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ASSESSMENT OF VETERINARY DRUGS REGULATORY FRAMEWORK IN ETHIOPIA

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A THESIS SUBMITTED TO THE SCHOOL OF PHARMACY, COLLEGE OF HEALTH SCIENCE, ADDIS ABBABA UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN REGULATORY AFFAIRS (MEDICINE TRACK).

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This is to certify that the thesis undertaken by Hailu Zeru Berhe, entitled *"Assessment of veterinary drugs regulatory framework in Ethiopia"* and submitted in partial fulfillment of the requirements for the Degree of Master of Science in Regulatory Affairs (Medicine Track) complies with the regulations of the university and meets the accepted standards with respect to originality and quality.

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LIST OF ACRONYMS

AMR	Antimicrobial Resistance
AMU	Antimicrobial Use
EAC	East African Community
FAO	Food and Agricultural Organization
FMHACA	Food, Medicine and Health Care Administration and Control Authority
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
IT	Information Technology
MAH	Market Authorization Holder
MRL	Maximum Residue Limit
NRA	National Regulatory Authority
OIE	World Organization for Animal Health
PhV	Pharmacovigilance
PIC/S	Pharmaceutical Inspection and Cooperation Scheme
PMS	Post-marketing Surveillance
QC	Quality Control
QMS	Quality Management System
SOP	Standard Operating Procedure
SRA	Stringent Regulatory Authorities
TC	Technical Committee
USFDA	United States of America Food and Drug Administration
VDFACA	Veterinary Drugs and Animal Feed Administration and Control Authority
VICH	Veterinary Medicines International Cooperation for Harmonization
WHO	World Health Organization

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ABSTRACT

Assessment of Veterinary Drugs Regulatory Framework in Ethiopia

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Strong regulatory framework enables to ensure that the manufacture, trade and use of veterinary drugs are effectively regulated, and to protect and promote animal health, animal production and public health at large. To perform core regulatory functions efficiently, the regulatory bodies require having adequate legislations and regulatory tools, appropriate organizational structure, adequately trained human resources, sustainable finance, and effective cooperation between different regulatory bodies and with other law enforcing bodies. This study therefore aimed to assess veterinary drugs regulatory framework in Ethiopia. An archival review and expert panel based qualitative study was conducted from April to September 2019. A detailed review of legislations, regulatory activity plans and reports, and human and financial resource archives was conducted. Forty experts, 33 of them working in veterinary drug regulatory authority and seven from private veterinary drug traders, were grouped in to six groups for a panel discussion. Experts were allowed to dialogue on each semi-structured questions until they reach consensus. Narrative description of the experts' consensus and linking them with the archival review findings were conducted to report findings. This study revealed that the federal regulatory body had adequate human and financial resources. However, the federal regulatory body was poorly structured and regions have neither their own legislations nor regulatory bodies. Unavailability of guidelines for registration of traditional medicines, post-marketing surveillance and good manufacturing practice procedure, poor regulation of government owned entities and poor communication of regulatory activities to the public were also shortcomings of the regulatory system. Generally, limited regulatory legislations and tools and poor organizational structures were identified as the major gaps of the regulatory framework. Therefore, development and adoption of the lacking legislations and tools as well as re-structuring of the federal regulatory body and establishment of regional regulatory bodies should be done to strengthen the regulatory framework.

Key words: *Ethiopia*, p*roducts*, *regulation, regulatory authority*, *veterinary drugs*

1. INTRODUCTION

Veterinary drugs are fundamental for treatment, prevention and control of both infectious and noninfectious animal diseases. The provision of successful animal health service requires sustainable and adequate availability of safe, effective and quality veterinary drugs. The use of ineffective, poor quality, harmful drugs can result in therapeutic failure, exacerbation of disease, resistance development to drugs and sometimes death (FAO, 2004). It also undermines confidence in animal health systems, animal health professionals, pharmaceutical manufacturers and distributors. Money spent on ineffective and poor quality drugs is also wasted whether by consumers or governments (Rago and Santoso, 2008). Thus, governments need to establish strong national regulatory authorities (NRAs), to ensure that the manufacture, trade and use of veterinary drugs are effectively regulated, and to protect and promote animal health, animal production and public health at large (Smith, 2013).

Drug regulation has developed over the past 50 years in response to crises to pharmaceutical products. The initial regulatory standards were primarily related to ensuring the pharmaceutical quality of medicinal products and subsequent developments in the early 1960s that led to the development of standards for testing efficacy and safety of new medicines as well (Suzanne and Kent, 2004). The structures of drug regulation that exist today including drug laws, drug regulatory agencies, drug evaluation boards, quality control (QC) laboratories, drug information centers, etc. have evolved over time. During this process, the scope of legislative and regulatory powers has been gradually expanded, in response both to the ever-increasing complexity of an increasingly sophisticated pharmaceutical sector, and to the perceived needs of society (Ratanwijitrasin and Wondemagegnehu, 2002).

Effective regulation of drugs requires political will and commitment of the government which enables the regulatory authorities to make an independent science based decision, adequate legislations, appropriate organizational structure and facilities, clearly defined roles and responsibilities of the regulatory body, sufficient qualified and experienced human resource, adequate and sustainable financial resources, and effective cooperation between the regulatory authority and other government institutions including those dealing with law enforcement (e.g. customs and police) (Rago and Santoso, 2008). The core national drug regulatory authorities

functions include marketing authorization (registration) of products; licensing of drug establishments; import and export control; inspection of manufacturing premises and distribution channels; market surveillance (product quality monitoring, pharmacovigilance, control of drug promotion and advertising); and quality control (WHO, 2010).

Many developing country regulatory systems have not been able to respond effectively due to lack of effective legislation, lack of adequate regulatory skill and knowledge, lack of adequate human resources, and inadequate funding for drug regulatory activities (Suzanne and Kent, 2004). A huge variety in national regulatory capacity does also exist and not all national regulators can effectively implement even minimum regulatory oversight of pharmaceutical market in their jurisdiction. Thus, substandard and counterfeit medicines are still common in many parts of the world (Rago and Santoso, 2008).

Ineffective regulation of veterinary drugs may lead to introduction of drugs of unknown quality; inadequate labeling of drugs (a particular problem where many people are illiterate), so that users are not properly informed on dosage, expiry date, dangers and precautions; breach of special requirements (e.g., refrigeration) for storage of certain drugs; and drug residue build-ups in livestock products, a threat to local consumers and to export markets. A drug which is inadequately regulated is inappropriately used and animals are ineffectively treated resulting in the failure of treatment and development and spread of drug resistance (FAO, 2004). The risks of illegal veterinary medicines are not only lack of efficacy and safety for animals given the products, but also risks to human safety through food from animals treated with illegal veterinary medicines, less effective control of zoonotic infections and risks of increasing antimicrobial and antiparasitic resistance (Health for Animals, 2017).

2. STATEMENTS OF THE PROBLEM

The estimated annual global loss due to illegal veterinary medicines is US $1-2billion (HealthforAnimals, 2017). The International Federation of Animal Health estimates that the trade of sub-standard and non-registered drugs in Africa is worth US$400million a year, the same size as the official market (Kingsley, 2015). Illegal trade and irrational use of veterinary drugs are also common in Ethiopia. The survey conducted by VDFACA on the status of illegal veterinary drugs in Ethiopia (VDFACA, 2016) showed 12% of veterinary drug shops found selling non-registered drugs. This survey also revealed that there are 26.2% and 23.3% prevalence of illegal veterinary drugs trade on open markets and in other shops with other commodities, respectively. The study conducted by Achenef *et al*. (2017) also reported that 87.08% of the animal health professionals and animal owners included in the study mentioned the presence of illegal drug handlers and sellers. In this study, 72.2% of the respondents stated that veterinary drugs used in the country have poor quality.

As to my knowledge there is no study conducted on the veterinary drugs regulatory system in Ethiopia. Minimum awareness of animal health professionals (48.45%) on the veterinary drug legislations is also reported by Achenef *et al*., (2017). Therefore, studying the regulatory framework of veterinary drugs will help increase the awareness of the community and to highlight the specific issues to the regulatory bodies and strengthen their regulatory structure to improve their efficiency and capacity of regulating veterinary drugs. It is also important for the policymakers in designing or updating policies and strategies to prevent livestock and public health from the effects of substandard, unauthorized and falsified veterinary drugs. This would then help to ensure the delivery of safe, quality and efficacious veterinary drugs to the end users and its rational use.

