] Could be last up to 30 months (according to company experience).
Stability studies	Climatic zone: IVb. Stress studies for biologic/ biotech (possible exposure of the product outside recommended conservation care should be evaluated, such as high temperatures and/or freezing). [*1]
Critical and/ or recent issues	Inspection request(s) of manufacturing facilities must be filed before MA filing.*[1] Similar or "me-too" medicines must be phased out by 2014.

Sources: [1]Ref. 71, [2]Ref. 72, [3]Ref. 73, * Information available only for human medicinal products.

5.2 Russia

Table 6a. Russia: General regulatory requirements and considerations

Requirements / Considerations	Russia
Time limit for VMP licence	Fed. law N 61, Art. 28: For newly registered medicines: 5 years
Renewal	Fed. law N 61, Art. 28: After first renewal the registration has un-limited validity. Time limit for submission: not specified.
Variations	Fed. law N 61, Art. 31: Variations are reviewed within 90 working days.
Data protection periods for new products	Fed. law N 61, Art. 18: During 6 years since medicine registration, usage of information about pre-clinical and clinical studies for medicine registration is prohibited without permission of the applicant. This requirement is effective since Russia's entry into the World Trade Organization (WTO) on 22.08.2012. Since this time, marketing of medicines registered with violation of this law is prohibited. Further amendments to the Law No 61 are expected to be introduced in the next future. In addition, the Civil Code of Russian Federation (Federal Law N 230-FZ of 08-Dec-2006 implementing Civil Code of the Russian Federation Part IV, as amended) also provides protection for innovative medicines (medicine combination, method of manufacturing, methods of application). [1]
Manufacturing licence	Not specified.
CPP	CPP is required for submission. [2]
Labelling requirements	Mock-ups are presented in two copies in the book format of A4. Labelling should satisfy requirement of Federal Law N 61 of 12-Apr-2010.[1]
MRL	Member of Codex Alimentarius. Hence, the limits are often more restrictive than the MRL data published by the Codex Alimentarius Commission (according to company experience). Russia maintains a national MRL list. Russia is also part of the Customs Union of Belarus, Kazakhstan, and Russia; MRLs established by the Customs Union apply to Russia. The Federal Service for the Protection of Consumer Rights and Human Well-Being of the Ministry of Health and Social Development (Rospotrebnadzor) is responsible for establishing MRLs for pesticides, veterinary medicines, and other contaminants in food. Rosselkhoznadzor is the primary implementer of Russian MRLs.[3]
Review time	MAA expertise of the product quality and benefit–risk ratio is conducted within 110 working days. [2] Fed. law no. 61, Art. 13: The overall new registration process is performed within 210 working days with a clock-stop for conducting a registration clinical trial, if required. **Generic products** can be reviewed in accordance with an accelerated procedure (Fed. law no. 61, Art. 26). Clinical trial application assessment within 15 working days and assessment of the product quality and benefit-risk ratio within 45 working days, so overall the review procedure is completed within 60 working days[2].

Sources: [1] Ref. 74, [2] Ref. 6, [3]Ref. 75

Table 6b. Russia: General regulatory requirements and considerations

Requirements / Considerations	Russia
Stability studies	Stability Zone II. Methods of analyzing medicine stability are determined in General Pharmacopoeia Article N 42-0075-07 of State Pharmacopoeia Issue XII Volume I. [1]
Critical and/ or recent issues	For each MA application (including generics) clinical studies must be conducted in Russia. [2]

Sources: [1] Ref. 74, [2] Ref. 6, [3]Ref. 75

5.3 India

Table 7. India: General regulatory requirements and considerations

Requirements / Considerations	India
Time limit for VMP licence	Registration Certificate is valid for a period of 3 years. [1]
Renewal	The following documents must be renewed regularly: - Import Licence: submission 3 months before expiry - Registration Certificate: submission 9 months before expiry - Manufacturing Licence: submission 6 months before expiry.[1]
Variations	- Import Licence/ Manufacturing Licence: changes in the company immediately submission of new data - Registration certificate: variations must be classified in minor and major changes. [1]
Data protection periods for new products	Today, there is no specific law for data exclusivity in India. Indian Patents Act, 1970: Applicable only to patentable inventions, no protection for new use of a known substance or formulations by combinations. Further patent protection extends only to the invention but not to the data generated by the originator. The CDSCO does not provide any exclusivity for the 1st Biologic. But since all biologics are considered "New Medicines" any subsequent similar biologics need to go through the tedious process of a "New Medicine" approval. [2]
Manufacturing licence	A manufacturing license is valid for a period of 5 years. [2]
CPP	For import of VMPs submission of a CPP is necessary. [3]
Labelling requirements	Not specified.
MRL	Maintains national MRL list. Defers to Codex Alimentarius when national MRL not established. The Food Safety and Standards Authority of India is responsible for specifying MRLs of pesticides and agrochemicals in food products. [4] (For VMP residues, there is no specific regulation available)
Review time	Import registration approval: approx.: 6-9 months; New medicine registration approval: approx.: 12-18 months The process of receiving import registration can take up to 12 months.[3]
Stability studies	Climatic zone IV.
Critical and/ or recent issues	A pharmaceutical manufacturer, located outside India has to obtain a: - Import Licence; (Responsibility of CDSCO) - Registration Certificate; (Responsibility of CDSCO) - Manufacturing Licence. (Responsibilities of CDSCO & State Licensing Authority) and - Licence for sale [5]