3. LITERATURE REVIEW

3.1. Veterinary Drugs

Veterinary drugs are defined as any substance or mixture of substances which is used, or is manufactured, sold or represented as suitable for use, in the diagnosis, treatment, mitigation or prevention of disease or abnormal physical or mental state or the symptoms thereof in an animal, or restoring, correcting or modifying any physical, mental or organic function in an animal (FAO, 2004). It also includes products used to treat against internal and external parasites and disease transmitting vectors, biological products, sanitary items and veterinary instruments (FDRE, 2012).

Veterinary drugs are used throughout the world and they comprise a broad variety of classes of chemical compounds including vaccines, antimicrobials, antiparasitics and β-agonists (Ture M, *et al*., 2019). The most commonly used antibiotics in food producing animals are the β-lactams, tetracyclines, aminoglycosides, lincosamides, macrolides and sulfonamides (Bayou and Haile, 2017). According to Beyene T. *et al*., (2015), Penicillin-streptomycin combination (penstrep), oxytetracycline, amoxicillin, sulphamethoxazole-trimethoprim combination, diaminazine diaceturate, amprolium, albendazole, ivermectin, tetramisole, levamisole, oxyclozanide, piperazine and diazinon are among the most commonly used veterinary drugs in Ethiopia.

These products must be safe for the animal, for the humans consuming food derived from the treated animal, for the user or the person administering the product, and for the environment; effective for its intended uses; quality manufactured product in accordance with current good manufacturing practices (GMP); and properly labelled to inform the user not only of how to use the product, but also of any safety considerations, drug withdrawal times, and storage and handling procedures (Smith, 2013).

3.2. Regulation of Veterinary Drugs

Government regulatory agencies have the crucial responsibility of ensuring that only safe, effective, high-quality, well manufactured and properly labelled veterinary drugs are available in the marketplace for use, and that unsafe and ineffective products, such as counterfeit and illegally compounded medicines, are not available (Smith, 2013). Adequate drug legislations and

regulatory tools, such as policy, proclamation, standards and guidelines, appropriate organizational structure, good cooperation between different regulatory bodies and other law enforcing bodies (e.g. trade, customs and police) (WHO, 2003), sufficient qualified and experienced human resources, adequate and sustainable financial resources, and transparency and accountability combined with good management are essential for effective drug regulation (Rago and Santoso, 2008; MSH, 2012).

3.2.1. Regulatory Legislations

Legislations provide the basis for drug regulation. Regulatory tools such as standards and guidelines equip drug regulatory authorities with the practical means of implementing those laws. The absence of regulatory tools may lead to variations in the implementation of the law, or even lead to questions about the transparency of law enforcement. Standards and guidelines should be established in a written form for all drug regulatory functions, as well as being made publicly available to all the parties involved in order to bring transparency to the drug regulatory process (Ratanwijitrasin and Wondemagegnehu, 2002; Prat, 2007). The competent authorities should have the necessary primary and secondary legislation adopted for their activities at all levels of their functional or territorial organization. The legislations should also be consistent with each other and with other national and regional laws to ensure the effectiveness of regulation through unity of command over the regulatory functions and bridging missing links resulting from fragmentation between the regulatory bodies (Ratanwijitrasin and Wondemagegnehu, 2002; OIE, 2017). Laws, regulations, guidance and/or policies relevant to the control of veterinary medicines may also make reference to, or be based on, product standards or conformity assessment procedures that have been developed and/or harmonized by international or multilateral organisations, such as the Codex Alimentarius Commission (Codex), the World Organisation for Animal Health (OIE), the World Health Organization (WHO), or the International Cooperation on Harmonisation of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH) (Smith, 2013).

3.2.2. Organizational Structure

The way a regulatory body is organized has implications for the execution of drug regulatory functions (Ratanwijitrasin and Wondemagegnehu, 2002). The regulatory structure could be a

single agency system in which both veterinary and human medicines are regulated by single authority under Ministry of Health, or a separate agency regulates the veterinary medicines under the supervision of the National Ministry of Agriculture (Chetana *et al.*, 2012; Smith, 2013). Our neighboring countries Kenya and Sudan have separate agencies called Veterinary Medicines Directorate (Regulations, 2015) and Ministry of Animal Resources (Omer, 2019) to regulate veterinary drugs, respectively. In United Kingdom, Veterinary Medicines Directorate is responsible to regulate the safety, quality and efficacy of veterinary drugs (VMD, 2013). Veterinary drugs in China and Russia are also regulated by independent agencies under the supervision of ministry of agriculture (Chetana *et al.,* 2012). In the study conducted by Hassan (2005) to assess the regulatory structure of eleven Middle East countries, in four countries the regulation falls under the responsibility of separate veterinary authority, while in the remaining countries, it is the responsibility of the Ministry of Health. In some countries, regulatory responsibilities may also be vertically distributed to federal, state and local governments (Ratanwijitrasin and Wondemagegnehu, 2002). The major drawback of the division of responsibilities between different administrative levels is risk of fragmentation due to lack of unity of command (WHO, 2003). Chowdhury *et al*., (2015) also reported lack of uniformity in interpretations of the laws and regulatory decision-making and limited institutional channels in India. But, the multiple functions across multiple agencies can be streamlined by establishing inter-agency standard operating procedures (SOPs) or creating a central coordinating and supervisory body (Ratanwijitrasin and Wondemagegnehu, 2002).

3.2.3. Human and Financial Resources

Regulatory authorities should have efficient scientific and technical staff for the purpose of taking the suitable decisions for the regulation of veterinary drugs (OIE, 2017). Most of the developing countries are affected by lack of adequate human resource which is largely caused by low salaries, scarcity of pharmaceutical professionals and shortage of training institutions and lack of career structure and incentives (Chejor *et al*., 2018). Suleman *et al.,* (2016) also reported that there are significant problems in hiring and retaining qualified and skilled personnel within Ethiopian Food, Medicine and Health Care Administration and Control Authority (FMHACA) due to low salary, lack of attractive career structure and incentives. In South Africa, the medicines regulatory authority lost close to 80% of its staff within 3-year period (1997-2000)

(Matsebula *et al.,* 2005). Newly recruited personnel came with relevant qualifications still need experience to become effective regulators. Adequate training should then be imparted to further enhance the capacity of newly recruited and existing personnel (Chowdhury *et al.*, 2015).

The financial sustainability of the drug regulatory authority is a critical factor in the continued implementation of the various drug regulatory functions. Government support in the form of a budget and fees charged for regulatory services are in general two different ways of financing the drug regulatory authorities. The government should thus be fully committed to ensuring the financial sustainability of the drug regulation (Prat, 2007). According to the report by Suleman *et al*., (2016), there is shortage of finance to perform the routine regulatory activities of human medicines in Ethiopia due to insufficient government funding and weak revenue generating system from services, although FMHACA is mandated to use the revenue it generates from service delivery.

3.2.4. Regulatory Cooperation and Harmonization

Enforcing drug legislation effectively requires medicines regulatory authorities and other government enforcement agencies, such as trade, customs, police and prosecutors, to work together, but in many countries cooperation is non-existent. NRAs should work with customs and police in inspecting products at ports, other points of entry and distribution outlets, detecting and investigating criminals involved in the illegal trade of medicines and counterfeiting, and apprehending and prosecuting criminals (WHO, 2003). They should also seek the cooperation of animal health professionals, livestock owners, animal products and byproducts consumers, and other interested parties. Suleman *et al*., (2016) reported poor coordination of stakeholders in regulation of human medicines due to unavailability of established system with clearly defined roles and responsibilities of parties involved including inter-agency standard operating procedures. This weak cooperation is boldly seen between the regulatory bodies and the prosecutors at court, and thus most illegal cases taken to court were not successful.

Lengthy registration time and country-specific registration requirements such as labeling and GMP requirements are the reasons for pharmaceutical companies either to cease to supply medicines or have made decisions not to supply new medicines to African countries (Narsai *et al*., 2012). Regulatory collaboration and harmonization across nations can simplify this process

and improve operational efficiency, saves time and resources and helps to ensure drug quality, safety and efficacy (Ball *et al*., 2016; GALVmed, 2016). Harmonization also improves the ability of pharmaceutical companies to comply with registration requirements and enter to new markets. So that, the public will benefit through improved supply of medicines, access to high quality medicines that comply with stringent requirements of safety, quality and efficacy and reduced risk of use of counterfeit medicines (Narsai *et al*., 2012).

3.2.5. Good Governance

Good governance is important to promote robust decision making, enhance accountability, reduce opportunities for corruption, and improve efficiencies to enable better access to and use of quality-assured medicines (Walkowiak *et al.*, 2018). Lack of accountability and transparency mean that communication on medicines regulation between regulatory authorities and their clients, government and the general public is likely to be lacking or highly unsatisfactory. Clients will not understand why certain regulatory decisions have been taken; governments will be ill-informed about the extent and significance of the activities of their regulatory authorities; and the public will be unable to question any aspect of drug regulation because of lack of understanding of individual components and how they should be undertaken (WHO, 2003). The drug regulatory authorities shall provide comprehensive and frequently updated lists of licensed or notified medicinal products and authorized dealers and importers which should be easily accessible to designated ports of entry and authorized dealers. Notifications on any product licenses that have been withdrawn on grounds of safety or quality and confirmed cases of imported counterfeit products and other illicit activities should immediately be communicated to all stakeholders (SADC, 2006). Inspections and other enforcement outcomes should also be independent of political influence and should be carried out by well-trained personnel who have a full understanding of the aims of the regulations and have the authority to enforce those regulations (WHO, 2016).

3.3. Functions of the Veterinary Drug Regulatory Authorities

According to WHO (2010) and Institute of Medicine (2012), the main functions of NRA include product registration (market authorization); control of distribution chain by licensing and inspection of manufacturers, importers, exporters, wholesalers and retail outlets; quality control

testing; post-marketing surveillance (PMS) of products for their safety and effectiveness; and provision of unbiased information. Regulatory authorities are also responsible to monitor antimicrobial resistance (AMR) and drug residues in animal derived food products (Smith, 2013).

Veterinary drugs must be authorised by the responsible authority of the country where it will be used before they can be sold or used. A marketing authorisation (also called 'registration') is the approval by the responsible authority in the country concerned that the product can be sold and used, specifying the details of the medicine (e.g. name of active substance, animals for which it can be used, indications for use, dose and duration of treatment), the conditions of use (e.g. storage conditions, shelf life, withdrawal period, instructions for safe use or instructions for safe disposal of waste) and any precautions or warnings for safe use, including possible contraindications (VICH, 2016). This market authorization should have a legal basis and the regulatory authority should set out the conditions, content and format of applications, and the detailed technical requirements against which dossiers will be assessed, based on scientific scenario and international guidelines (WHO, 2010). Regulatory agencies must have efficient processes that are responsive to their stakeholders' needs. These include timely review decisions, effective and timely communications and effective management of dossier or application reviews (Smith, 2013). An efficient and predictable registration timeline will promote access to new medicines by encouraging more companies to register medicines (Narsai *et al*., 2012). Some regulatory authorities speed the review of certain products to enable faster approval, called expedited review or fast track procedure, of these products. A decision on which product to grant expedited review is normally based on its importance (EFPIA, 2017).

The establishments where veterinary drugs are manufactured, stored and distributed play an important role in determining the efficacy, potency and safety of these products. The licensing of such establishments is thus as critical an issue as the registration of veterinary medicinal products (Hassan, 2005). Therefore, NRAs should certify all premises and practices used to manufacture, store, distribute and dispense veterinary products if they comply with current guidelines of GMP, Good Storage Practice (GSP) and Good Distribution Practice (GDP) (WHO, 2010). Sustainable compliance should also be ensured by continuous inspection and surveillance of the good practices. Activities include physical inspection and quality-testing of product samples. In order

to perform these duties, inspectors should be assigned and given necessary legal powers. They should also be suitably qualified and free from conflicts of interest and political pressure (Ratanwijitrasin and Wondemagegnehu, 2002). Each act of import and export should also be subject to authorization by the regulatory authority on the basis of the product's registration (marketing authorization) status (WHO, 2010). Inspectors in collaboration with customs officials will carry out physical examination of all imported consignment of products and their documentation. Where necessary, the pharmaceutical inspector will carry out random sampling of pharmaceutical products in accordance with laid down guidelines on sampling of medicinal products imported into the country for drug analysis (SADC, 2006).

Regulatory authorities are also responsible to verify compliance of medicinal products through post-marketing surveillance (PMS), including random sampling of registered medicines for quality control and pharmacovigilance. It is important that the veterinary medicine regulatory agency monitors the use of products after they have been approved and placed on the market. Studies that support pre-market approval requirements are based on a limited number of test animals. When these products are marketed, the number of animals exposed to them often increases by a hundred or a thousand times. The primary purpose of a reporting programme for adverse events (pharmacovigilance) is to provide early warnings of harmful effects and/or evidence of a lack of effectiveness that were not detected or predicted during the pre-market product testing (Smith, 2013). Reports of adverse events can be elicited spontaneously from animal health professionals and pharmaceutical manufacturers, or compulsory reporting can be required (Suzanne and Kent, 2004). PMS is also important to screen out products with questionable quality (substandard and counterfeit) from the market (Kang *et al*., 2017). In the European Union, surveillance of marketed drugs is a shared responsibility of the regulatory authorities and market authorization holders (EMEA, 2000). The market authorization holders should have pharmacovigilance system, report the spontaneous reports directly sent to them from professionals, and take appropriate actions. The regulatory authorities are also responsible to confirm availability of the system via inspection, conduct active surveillance, investigation of adverse event reports, and taking regulatory actions (Waller and Harrison-Woolrych, 2017). WHO (2016) recommends the regulatory authorities to issue legislations and guidelines to guide officials in conducting PMS.

Quality control (QC) of medicinal products is very crucial to verify the products compliance with the specifications of market authorization. It also serves to deter fraudulent manufacturing and trading practice of medicines (Chejor *et al*., 2018). QC facilities must have enough qualified personnel and the necessary equipment and materials, and must operate according to established standards. A Quality Management System (QMS), such as ISO 17025, provides a framework for QC laboratories to operate according to defined procedures and standards (WHO, 2010). Testing procedures and testing criteria for the purpose of registration should be according to listed specifications (Hassan A., 2005). The main categories of techniques for pharmaceutical analysis are visual inspection of product and packaging; tests for physical properties such as disintegration, reflectance spectroscopy, and refractive index; chemical tests including colorimetry and dissolution; chromatography; spectroscopic techniques; and mass spectrometry. Some of the technologies are appropriate for use in the field with minimal training, while others require sophisticated laboratory equipment and a high level of technical expertise. It is often difficult to test for drug quality in low- and middle-income countries. Poorly trained chemists and dilapidated infrastructure are common obstacles in performing accurate drug quality testing. Making detection technologies easily accessible in low- and middle-income countries will help curtail the trade in falsified and substandard medicines (Institute of Medicine, 2013).

Monitoring of AMR and drug residue is also among the functions of veterinary drug regulatory authorities. Regulatory authorities should monitor the development of AMR in order to target the regulatory interventions to minimize the development of resistance (Smith, 2013). According to European Medicine Agency (EMA, 2015), minimizing the development of AMR is only possible through the prudent use of antimicrobials if all parties involved are well informed. Awareness campaigns on AMR therefore play an important role, and need to be regularly repeated and updated. Committee for Veterinary Medicinal Products of EMA issued guideline for prudent use of antimicrobials (EMA, 2015) and updating its scientific and regulatory guidance documents in a way to minimize development of resistance. It has also taken steps to address the risks to public health from the use of critically important antimicrobials in food-producing animals by implementing risk management measures into the Summaries of Product Characteristics (SPCs) for systemically administered 3rd and 4th generation cephalosporins, orally administered colistin products, macrolides and lincosamides. This regulatory body also developed a five year strategy

on antimicrobials (EMA, 2016) with strategic objectives that can be achieved specifically by the veterinary medicinal products regulators.

It is crucial that regulatory agencies charged with controlling veterinary medicines should adequately monitor animal derived food products (meat, milk, egg, honey and fish) to ensure that those products contain no drug residues that violate established tolerance levels or maximum residue limits (MRLs). Most countries have lists of MRLs or tolerances that represent safe levels as a regulatory tool; either developed by themselves or adopted the Codex veterinary drug MRLs (Smith, 2013). If drug residues are not well regulated, humans may consume unacceptable level of veterinary drugs with their food which may cause health risk to consumers including allergic reaction, disruption of normal gut flora, toxicity (such as carcinogenicity and teratogenicity), and AMR development. Therefore, countries should have legislations and necessary resources to regulate the residue levels in foods of animal origin in-order to protect the consumers from unnecessary residual effects (Agmas and Adugna, 2018).