Sources: [1]Ref. 76, [2]Ref. 37, [3]Ref. 36, [4]Ref. 77, [5]Ref. 10

5.4 China

Table 8. China: General regulatory requirements and considerations

Requirements / Considerations	China
Time limit for VMP licence	Decree No. 44, article 27: "import veterinary certificate of registration" and "veterinary registration certificate" are valid for 5 years.
Renewal	Decree No. 44, article 27: Expiry of the need to continue to import, the applicant shall be six months before the expiry of the Ministry of Agriculture in the re-registration. Decree No. 44, article 29: Review of application for re-registration by MOA: 20 working days to review.
Variations	Decree 404, article 13: Variations of Veterinary Medicine Manufacturing Licence Decree 404, article 24: Variations of Veterinary Medicine Distribution Licence.
Data protection periods for new products	Data exclusivity is granted for 6 years starting from the marketing approval for new chemical entity products. [1]
Manufacturing licence	Decree 404, article 12: Veterinary Medicine Manufacturing Licence is valid for five years. Re-registration: six months before the expiration of the licence. Decree 404, article 33: On-the-spot inspections are possible. Requirements of GMP for VMPs will be inspected. MOA tests if the foreign company shall have the right to conduct tests on safety and efficacy of the medicine at an institution designated by MOA.
CPP	Yes, CPP is required together with a legalisation. [2]
Labelling requirements	Decree 404, article 20: In Chinese, requirements as indicated.
MRL	China maintains a national list of MRLs for pesticides (for VMPs there is no information available). MOA is responsible for establishing and publishing MRL standards, the country does not officially defer to Codex Alimentarius [3]
Review time	approx. 27 months for VMPs in total (Preliminary review by MOA and CVDE: 6 months, clinical trails and residue tests: 8 months, evaluation by CVDE: 6 months, quality tests: 5 months, approval of licence: 2 months) [4] On the contrary, according to MOA, the promised time frame for evaluation of imported VMPs is: 60 workdays (a maximum of 120 workdays for technical evaluation or experimental evaluation; a maximum of 150 workdays for special testing), for imported veterinary biologicals: 20 workdays. [5] Registration procedure for feed additives (type 1): 5 months in total (preliminary review by MOA: 1 months, quality tests: 3 months, approval of licence: 1 month) [4]
Stability studies **Critical and/ or recent issues**	Climatic zone IVa. Import: Conduction of clinical trials and verification tests in designated agencies (by MOA) within the territory of China. [4] Feed additives and VMPs must be registered separately. Moreover, the MOA distinguishes between 2 types of imported feed additives: Type 1: on the national list of approved feed additives; type 2: *not* on the national list of approved feed additives. Furthermore, there are different rules for a) vet. pharmaceuticals, herbal medicines and b) biologicals. [4] Decree 404: In addition to the medicine approval licence, the applicant needs a licence for manufacturing and medicine distribution.

Sources: [1]Ref. 64, [2]Ref. 40, [3]Ref. 78, [4] Ref. 65, [5]Announcement No. 442

5.5 European Union

Table 9a. European Union: General regulatory requirements and considerations

Requirements / Considerations	European Union
Time limit for VMP licence	Directive 2001/82/EC, article 28: 5 years.
Renewal	Directive 2001/82/EC, article 28: After 5 years a MA should be renewed. Once renewed, the MA shall normally be valid for an unlimited period of time. However, on justified grounds relating to pharmacovigilance, the competent authorities (RMS/CMS) may decide to proceed with one additional 5-year renewal.
Variations	Depending on the type of variation. The new introduced Regulation 1234/2008/EU (in force since 01.01.2010) differentiates between small and major variations or extensions. The regulation apply to human and veterinary medicines.
Data protection periods for new products	Directive 2001/82/EC, article 13, Regulation 726/2004, article 14 : - *Protection for original products:* 8 years of data protection, plus 2 years for preparation, application and receive of the MA for a generic MA. In summary, for a generic product, it is not allowed to enter the market until 10 years have been expired. - *New data required after grant of registration (for products mentioned in the items above):* +1 year to the above mentioned 10 years, if, during the first 8 years the MA-holder obtains an authorisation for one or more new indications which are held to bring a significant clinical benefit in comparison with existing therapies. (Special conditions apply to VMPs for fish and bees.) Directive 2001/82/EC, article 5 (Concept of global MA): After granting an initial authorisation "any additional species, strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions, shall also be granted an authorisation […] or be included in the initial MA. All these MAs shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of article 13(1)."
Manufacturing licence	Directive 2001/82/EC, article 44: Manufacturing authorisation is required (or equivalent outside of the EEA where mutual recognition agreement (MRA)/ protocol to the European agreement on conformity assessment and acceptance of industrial products (PECA) is in force).
Labelling requirements	Volume 6B, Notice to applicants, VMPs, Presentation and content of the dossier: European procedure: Mock-ups required for submission in English language. During national phase of the procedure: Translation into each national language which has taken part in the procedure.
MRL	See annex I-IV of Regulation (EEC) No 2377/90 and table 1 of annex of Regulation (EU) No 37/2010. Default MRL of 0.01 ppm applies for APIs not regulated by EU MRL regulation. (Ref. 79)