Generally, the veterinary medicines regulatory framework is considered to help enhance the quality, safety and efficacy of the medicines to animals, consumers of animal products, users of medicines and the environment. Therefore, effective drug regulation requires a host of factors, including strong political will, sound management for streamlining the procedures and uniform implementation of law, coordination among law enforcement agencies and all the other stakeholders, and transparent and speedy decision making that garner strong public support.

4. OBJECTIVE

4.1. General Objective

- To evaluate the regulatory framework of veterinary drugs in Ethiopia

4.2. Specific Objectives

- To assess the availability and adequacy of regulatory tools, resources, and functional organizational structures;
- To assess the availability and implementation of regulatory function elements;
- To identify major gaps of the veterinary drugs regulatory system in the country.

5. METHODS

5.1. Study Area Description

The study was conducted in veterinary drugs and animal feed administration and control authority (VDFACA) of Ethiopia. This authority is established in 2013 as per the council of ministers regulation number 272/2012 to execute the regulatory provisions given on veterinary drugs and animal feed administration and control proclamation number 728/2011 (FDRE Negarit Gazette, 2012). The authority is organized by four technical directorates and one quality control laboratory center. Head office of the authority is located in Addis Ababa at Côte D'Ivoire Street, 9°01'42.5"N latitude and 38°46'55.2"E longitude. The quality control center is located at 8°54'36"N latitude and 38°45'48"E longitude, Debrezeit Street, Addis Ababa. The authority also has five branch offices at Bahirdar, Mekelle, Diredawa, Hawassa, and Yabello to do the regulatory activities closely. The authority has a total of 136 technical human resources and 223 administrative staff.

5.2. Study Design

A qualitative study was conducted between April and September 2019 to assess veterinary drugs regulatory framework in Ethiopia. Archival review and expert panel were used to collect the qualitative data.

5.3. Sampling Procedure

Regulatory experts who are permanent employees of the regulatory authority and with more than two years working experience in the authority were purposively selected and included in the panel to get an in-depth knowledge. Team leaders and senior experts were given a first chance to be included where more than nine experts had the chance to be included. However, all heads of technical directorates and the director general were directly included. Private veterinary drug importers and distributors with more than five years of active experience in the sector were purposively selected and technical managers of these companies were included in the study based on their experience.

5.4. Grouping of Study Participants

A total of 40 experts participated in six panels. One panel included a minimum of five and maximum of nine experts. Grouping was conducted based on the similarity and/or relatedness of the job responsibility of the experts. The first group included seven experts to discuss on the elements related to product registration/ market authorization. Issues related to certification and licensing of institutions and professionals and regulatory information were discussed by the second group included six experts. The third panel, conducted by six experts, discussed on the inspection, PMS, and enforcement related issues. All elements related to product quality analysis were discussed by the fourth group composed of nine quality analysts. The fifth group which included all heads of technical directorates and the director general discussed the general regulatory system and to summarize issues pending or not reached to consensus on the last four panels. Seven technical managers of private veterinary drug importers and distributors were included in one panel to get external opinions beyond the regulatory body experts.

5.5. Data Collection Procedure

Data were collected using an archival review and expert panel using semi-structured tools (annexes IV-VII) developed based on Systems for Improved Access to Pharmaceuticals and Services (SIAPS) regulatory systems assessment tool (Thumm *et al.*, 2017) and World Health Organization (WHO) data collection tool for the review of drug regulatory systems (WHO, 2007). A detailed review was conducted on legislations related to veterinary drugs regulation and documents related to regulatory activities (plans, reports, databases, etc.) and human and financial archives filed in the regulatory authority. To get consensus and a good summary of issues, the expert panel was conducted following lower to top approach, i.e. we started from experts and ended with the heads of directorates and director general of the regulatory authority. All panels were conducted in English language as all participants are experts. Questions were raised by the principal investigator based on the developed tool and panel participants were allowed to freely forward their thoughts and dialogue on specific issues until they reach consensus. Issues not reached on consensus were taken to the fifth panel composed of heads of technical directorates and the director general for final discussion and to get summary of issues. But, there were consensuses in all panels on most of the issues. Ideas of the majority were then taken to synthesize results. A draft organogram was also developed based on the organizational

structure gaps identified by this study and distributed to all technical directorates. Comments were then collected from the directorates to build-up the organogram and the final proposed organogram is annexed at the end of this document (annex II).

5.6. Data Analysis

Consensus based narrative description method of analysis was used to report results. The dialogues of panel discussions were recorded and ideas reached on consensus or ideas of majority of the panel participants were taken to synthesize results. Some individual thoughts were also used "as quotation" to strengthen the summary of group thoughts. Related information obtained from both data collection instruments were also linked together to synthesize strong description of results.

5.7. Researcher's Position and Reflexivity

The researcher is veterinarian by background and working as veterinary drugs registration expert at VDFACA since 2013. The study participants are either his colleagues or known them as clients of the authority. But, the study was conducted in consistency with the study methods by maintaining the distinction between the study and the researcher's affiliation in the organization.

5.8. Data Quality Assurance

Documents for archival review were received from respective departments following written requests. Data obtained from both data collection instruments were carefully recorded in writing. At the end of each panel discussion, brainstorming of the summary of each issue was conducted to validate the quality of data. Distinction of researcher's personal understanding and participants thoughts was maintained to avoid any intrusion and influence during data collection and analysis.

5.9. Ethical Considerations

Ethical clearance was obtained from the School of Pharmacy Ethical Review Board (ERB/SOP/125/11/2019) (annex III). All participants of the panels were informed individually about the purpose of the panel and only volunteer experts who gave oral consent were involved in the study. Confidentiality of the study data is maintained by handling all data in personal locked shelves and computer. All data are also used only for the study purpose.

6. RESULT

6.1.Socio-demographic Characteristics of Study Participants

A total of 40 experts participated in the expert panels. Majority of the experts are doctor of veterinary medicine (DVM) professionals (57.5%) and male (87.5%). Sixty percent of the participants had more than five years of work experience. The average age of the experts is 39±15.2 years, ranged from 28 to 57 years.

Table 1: Socio-demographic characteristics of study participants

Variables	Frequency (n)	Percent (%)
Gender		
Male	35	87.5
Female	5	12.5
Age (in years)		
25-35	17	42.5
35-45	10	25
>45	13	32.5
Qualification		
DVM	23	57.5
BVSc	2	5
B.Pharm	4	10
BSc (Chemistry/biology)	2	5
DVM+MSc	9	22.5
Work Area (department)		
Veterinary Drug Registration	8	20
Veterinary Drug Institutions Certification	7	17.5
Inspection	8	20
Quality Control	10	25
Technical managers (import/wholesale)	7	17.5
Experience (in years)		
2-5	16	40
>5	24	60

6.2. Regulatory Legislations, Organizational Structures and Resources

6.2.1. Regulatory Legislations

Ethiopia is using a single drug policy called "National drug policy of the transitional government of Ethiopia" issued in 1993, for both human and animal health care. "The Pharmacy and Laboratory Department" was the first regulatory body to regulate both human and veterinary drugs established under ministry of health by the Regulation Number 288/1964. Drug Administration and Control Proclamation No. 176/1999 was the subsequent legislation which transformed the pharmacy and laboratory department to an independent authority called "Drug Administration and Control Authority (DACA)." Currently, a separate veterinary drugs and feed administration and control proclamation no. 728/2011 issued by the parliament is being used as the legal tool for regulation of veterinary drugs in Ethiopia.

The scope of regulatory functions given to veterinary drug regulatory bodies legislated on proclamation no. 728/2011 includes: setting standards in relation to veterinary drugs and veterinary drug professionals; registration of veterinary drugs after evaluating their safety, quality and efficacy; issuing certificate of competence to veterinary drug manufacturers, importers, exporters and distributors; inspection of the production and distribution channel of veterinary drugs to ensure their compliance with the provisions of legislations; control of import and export; and post-marketing surveillance with a view to assessing the resulted benefit and risk of registered veterinary drugs. Regulation of traditional and complementary medicines used in veterinary practice, control of promotion of veterinary drugs and evaluation and authorization of clinical trials of veterinary drugs are also included under the legal scopes of the authority.