Table 9b. European Union: General regulatory requirements and considerations

Requirements / Considerations	**European Union**
Review time	Depends on the chosen type of registration procedure. In addition, during the national phase of European procedures there may be a delay in the predicted time period.
Stability studies	Climatic zones: I and II. Various guidelines published by the VICH and CVMP.
Critical and/ or recent issues	Directive 2001/82/EC will amended in the next future. Points of special interest are, among others: a) data protection periods (maybe extended); b) how to deliver a true single market by simplification of the MA procedures; c) how to bring existing nationally registered VMPs into a true EU single market.

6. Discussion

Due to the complexity of the regulatory environment of the BRIC countries and the EU, it is hardly possible to discuss similarities and differences of their legislation in every aspect. For this reason, this following chapter gives the reader a comparative overview on some selected major aspects of regulatory legislation. In detail, these aspects are:

- Structure and transparency of legislation
- Generic VMPs
- Recent changes and predicted developments in law

Structure and transparency of legislation

Major differences can be observed when comparing the degree of transparency and the structure of regulatory framework in each of the four BRIC countries and the EU.

In general, the structure of legislation of each of the BRIC countries is different and complex, with little explanatory notes of the NCAs. For instance, in some cases it was unclear if the veterinary regulatory law is included in the human law or if there is a separate legislation. (In India and Russia, there is only one law for human and veterinary medicines. In Brazil and China, there is a separate legislation for veterinary medicine.) In addition, the national competent authorities of India, China and Russia provide, if at all, only little information about changes in their law.

In Brazil, the information policy of the competent authority MAPA appears to be "more open", if compared to the other three BRIC countries. For example, the MAPA publishes its complete veterinary legislation on its web page (Ref. 54). The presented information clearly indicates that there is a separate veterinary legislation, and it provides short notices about recent changes and draft versions of e.g. guidelines. Unfortunately, the internet presentation of MAPA and the complete legislation is only available in the national language Portuguese.

However, compared to the four BRIC countries, the information policy and legislation of the EMA appear to be the most clear and transparent one, from the authors point of view.

As explained for Brazil, the EMA allows interested parties to follow recent changes in law, too. Moreover, draft versions of laws, guidelines, etc. are published regularly before the finalised version of the new legislation comes into force. Also, the question "Combined human and veterinary law or separate legislation for VMPs?" can be easily answered in the EU at a glance on the EMA homepage (Ref. 17) or the web page of the European Commission for EU legislation on pharmaceuticals (Ref. 18). Above all, the latter provides the reader with translations of the legislative acts in 21 of the currently 24 languages of the EU on the same web page (Ref. 18).

Furthermore, the structure of law differs between the BRIC countries and the EU. For instance, the Indian organisation of legislation appears to be unique among the BRIC countries and the EU. In detail, the Indian D&C Act and Rules, lists all kinds of medicines in schedules and gives information under which these specific medicines should be manufactured. With attention to VMPs, the law lists only a few specific requirements for biological VMPs (vaccines of bacterial and viral origin laid down in Schedule F); other veterinary medicines should be manufactured according to the British Veterinary Pharmacopoeia.

Information on the question “How to proceed with applications in general?” can be hardly found in the enormous amount of application forms. As a result, for persons who are unfamiliar with the Indian law, it is a challenge to obtain the specific requirements stated only in single law.

Another example for a complex legislation framework is the Russian federal law N 61-FZ “On circulation of medicinal products”. In in this case, the law also has its own unique structure and it is only published in Russian by the NCA. (Translations and guidelines on how to obtain MAs in Russia can be found on the global regulatory database from ThomsonReuters IDRAC. (Ref. 19)

Despite the transparent and well structured EU legislation, disparities in national legislative frameworks in different EU member states can cause problems. For instance, a delay of MA approval is not uncommon in the national phase of an EU procedure, such as the DCP. In particular, *“procedures,* (such as CP, DCP and MRP) *still give opportunities for member states to disagree with marketing authorisation on grounds that are often rejected on appeal at European level. In addition, there is still no alignment of best practice across national agencies. This affects all stages of the regulatory chain and appears to be based on a lack of trust between agencies.”* (Ref. 80) For those reasons, the IFAH and other organisations require a simplification of the currently existing various EU procedures (CP, DPC, MRP and national) for the next future. (Ref. 69)

Generic VMPs

Paying particular attention to the length of an application for a generic VMP, there are differences between each of the BRIC countries and the EU.

For instance, in China and India, a generic VMP application is not subject of an accelerated registration procedure, as this is the case e.g. in the EU. A reason for this equal treatment of new medicines and generic applications in India and China (only in regard to the time period of the procedure) might be the fact that there is currently no specific law for veterinary generics in those countries. In India, the Drugs and Cosmetics Act and Rules do not directly provide specific statutory provisions and regulations concerning generics. Also, China has no law for generics, but there are specific regulations for human medicines since 2005 and 2007. (Ref. 64)

In Russia, the procedure is accelerated, but the requirements for a MA of a generic product are more comprehensive than those specified in the EU. It is mandatory, that local toxicological studies following the specific requirements of the NCA are conducted in addition to bioequivalence studies, local toxicological studies. There have not been any agreements signed between Russian and other national authorities on recognition of clinical data. (Ref. 6)

In Brazil a specific legislation for generics was just adopted in 2012. The author does not found any evidence for an accelerated procedure for generics.

Recent changes in legislation

There have been major changes in the veterinary legislative framework of the BRIC countries in the last decade, such as the increasing requirements for GMP in China, the tightened legislation for the importation of medicines to India and Brazil, the phasing-out of similar medicines in Brazil at beginning of 2014, and the increased requirements for clinical trials in Russia.

Most changes were introduced, because the governments intended to increase the manufacturing, quality and inspection requirements of the pharmaceutical products. Unfortunately, the main part of the changes is associated with higher bureaucratic burdens and costs for the industry, but the prices for VMPs have not roused in the same way. (Ref. 4)
The IFAH considers the NCAs as having "overly stringent standards" concerning the development of the last years, which in the end will eventually hinder the introduction of new VMPs in many countries. (Ref. 80)
Correspondingly, in the EU the IFAH noticed a similar development where the veterinary pharmaceutical industry "*…must submit the results of extensive post-development tests to national and sometimes supranational authorities before a product can be made available on the market. Companies also incur considerable costs in maintaining and defending their existing portfolio of animal health products. While quality control and post-development tests are essential, the rigidity of the approval process often delays the deployment of much-needed animal medicines."* (Ref. 80)
As a result, either regulatory standards need to be reduced or prices for VMPs on the national markets need to be increased. However, the latter seems to be not feasible for the most parts of the emerging markets.

7. Conclusion and outlook

In conclusion, the author has observed great variations in the national legislation of each of the BRIC countries among themselves and in comparison to the EU law. Each of the countries has their own key legislation, based on historic developments such as the colonial past of India and Brazil or the centrally-planned economy of Russia and China. Also, the EU law was affected by a unique development in the past; influenced by the goal to harmonise the regulatory framework of a huge number of independent EU member states.
For these reasons, tendencies of the VICH outreach forum to harmonise global legislations appear to be difficult and there is still a long way to go.

Moreover, the author has the strong suggestion that there is no possibility of authorising a VMP in any of the four BRIC countries without a legal representative on the spot. On the one hand, the regulatory requirement in all of the BRIC countries requests a legal representative for submission of applications for MA. On the other hand, a well educated and loyal national partner could of advantage to accelerate MA in a BRIC country.

This document displays “a part of the big picture”, because the basis of interpretation of the regulatory environment in the BRIC countries was based on internet sources, such as the IDRAC database (specialised in human regulatory law) the publications from TOPRA (which gives only limited information about veterinary law) and public web pages. As a result, the reader cannot be provided with information on every aspect of veterinary legislation for all of the BRIC countries. This is in contrast to the opportunities, opened by e.g. the EMA through their internet presence, to investigate the European law.

In any case, the author suggests that the market for VMP will continuously expand in the next future. This assumption is based on of the growing demand of meat of good quality in the emerging markets, and increase of western lifestyle in the BRIC countries, especially in terms of companion animal bound. As a result, that trend will attract a rising number of international pharmaceutical companies to invest in the AH market of the BRIC countries. However, the new market will remain a big challenge, because of the increasing regulatory burdens implemented by NCAs.