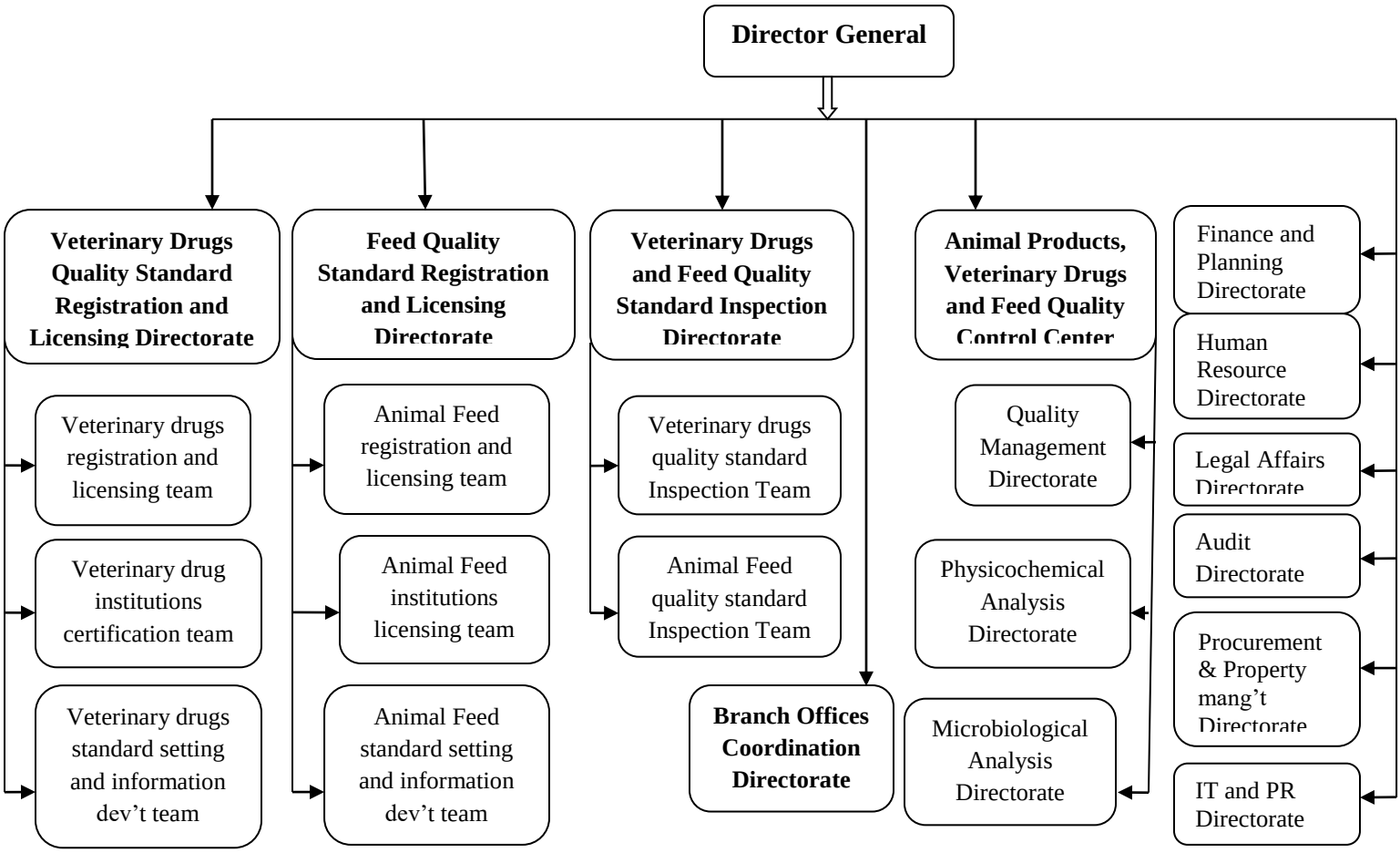
Setting standards in relation to veterinary drugs and veterinary drug professionals; and regulating trans-regional veterinary drug production, distribution, promotion, storage and quality control, and import and export activities are autonomously given to the federal regulatory body, VDFACA. Whereas regulatory activities other than those given to the authority are given to regional states regulatory bodies. These regional bodies are also responsible to report to the federal regulatory body on regulatory activities they have done in order to document information centrally (FDRE Negarit Gazette, 2012).

However, implementation regulation subsequent to proclamation no. 728/2011 is not yet issued. Regional states don't also have their own proclamations and regulations to establish regional regulatory bodies and to efficiently accomplish their regulatory mandates. A directive called "Veterinary Drug Retail Outlets Certification and Control Model Directive" issued by VDFACA is the only regulatory tool regions were using. According to the study participants, this model directive was issued by VDFACA in order to harmonize the certification and control of retail outlets across regions.

6.2.2. Organizational Structure

VDFACA was established in 2013 by the council of ministers regulation no. 272/2012 to regulate veterinary drugs at federal level. VDFACA is structured in to four functional directorates and one quality control laboratory as shown in Figure 1. The veterinary drugs quality standard registration and licensing directorate is responsible to register veterinary drugs and licensing of veterinary drug institutions. Monitoring pharmacovigilance reports and control of promotions are also under this directorate. Inspection of veterinary drug facilities and the distribution channel as well as conducting of PMS are responsibilities of the inspection directorate. The branch offices coordination directorate is handling the import and export control activities and liaising the licensing and inspection of premises and market channel in different regions of the country. Quality analysis of veterinary drugs and residue test in animal products are carried out at the quality control center. The laboratory is designed to conduct the test and to issue the quality certificate for the products to prove that they meet the required standards. The authority has also human resource, finance and plan, audit, procurement and property management, legal affairs, and IT and communication directorates to support the technical activities.

Figure 1: Organogram of VDFACA



Related regulatory activities scattered in different directorates plus poor coordination and communication between them were raised as the major obstacles of the organizational structure to achieve the ambitious targets of the authority. The conflicts between the institutions certification team and inspection directorate during the annual renewal of certificate of competence was raised as an example by the panelists. The institutions certification team conducts pre-certification inspection of institutions and gives them certificate of competence if they found compliant to the legislative provisions. During renewal period of the certificate this team wants to re-inspect institutions to ensure that they are keeping compliant. But, the inspection directorate claims itself as the only inspectorate and says continuous reports of the routine inspections are enough to decide renewal of the certificates. One certification expert strengthening this by raising the idea;

"We are relying on the third party's evidence to renew certificates. So, either the certification team should inspect institutions before renewal or these two activities better to be commanded under a single directorate [L01]."

The panel group discussed on the inspection of veterinary drugs also added that PMS and PhV are being conducted by separate directorates although these two regulatory activities are almost familiar. The inspection directorate is conducting PMS while PhV is being conducted by veterinary drugs registration directorate. The experts suggested that it would be better if one team can be established under inspection directorate to do these activities.

As shown in Figure 1, the QC laboratory is structured based on test methods. But, the laboratory panel participants claimed difficulty in implementing QMS due to this method of arrangement. They recommended a sample based method of organizational structure which is important to simply manage human resource and laboratory facilities and to ensure the quality of analytical results.

The experts said that the regions don't have well structured regulatory bodies. The regulatory activities are either done as a secondary job together with animal health care activities by animal health officers or given to a single expert to follow all regulatory issues within the region. Regulatory capacity of the regions is also variable. The level of coordination and communication with the federal VDFACA is also very loose due to absence of established structural, functional and communication platforms. One of the higher officials of the authority stressed this issue as;

"The initiative to work together is always from one side that VDFACA tries to create coordination bonds and to support and improve the regulatory capacity of the regional regulators. But, the regions only knock the doors of the authority when product related crisis arose [M01]." The regional regulatory bodies aren't also sending regular reports to the authority on the certificates of competence issued, suspended and revoked, even though the proclamation gives them the mandate to do so.

6.2.3. Human and Financial Resources

VDFACA has a total of ninety-six veterinary drug regulatory experts with different professional qualifications including Doctor of Veterinary Medicine (DVM), Bachelor of Veterinary Science

(BVSc.), Bachelor of Pharmacy (BPharm), Biology and Chemistry (Table 2). Twenty-one (22%) of these employees had masters degree (MSc.). Fourteen (14.6%), 52(54.2%) and 30(31.2%) of the total experts and analysts have less than five, five to ten and more than ten work experience, respectively. Staff turnover is not much problem for the authority now. But most of the research participants raised their fear of high employee turn-over the authority may face in the future if it doesn't create a favorable environment for the employees. One expert strengthened this idea by stating;

"*I'm not happy with the salary and there are no incentives that can make me stay for a long time in this authority. If I get a better option I don't hesitate to leave this authority [L06]*."