8. Summary

Today, European companies which produce veterinary medicines prefer to register the major part of their products in several countries of the European Economic Area (EEA) via European procedures, such as the decentralised procedure (DCP), the mutual recognition procedure (MRP), or the centralised procedure (CP). The liberalisation of markets, the increasing global trade with livestock products, and the growing demand for middle-class pursuits such as companion animal bond in the developing countries has resulted in a rising demand for veterinary medicinal products (VMPs) in countries such as Brazil, Russia, India and China (BRIC countries).
In order to successfully register VMPs in the BRIC countries, it is essential to be familiar with the national law and the trends in the veterinary regulatory environment, which will emerge in the near future. Unfortunately, today, the national regulatory law displays a high diversity, the comparableness to the EU legislation is limited, and above all, all of the four BRIC countries have most recently tightened huge parts of their regulatory legislation, For those reasons, the successful authorisation and marketing of VMPs in the BRIC countries have been a great challenge for European companies in the past, and will be even more in the near future.

The aim of this thesis is to give the reader an overview on the animal health (AH) market of the emerging countries Brazil, Russia, India and China. Furthermore, this thesis highlights similarities and differences between the pharmaceutical regulatory environment in the BRIC countries and that in the European Union (EU).

References

1. European Economic Forecast. Autumn 2011. European Commission. Directorate-General for Economic and Financial Affairs. Commission staff working document

2. The BRICS report. A Study of Brazil, Russia, India, China, and South Africa with special focus on synergies and complementarities. 2012. Oxford University Press. New Delhi, India.

3. Brazil's Pharmaceutical Industry. Opportunities for Swiss Suppliers. Juni 2010. Business network Switzerland. osec.ch

4. IFAH-EUROPE. Benchmarking the Competitiveness of the Global Animal Health Industry. 2011. Survey Europe. A report by BioBridge Ltd for IFAH and IFAH-EUROPE

5. IFAH Global Benchmarking Survey. 2011. Concise Board summary. Summary of the reports by BioBridge Ltd for IFAH BOARD.

6. A. Harrington-Morozova. International focus – Russia. 2011. Overview and update of changes in the Russian regulatory environment. Regulatory Rapporteur – Vol 8, No 6, June 2011.

7. How to market generics and biosimilars (Russian Federation). August 2013. IDRAC 54407. Regulatory summary. ThomsonReuters

8. Brazil's Pharmaceutical Industry. June 2010. Opportunities for Swiss Suppliers. Osec - Business Network Switzerland.

9. S. Schmitt. Focus China. 2010. The Chinese pharmaceutical environment. Regulatory Rapporteur – Vol 7, No 2, February 2010.

10. Import/Export (India). July 2013. IDRAC 61372. Regulatory summary. ThomsonReuters

11. Recommendations of the "Confluence on Veterinary Regulatory Reforms in India". October, 2012. Indian Veterinary Journal

12. vich.org. Official homepage of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) (last visit on 18.12.2013) http://www.vichsec.org/

13. VICH and its role for authorisation of veterinary medicinal products. Executive Summary, May 2010. VICH/10/008 http://www.vichsec.org/

14. Report by the VICH Steering Committee on issues raised by Forum members during the 1st Outreach Forum meeting. February 2012. Powerpoint presentation

15. Survey of the pharmaceutical industry in Russia 2012. Ernst & Young

16. The Heads of Medicines Agencies (HMA) Official homepage. (last visit: 18.12.2013) http://www.hma.eu/cmdv.html

17. EU legislation – Eudralex, Official homepage. (last visit: 29.01.2014) http://ec.europa.eu/health/documents/eudralex/index_en.htm

18. ema.europa.eu. Official homepage of the European Medicines Agency (EMA) (last visit on 18.12.2013) http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/regulation.jsp&mid=

19. IDRAC, a global regulatory database from ThomsonReuters. Official homepage. (last visit: 18.12.2013) http://www.idrac.com/FrontPage.aspx

20. TOPRA. Official homepage of The Organisation for Professionals in Regulatory Affairs. (last visit: 29.01.2014) http://www.topra.org/

21. M. Schneidereit. April 2009. „Nationaler und Internationaler Tierarzneimittelmarkt“, BfT VDL Journal, Bonn.

22. IFAH Annual report 2006. Improving the quality of life for animals and people

23. IFAH annual report 2012. The costs of animal diseases and societal benefits from healthy animals.

24. IFAH-Europe. Annual Report 2012. International Federation for Animal Health-Europe AISBL

25. C. Haub. The BRIC countries. April 2012. (last visit: 18.12.2013) http://www.prb.org/Publications/Articles/2012/brazil-russia-india-china.aspx

26. The Costs of Animal Disease. October 2012. A report produced for the International Federation for Animal Health (IFAH). Oxford Analytica

27. C. Narrod, M. Tiongco & R. Scott. 2011. Current and predicted trends in the production, consumption and trade of live animals and their products. Rev. sci. tech. Off. int. Epiz., 30 (1), 31-49. International Food Policy Research Institute, Washington, DC.

28. Delgado C., Rosegrant M., Steinfeld H., Ehui S. & Courbois C. 1999. – Livestock to 2020: the next food revolution. Food, Agriculture and the Environment Discussion Paper, No. 28. International Food Policy Research Institute, Washington, DC.

29. L. Msellati. August 2012. Good governance and financing of efficient Veterinary Services. Scientific and technical review. OiE (World Organisation for Animal Health)

30. The Worlds Factbook. (last visit: 18.12.2013) https://www.cia.gov/library/publications/the-world-factbook/

31. Animal Health 2013 – Brazil and Latin America. A review of markets and leading companies. Animal pharm reports.

32. WHO Technical Report Series, No. 953, 2009. Annex 2. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products

33. Lifestock Sector Brief, Brazil. July 2005. FAO, Livestock Information, Sector Analysis and Policy Branch (AGAL)

34. Authorities and Organisations (India). Central drug standard control organisation (CDSCO). January 2013. IDRAC 60517. Regulatory summary. ThomsonReuters

35. India Pharma Inc.: Capitalising on India's Growth Potential, 2010. PwC PricewaterhouseCoopers Private Ltd.

36. S. Naralkar, K. Karande, P. Vasani. Focus – India. 2010. The Indian pharmaceutical environment. Regulatory Rapporteur – Vol 7, No 2, February 2010 www.topra.org

37. How to market generics and Biosimilars (India). June 2013. IDRAC 62141. Regulatory summary. ThomsonReuters

38. Indian Animal Healthcare Market 2013: Trends & Opportunities (2012-2017) (last visit: 18.12.2013) http://www.researchandmarkets.com/reports/2375866/

39. Lifestock Sector Brief, India. July 2005. FAO, Livestock Information, Sector Analysis and Policy Branch (AGAL)

40. J. Fletcher, M. Ahmed, C. Pharo. ASEAN-China drug development. 2012. A comparison of ASEAN and Chinese drug registration requirements. Regulatory Rapporteur – Vol 9, No 7/8, July/August 2012

41. Animal Health in China. 2011. Issued: 2013-10-28. Source: Veterinary Bureau. Ministry of Agriculture, P. R. China (last visit: 18.12.2013)
http://english.agri.gov.cn/hottopics/ah/201310/t20131028_20492.htm

42. P. Griffin, A. Sibal. TOPRA editorial. 2010. Travelling the regulatory silk road. Regulatory Rapporteur – Vol 7, No 2, February 2010. www.topra.org

43. Lifestock Sector Brief, China. July 2005. FAO, Livestock Information, Sector Analysis and Policy Branch (AGAL)

44. Livestock and Poultry: world exports. April 2013. USDA – United States Department of Agriculture, Foreign Agriculture Service

45. Annual report 2011-12 (India). Department of Animal Husbandry, Dairying & Fisheries, Ministry of Agriculture, Government of India, New Delhi

46. Agriculture, Forestry and Fishery Statistics. Nov. 2013. Eurostat Pocketbooks. 2013 Edition. Eurostat European Commission.

47. Regionen 2020, Bewertung der künftigen Herausforderungen für die EU-Regionen, Arbeitspapier der Kommission November 2008

48. T. Bradley, R. King. Nov. 2012. The Dog Economy Is Global—but What Is the World's True Canine Capital? The Atlantic.com (last visit: 18.12.2013)
http://www.theatlantic.com/business/archive/2012/11/the-dog-economy-is-global-but-what-is-the-worlds-true-canine-capital/265155/

49. Maps of the World. (last visit: 18.12.2013) http://www.mapsofworld.com/

50. Euromonitor.com (last visit: 18.12.2013) http://www.euromonitor.com/

51. OiE animal welfare standards in the legislation: Experience of China. Third OIE Conference on Animal Welfare Nov 6~ 8 2012, Kuala Lumpur. Dr Lu CP & Dr Fei RM Nanjing Agricultural University

52. IFAH-Europe 2012. Companion animal leaflet

53. EPHA. European Public Health Alliance (last visit: 29.01.2014) http://www.epha.org/spip.php?article3765

54. Ministry of Agriculture, Livestock and Supply (MAPA), Brazil. Official homepage. (last visit: 18.12.2013) http://www.agricultura.gov.br/portal/page/portal/Internet-MAPA/pagina-inicial/ministerio/estrutura-organizacional

55. Russian State Centre of Quality and Standardization of Animal Drugs and Feeds" (VGNKI). Official homepage. (last visit: 18.12.2013) http://translate.google.de/translate?hl=de&sl=ru&tl=en&u=http%3A%2F%2Fwww.vgnki.ru%2Fabout%2F

56. Indian Veterinary Research Institute. Official homepage. (last visit: 18.12.2013) http://www.ivri.nic.in/about/organ.aspx

57. Format and content of applications (Brazil) Standard format. December 2013. IDRAC 26205. Regulatory summary. ThomsonReuters

58. Brazilian veterinary law. (last visit: 18.12.2013) http://diblasi.com.br/en/newsletter/enacted-brazilian-law-no-126892012-introducing-similar-and-generic-veterinary-medicines/