High safety risk was also mentioned by the quality control analysts. One analyst explained this idea as; "*Our day-to-day activity is affiliated with chemicals. Even though we are exposed to high safety risks, the authority neither gives us insurance coverage nor health compensations and incentives.*" The ethics of employees in the authority is positively appreciated by the private sector panel participants.

Table 2: Human resource composition of VDFACA

Roles	**Qualification**						**Experience (Years)**		
	DVM	BPharm	BVSc	Biology	Chemistry	DVM + MSc	<5	5-10	>10
Registration Experts	3	4	0	0	0	1	0	3	5
Establishment Certification Experts	4	0	0	0	0	1	0	3	2
Standard Setting and Information Development	2	0	1	0	0	1	0	2	2
Inspectors	38	0	2	0	0	12	9	32	11
QC Analysts	16	0	2	2	1	6	5	12	10
Total	**63**	**4**	**5**	**2**	**1**	**21**	**14**	**52**	**30**

Government budget is the only source of finance of the regulatory authority. The average annual expenditure is 91% of the allocated budget. Regulatory incapability due to shortage of finance

was not mentioned in any of the panel discussions. The authority also collects money from service fees and is directly deposited to the national treasury. The authority couldn't able to re-use the money collected from service fees due to the financial policy of the country.

Table 3: Annual budget and expenditure of VDFACA

Year	**Annual budget** (ETB*)	**Actual expenditure** (ETB)	**Service fees collected** (ETB)
2013/14	16,962,074.00	15,287,979.71	0.00
2014/15	41,309,826.06	38,249,255.60	87,296.34
2015/16	43,679,450.00	39,761,336.56	2,638,450.16
2016/17	59,631,502.58	55,071,568047	1,174,562.91
2017/18	67,324,947.21	59,900,532.89	2,144,970.78
Total	**228,907,799.85**	**208,270,673.23**	**6,045,280.19**

*ETB: Ethiopian birr

6.3. Product Registration

According to article four of proclamation no. 728/2011, all veterinary drugs locally produced or imported should be registered by the regulatory authority after being evaluated for its safety, efficacy, and quality. The authority has also mandated to directly authorize drugs to enter to the market, in compelling circumstances of natural disaster causing high animal migration such as drought, flood and earth quick, or in cases of an epidemic of exotic animal disease, or for animal health research, or for preregistration quality test.

The authority was using veterinary drugs registration guideline issued in 2002 (DACA, 2002) to assess and authorize veterinary drugs. All requirements for new and generic products, medical devices, re-registration and variation applications are included in this single guideline. However, this guideline is outdated and lacking some important regulatory requirement developments such as user, consumer and environmental safety and AMR issues. An East African Community (EAC) harmonized registration requirement for immunological products, called "Guideline on the technical documentation required to be included in a registration dossier for an immunological veterinary product (EAC, 2015)", is used to evaluate and register veterinary

vaccines. According to the panelists, Ethiopia is neither an active member of the EAC nor participated in the development of this document. VDFACA only participated in the validation workshop of the guideline. The authority didn't have guideline for registration of immunological products at that time and it was decided to adopt this guideline after that.

Traditional veterinary medicines registration guideline wasn't developed due to limited knowledge and awareness of the authority on the regulation of traditional veterinary medicines. One expert explained this issue as; "*Some traditional medicine registration applications are coming. But, we are rejecting these applications due to unavailability of specifically trained assessors and registration guideline [R04]*."

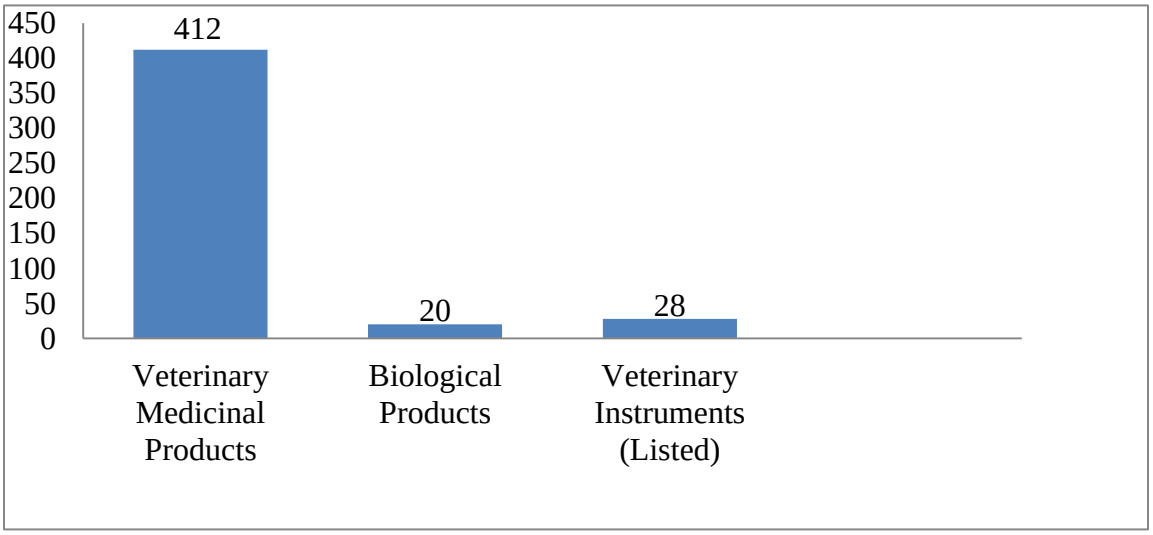
The experts described that assessment of registration application is conducted by peer assessors and checked by team leader before the final release of the assessment result to ensure the quality of dossier assessment. Assessors are continuously being trained to develop their capacity in order to improve the quality and efficiency of dossier evaluation. Applications are also evaluated chronologically based on their application date to ensure the fairness of the registration system. There is also a procedure of fast track registration, evaluation of dossiers without waiting for a queue, for products with limited market availability (minor-use/minor-species) such as vitamins, hormones, minerals, anesthesia and medicines for pet animals.

A total of 334 new, 94 renewals and 65 variation applications were approved and issued market authorization in the last five years (2014-2018). This accounts 70.6%, 92.2% and 80.2% of the evaluated dossiers at the same years, respectively. Among these authorized products 412 are veterinary drugs, 20 are biological products (vaccines and hormones), and 28 of them are listed veterinary instruments (Figure 2). Four hundred nineteen new, 97 re-registration and 81 variation applications are submitted to VDFACA in the last five years. The higher number of evaluated documents than the applications shown in (Table 4) is because of backlogged documents before the study years.

Table 4: Number of registration applications, evaluated applications and registered products in the last five years

Activities	**Type of application**	**2014**	**2015**	**2016**	**2017**	**2018**	**Total**
Total number of applications	New	43	106	89	78	103	419
	Renewal	39	12	28	10	8	97
	Variation	4	9	24	34	10	81
Number of evaluated applications	New	69	74	71	100	159	473
	Renewal	42	15	27	10	8	102
	Variation	4	9	24	32	12	81
Number of approvals	New	29	17	90	47	123	334
	Renewal	14	46	65	25	29	94
	Variation	3	7	19	27	9	65

Figure 2: Product categories issued registration certificate in the last five years (2014-2018)



Lengthy registration time is the major problem claimed by panel participants from the private sector. One technical manager with more than 25 years work experience said that *"We are waiting five years to get registration certificates of some products"* to stress this issue. The registration experts were also agreed that registration of veterinary drugs that are not found on the national veterinary drugs list, either the chemical substance or strength and dosage form of a product in the list, and those new to the Ethiopian market is taking longer time. Registration of these products is approved by technical committee (TC), composed of team leaders and directors of different technical departments, after evaluated by the registration team. The TC evaluates the document and decides on technical and administrative issues, which is taking longer times. These tasks are given to the committee members as a secondary job and it takes times to get all the members and sit together to give decisions. Besides these, the committee needs regular updates from veterinary epidemiology department at the Ministry of Agriculture on disease epidemiology to authorize the entrance of new veterinary drugs to the market. But, poor quality of dossier submissions and lack of proper knowledge on dossier compilation are also mentioned by the registration experts as challenges for the assessors and a means for delayed registration approval.