59. The Intellectual Property Review, July 2012. Editor: Robert L Baechtold. Law Business Research Ltd, London

60. Life Sciences in Brazil. No. 74. July 2012. Pinheiro Neto Advogados.

61. Legal definitions & marketing requirements (Russian Federation) November 2013. IDRAC 117637. Regulatory summary. ThomsonReuters

62. Import / Export (Russian Federation). October 2013. IDRAC 51678. Regulatory summary. ThomsonReuters

63. India: Guidelines for Bioavailability & bioequivalence studies. Central Drugs Standard Control Organization, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India, New Delhi. (March 2005). IDRAC. ThomsonReuters

64. How to market generics and biosimilars (China). March 2013. IDRAC 46817. Regulatory summary. ThomsonReuters

65. Information for Registration in China. Michael Boddington. (last visit: 18.12.2013) http://de.slideshare.net/MichaelBoddington/registration-in-china

66. China Institute of Veterinary Drug Control/ regulatory information/ legislation. (last visit: 18.12.2013)
http://www.ivdc.gov.cn/English/RegulatoryInformation/Legislation/201009/t20100903_34368.htm

67. P. Nivrutti et al. Review Article. Marketing Authorisation Procedures in Europe: A Regulatory Perspective International Journal of Pharmacy and Pharmaceutical Science Research 2011; 1(1): 13-19, India

68. M. Baccouche, P. Bachmann, J. Hofer, B. Lehmann, C. Wirthumer-Hoche. Modul 1 - MDRA-15, 2013. DGRA Studiengang, Bonn. Powerpoint Presentation

69. Focus – Veterinary medicines. The review of the veterinary medicines legislation:
An update. Regulatory Rapporteur – Vol 9, No 2, February 2012

70. European Commission, EU legislation for VMPs (last visit: 18.12.2013)
http://ec.europa.eu/health/documents/eudralex/vol-5/index_en.htm

71. Adriana G Prat. A practical overview of requirements for drug registration in Latin America. Focus – Latin America. Regulatory Rapporteur – Vol 10, No 9, September 2013

72. Brazil Pesticide MRLs Market Information Page. December 2013. International Maximum Residue Level Database. A service of the Foreign Agricultural Service, United States Department of Agriculture. (last visit: 29.01.2014)
http://www.mrldatabase.com/results.cfm

73. PAMVet. Programa de Análise de Resíduos de Medicamentos Veterinários em Alimentos de Origem Animal (last visit: 29.01.2014)
http://portal.anvisa.gov.br/wps/content/Anvisa+Portal/Anvisa/Inicio/Alimentos/Assuntos+de+Interesse/Monitoramento+e+Pesquisa/2408e3804fddb924be6fffacfa6b37f1

74. Marketing authorisation procedures (Russian Federation) Standard format. November 2013. IDRAC 14142. Regulatory summary. ThomsonReuters

75. Russia Pesticide MRLs Market Information Page. December 2013. International Maximum Residue Level Database. A service of the Foreign Agricultural Service, United States Department of Agriculture. (last visit: 29.01.2014)
http://www.mrldatabase.com/results.cfm

76. Marketing authorisation procedures (India) Procedure for renewal. December 2013. IDRAC 61904. Regulatory summary. ThomsonReuters

77. India Pesticide MRLs Market Information Page. February 2013. International Maximum Residue Level Database. A service of the Foreign Agricultural Service, United States Department of Agriculture. (last visit: 29.01.2014)
http://www.mrldatabase.com/results.cfm

78. China Pesticide MRLs Market Information Page. March 2013. International Maximum Residue Level Database. A service of the Foreign Agricultural Service, United States Department of Agriculture. (last visit: 29.01.2014)
http://www.mrldatabase.com/results.cfm

79. European Union Pesticide MRLs Market Information Page. October 2013. International Maximum Residue Level Database. A service of the Foreign Agricultural Service, United States Department of Agriculture. (last visit: 29.01.2014)
http://www.mrldatabase.com/results.cfm

80. IFAH White paper 2013. EMERGING AND RE-EMERGING ANIMAL DISEASES. Overcoming barriers to disease control. Oxford Analytica

Legislation / Guidelines / Other legal texts

Brazil

LEGISLAÇÃO RELACIONADA AOS PRODUTOS DE USO VETERINÁRIO. Ministério da Agricultura, Pecuária e Abastecimento. Brasília, DF / 2012.
Collection of Brazilian veterinary legislation, including:

DECRETO-LEI
- DECRETO-LEI N° 467, DE 13 DE FEVEREIRO DE 1969

DECRETO
- DECRETO Nº 5.053, DE 22 DE ABRIL DE 2004

INSTRUÇÃO NORMATIVA
- INSTRUÇÃO NORMATIVA SDA N° 6, DE 28 DE MARÇO DE 2012
- INSTRUÇÃO NORMATIVA SDA N° 25, DE 20 DE AGOSTO DE 2008
- INSTRUÇÃO NORMATIVA SDA Nº 29, DE 14 DE SETEMBRO DE 2010