6.4. Certification and Licensing of Institutions

Veterinary Drugs Import, Export and Wholesale Certification and Control Directive (VDFACA, 2014) and Veterinary Drug Retail Outlets Certification and Control Directive (VDFACA, 2015) are the two legislative tools used for certification and licensing of veterinary drug institutions. Applicants should fulfill the professional, warehouse and dispensary, and office requirements stated on the directives to get a certificate of competence. Certification of importers and trans-regional wholesalers is conducted by the federal regulatory body, while certification and control of retailers and wholesale institutions having business limited within one region is the responsibility of regional regulatory bodies. But, the certificates of competence given to the institutions in different regions are not in a uniform format. Only a few regions issue a standard certificate while the others give a letter of support to the bureau of trade to get a trade license.

There is no certification and licensing of government-owned veterinary drug entities such as regional and woreda storehouses and dispensaries at veterinary clinics. According to the

panelists' opinion, mixed structure of the veterinary service and regulation, poor commitment of the government facilities to comply with regulatory requirements and political interference, are the reasons for the stunted regulation of public veterinary drugs distribution channel.

Three manufacturers, 84 importers, 85 wholesalers, and 1214 retail outlets are certified and licensed until 2018 (Table 5). But, the list of these institutions and those suspended and revoked their certificate of competence is not displayed or publicized in a way the public can easily access it. The experts explained that "some suspended institutions were found selling products because the buyers don't have information on which institutions are active, suspended or revoked." The list of retail outlets is not available centrally at VDFACA because regional regulatory bodies are not periodically reporting although article 23(4) of proclamation 728/2011 mandates them to submit reports to the Authority on certificates of competence they have issued, suspended and revoked.

Table 5: The number of certificate of competence (CoC) issued in the last five years

Institutions	**2014**	**2015**	**2016**	**2017**	**2018**	**Total**
Manufacturers	3	0	0	0	0	3
Importers	25	10	14	19	16	84
wholesalers	2	6	23	26	28	85
Retail outlets	NI*	NI	NI	NI	NI	1214

*There is no compiled information on the trend of certification

6.5. Inspection and Enforcement

6.4.1. Inspection of Veterinary Drugs Manufacturing Facilities

Compliance of manufacturing companies to GMP is one requirement for market authorization of products. VDFACA is using World health organization (WHO), United States Food and Drug Administration (USFDA), and Pharmaceutical Inspection Cooperation Scheme (PIC/S) GMP guidelines to conduct an on-site inspection of the manufacturers. The authority is following a line-based inspection and approval approach. There is no guideline on the selection criteria of GMP inspectors, reporting of findings, categorization of deficiencies and follow-up of corrective

measures to the findings. The inspectors complained that "due to absence of this guideline there are questions on the quality of inspection, subjective categorization of deficiencies and decisions, and reporting of inspection findings is sometimes taking more than six months".

In the last five years (2014-2018), 59 manufacturing plants were inspected and 55 of them found compliant and issued GMP certificate, while the rest four are dropped due to their non-compliance (Table 6). From those accepted manufacturing plants four lines are rejected because of their unsuitability for the production of products dedicated to those lines. Issued GMP certificates are valid for five years and shall be re-inspected to continue supplying products. There is also an immediate recognition procedure of cGMP certificates issued by countries with stringent regulatory authorities (SRA) (European Union member countries, USA, Canada, Australia & Japan) to manufacturing sites located in these countries. However, the authority is not accepting certificates issued by SRA countries to companies located outside of these countries. In the last five years, 26 GMP certificates of veterinary drug manufacturing companies issued by SRAs are accepted without a need for onsite inspection.

Table 6: GMP compliance status of manufacturing facilities inspected by VDFACA in the last five years

Facilities	**Quantity**
Total number of manufacturing facilities inspected	59
Compliant and issued GMP certificate	55
Non-compliant facilities	4 companies and 4 lines
Manufacturing companies got waiver of inspection	26

6.4.2. Inspection of Import, Wholesale and Retail Premises and Enforcement Procedures

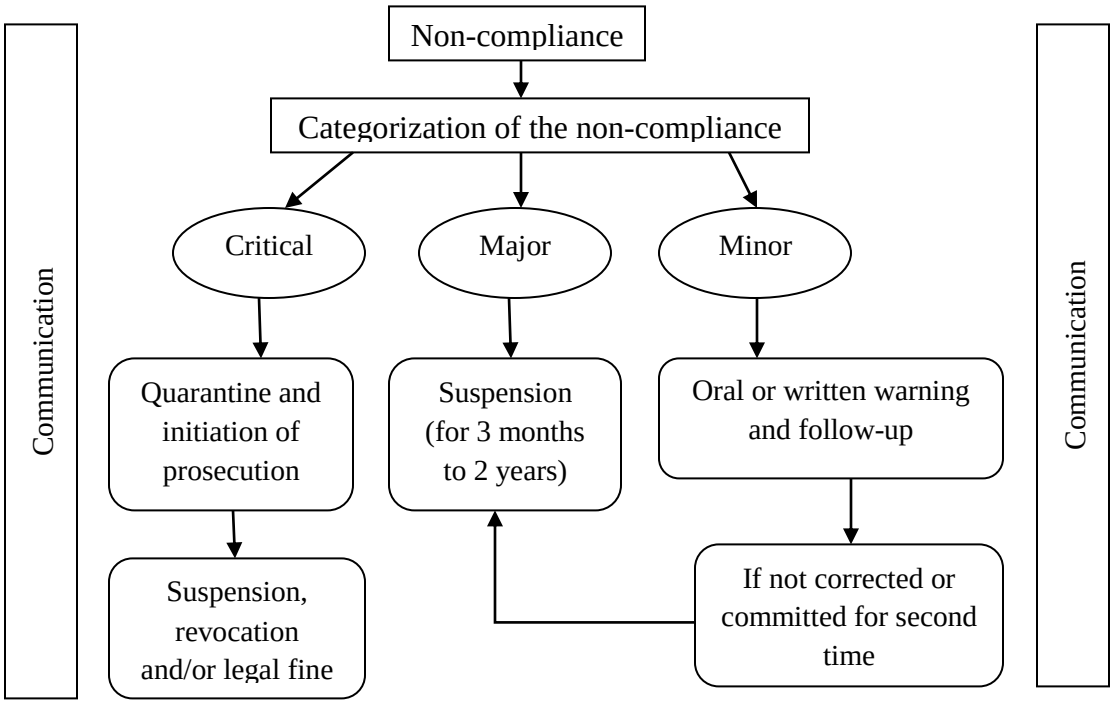
The authority has an inspection and branch offices coordination directorates with inspectors to inspect the premises and market channels and products at the ports of entry. The inspectors are given, by proclamation no. 728/2011, extensive powers and duties to control illegal veterinary drugs trade. The inspectors have the power to order quarantine of veterinary drugs suspected of being adulterated, counterfeited, contaminated, or those suspected to be dangerous to users until

such products undergo quality control test and the results are known. The inspector has also the power to enter, during working hours, any premise where veterinary drug trade is carried out or veterinary drug is stored; or stop any carrier loaded with veterinary drug and undertake inspection. He/she may inspect documents, records, prescriptions, and computers related to veterinary drug and take copies of such documents as may be necessary. The inspectors are also authorized to take samples of products for further regulatory investigations.

Veterinary Drugs and Animal Feed Administration and Control Proclamation no. 728/2011, Veterinary Drugs Import, Export and Wholesale Certification and Control Directive (VDFACA, 2014) and Veterinary Drug Retail Outlets Certification and Control Directive (VDFACA, 2015) are used as an inspection and enforcement tools. Inspection of the premises is conducted at least twice a year with the frequency varying depending on the compliance profile of the institutions. Physical inspection of imported products at ports of entry is also conducted to ensure their quality and rightful or validity. The coordination and communication between the port and market channel inspectorates is poor, as said by the panelists. They also exemplified this as "the port inspectorate is not routinely sharing the list of products released from the ports which could help the market channel inspectors for further follow-ups and to identify illegal veterinary drugs easily. The market inspectors are not also supporting the port inspectors in which products and on what issues to highly focus from their experience." The inspectors also mentioned that they found products in the market which do not have legal documents from the port inspection department. But, they couldn't get any information whether these products enter to the market through the legal routes or illegally via unauthorized borders.

Administrative and legal measures are being taken by the authority based on the level of noncompliance of the institutions and/or products. Once noncompliance is identified, it will be categorized as minor, major and critical deficiency and an enforcement measure will be initiated. Categorization of the deficiencies is made based on the certification and control directives and the internal SOP. The measures could be oral or written warning, suspension or revocation of the certificate, or penal fines depending on the level of violations of the legislation(s).