ATO
- ATO Nº 4, DE 24 DE ABRIL DE 2007

Russia

Federal Law N 3-FZ of 8-Jan-1998: on Narcotics and Psychotropic Substances, as amended

Federal law of the Russian Federation No. 61. “On circulation of medicinal products” 31.03.2010. English translation by IDRAC. Thomson Reuters. IDRAC No. 61-FZ

Federal Law N 230-FZ of 08-Dec-2006 implementing Civil Code of the Russian Federation Part IV, as amended

Federal Law N 271-FZ of 11-Oct-2010: Amending Federal Law N 61-FZ of 12-Apr-2010

Decree N 771 of 29-Sep-2010 on the Procedure of Import of medicines for medical use into the Russian Federation

Ministerial Order of November 7, 2011 N 404. “Approval of administrative regulation of the federal service for veterinary and phitosanitary surveillance on the provision of public service for the issuance of permits to import into, export from and transit through the territory of the Russian federation of animals, products of animal origin, veterinary medicines, feed and feed additives doe animals.”

Ministerial Order N 759n of 26-Aug-2010: on Procedure of the Submission of Medicinal Product Dossier Documentation for the Registration Purpose

Ministerial Order N 760n of 26-Aug-2010: on the Adoption of an Application Form for a Variation to a Registration Dossier of a Registered Medicinal Product

Ministerial Order N 1413n of 23-Nov-2011: On Approval of the Guideline on the Format and Content of the Registration Dossier of a Medicinal Product

India

THE DRUGS AND COSMETICS ACT AND RULES. THE DRUGS AND COSMETICS ACT, 1940 (As amended up to the 30th June, 2005) and THE DRUGS AND COSMETICS RULES, 1945. (As amended up to the 30th June, 2005). Government of India. Ministry of Health and Family Welfare, Department of Health

FOREIGN TRADE (DEVELOPMENT AND REGULATION) ACT, 1992, Act 22. IDRAC. Regulatory report

THE CUSTOMS ACT, 1962, Act 52: (Consolidated Version up to 2006). IDRAC. Regulatory report

THE PATENTS ACT, 1970 (39 of 1970). 19th September, 1970

THE CUSTOMS TARIFF ACT, 1975 (51 Of 1975) 18-Aug-1975 (Consolidated Version up to 2006) IDRAC. Regulatory report

Notification No. G.S.R. 604(E). 24.8.2001. Gazette of India.

Guidelines for Bioavailability & bioequivalence studies. Central Drugs Standard Control Organization, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India, New Delhi. (March 2005). IDRAC. ThomsonReuters

China

Regulations on Administration of Veterinary Drugs (China). Decree No. 404. Adopted at the 45th Executive Meeting of the State Council on March 24, 2004, promulgated by Decree No. 404 of the State Council of the People's Republic of China on April 9, 2004, and effective as of November 1, 2004

Registered Veterinary Measures (China). Decree No. 44. November 24, 2004 the Ministry of Agriculture issued Decree No. 44, since January 1, 2005 into force

SFDA Order No. 28: Regulations on Drug Registration Administration, Oct. 01, 2007

The Technical Guidelines of Bioavailability and Bioequivalence Study of the Medicinal Products for Human Bodies, 18-Mar-2005

Announcement No. 442 of the Ministry of Agriculture of the People's Republic of China. Registration requirements for imported veterinary drugs in China.

Administrative Measures for Imported Animal drugs (Order No. 2 of the Ministry of Agriculture of the People's Republic of China)

Administrative Measures for Labels and Instructions of Animal Drugs (issued: 03.01.2010)

Inspection and Acceptance Measures for Quality Management Standards in Production of Animal Drugs (issued: 09.01.2010),

Norms for the Business Operation and Quality Management of Animal Drugs (issued: 03.01.2010)

European Union

DIRECTIVE 2001/82/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to veterinary medicinal products

Directive 2004/28/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products

REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

COMMISSION REGULATION (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin

COUNCIL REGULATION (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin

COMMISSION REGULATION (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

Guideline on the conduct of bioequivalence studies for veterinary medicinal products.
11 April 2011. EMA/CVMP/016/00-Rev.2. Committee for Medicinal Products for Veterinary Use (CVMP)

Notice to Applicants:

- Volume 6: Detailed explanation of the MA procedures and other regulatory guidance intended for applicants
- Volume 6B, Notice to applicants, VMPs, Presentation and content of the dossier
- Volume 7: Scientific guidance on the quality, safety and efficacy
- Volume 4: Specific guidance on the legal requirements for GMP
- Volume 8: Specific guidance on the legal requirements for maximum residue limits
- Volume 9: Specific guidance on the legal requirements for Pharmacovigilance

Other

Agreement on Trade-Related Aspects of Intellectual Property Rights. April 15, 1994. World Trade Organization

Declaration - Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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