Figure 3: Enforcement procedure of veterinary drugs



In the years 2016-2018, a total of 65 regulatory non-compliances were registered. Within the indicated period, 52 written warnings were given, four institutions are suspended their license and one institution completely cancelled its certificate of competence (Table 7). There are also legal cases in the hands of prosecutors and judges.

Table 7: number of violations registered and enforcement measures taken

Violations and measures	**2016**	**2017**	**2018**	**Total**
Total number of violations registered	6	44	15	65
Enforcement measures				
Written warning	6	40	6	52
Fine	0	0	0	0
Imprisonment	0	0	0	0
Suspended certificate of competence	0	2	2	4
Revoked certificate of competence	0	0	1	1

Three products were suspended from three to six months because of adverse drug reaction reports from users; while 12 registration certificates were revoked because of quality defects identified through PMS (Table 8).

Table 8: Number of products suspended and revoked their market authorization

Measures	**2016**	**2017**	**2018**	**Total**
Suspended	0	1	2	3
Revoked	2	8	2	12

Unavailability of disposal directive and disposing facility were raised by the panelists as a challenge in control and disposal of veterinary drug wastes. They also added that large quantity of expired veterinary drugs are inappropriately stored allover the country waiting for disposal. According to the panelists, the inspectors are not independent to decide on the inspection findings. There are intrusions from the higher officials of the authority and coercing the inspectors to change their decisions. Low awareness of the law enforcing bodies (such as police, prosecutors and judges) on the veterinary drugs legislations and poor communication and harmonization between them are also resulting in dropping off enforcement cases.

6.6. Post-marketing Surveillance

The proclamation 728/2011 under its article (7) gives the mandate of carrying out post-marketing surveillance with a view to assessing the resulted benefit and damage of registered veterinary drugs to the authority. The market authorization holder (MAH) is also responsible to supply to the Authority the pharmacovigilance (PhV) information that he possesses related to the veterinary drug during the post-market surveillance. Inspection directorate is responsible to collect products from the market and submitting them to the quality control laboratory for quality analysis. However, guideline is not yet developed on the criteria for selection of products to be included in the surveillance, sampling procedure, and regulatory actions following surveillance reports.

The authority is now setting up a PhV system to monitor post-marketing safety and efficacy of products. “Guideline for adverse veterinary drugs event monitoring (pharmacovigilance)” is

developed and a reporting format (annex I) is under distribution to animal health facilities and professionals. Only a few awareness creation training has been given to professionals on the importance and procedure of adverse drug event reporting, due to financial constraints. Only free postage is set up as a media of reporting. Other media such as online reporting platforms are not optimized. The mandatory requirement of MAHs to conduct PhV and submit reports to the authority is not also implemented.

A total of 105 products were collected from market and tested in 2017 and 2018 and six of them found non-compliant. As the panelists said, product defects identified by PMS are communicated to regions and MAHs by written letters to take appropriate actions. Enforcement measures are being taken based on the legislative provisions depending on the levels of non-compliance. However, dissemination of this information to field veterinarians and animal owners is limited because the department doesn't issue regular bulletins and does not have a website through which it can disseminate information electronically.

6.7. Product Quality Analysis

The authority has a quality control laboratory, started operation in 2016, to analyze the quality of veterinary drugs. Animal products such as meat, milk, and honey are also tested in this laboratory to control residue level of veterinary drugs and pesticides in these products. The laboratory started implementing ISO 9001:2015 and ISO 17025:2017 to ensure the quality of the analysis. But, test methods are neither validated nor accredited by national accreditation office.

The authority is using official pharmacopeial (USP, Eur.Ph, BP, and JP) analytical methods and specifications for analysis of products. For those products not found on the stated pharmacopeias, validated manufacturer methods are used. However, there is no guideline to uniformly decide the acceptable limit of test parameters of different methods of different applicants for the same product. It was exemplified by panelists by citing antitrypanosomiasis drug products.

The laboratory is now conducting several test parameters such as appearance, identification, assay, physical tests (disintegration, pH, weight/content uniformity, solubility, and dispersibility), sterility and microbial limit tests (Table 9). Analysis of vaccines is currently outsourced to African Union Pan-African Veterinary Vaccine Center (AU-PANVAC), due to

shortage of trained analysts and analytical technologies. Biological assay methods required for analysis of some specific products are not started due to skill gap and shortage of consumables.

Table 9: Major test parameters conducted in VDFACA QC laboratory

Test Parameters	**Analytical techniques used**
Appearance	Visual inspection
Identification	High performance liquid chromatography (HPLC)
	Gas chromatography
	Fourier-transform infrared spectroscopy (FTIR)
	Ultra Violet (UV) Spectrophotometer
	Chemical test (color)
Assay	HPLC
	Gas chromatography
	Titration
	UV Spectrophotometer
Physical tests	Disintegration test
	Solubility test
	pH
	Weight/content uniformity
	Disperseability
Microbial limit test	Culture media
Sterility test	Culture media

According to the laboratory experts, the laboratory center is facing challenges related to legal mandates and shortage of laboratory equipments and consumables. There are hassles on the legal responsibility of animal products quality analysis while analytical facilities are established and analysts are recruited and trained. Hence, the authority is unable to make decisions on the quality of animal products. According to the panelists, there are difficulties to purchase specific

laboratory equipments and consumables due to tying articles in the national procurement directive and shortage of suppliers.

6.8. Monitoring of AMR and Drug Residues

Ethiopia has a strategy for the prevention and containment of antimicrobial resistance (FMHACA, 2015), which contains five strategic objectives with different priority actions to be conducted by both human and animal health sectors. The five strategic objectives are; raise awareness and understanding on antimicrobial use (AMU), strengthen knowledge and evidence of AMU and AMR through surveillance and research, improve infection prevention and contain the spread of resistant microorganisms, optimize the use of antimicrobials in human and animal health, and Strengthen and establish national alliances and partnerships, management and governance arrangements, and resource mobilizations for the prevention and containment of AMR. According to the panelists, VDFACA is doing several actions to support the efforts to achieve the strategic objectives to prevent and contain AMR. The authority is revising the veterinary drugs registration guideline to include requirements on resistance development data. Rational veterinary drugs use training manual (Achenef *et al*., 2016) is issued and trainings are given to several animal health professionals to raise awareness of the professionals on AMU and to optimize the rational use of veterinary drugs. Veterinary standard treatment guideline is also under revision to update it with new scientific recommendations on prudent use of antibiotics.

Regulation of veterinary drugs residue in Ethiopia is at infant stage. One analytical team is established at VDFACA's laboratory to test residue levels on animal products. The laboratory experts said, "Codex Alimentarius Maximum Residue Limits (MRLs) of Veterinary Drugs in Foods" (CODEX, 2018) is adopted as a standard of reference to monitor drug residues in animal-derived food products. Tests may also be done with reference to other national and international standards based on the requirements of the importing countries if the products are for export purpose. Currently, the laboratory has trained analysts and well-functioning analytical facility and they are doing pilot tests to validate their methods. Unavailability of clear and detailed legislation and tools related to residue regulation are the main reasons for the laboratory to delay starting of full time analytical works.

7. DISCUSSION

Results from this study showed that poor organizational structure, unavailability and/or obsolete regulatory legislations, unfavorable working environment, limited use of IT, and poor coordination between regulatory bodies and with other law enforcing bodies were the major challenges of the authority to conduct the regulatory activities efficiently. Furthermore, delayed registration time period, poor regulation of government owned veterinary drug facilities, and delayed implementation of QMS in the quality control laboratory were also the major limitations of the authority in implementing the regulatory functions.

Veterinary drugs and animal feed administration and control proclamation number 728/2011 is the primary legislation to regulate veterinary drugs in the country. Since proclamations contain general provisions by their nature, detailed provisions should be issued through subordinate regulations and directives to effectively implement and for practical enforcement of the proclamation. Proclamation no. 728/2011 under its article 28(1) has also given the power for Council of Ministers to issue regulations necessary for the implementation of this proclamation. However, implementation regulation subsequent to proclamation no. 728/2011 that would give detailed description and clarity of the provisions indicated in the proclamation has not yet issued except the Veterinary Drugs and Feed Administration and Control Authority Establishment Regulation No. 272/2012 and Service Fees for Veterinary Drugs and Animal Feed Registration and Licensing Regulation No. 325/2014. Food, Medicine and Healthcare Administration and Control Council of Ministers Regulation No. 299/2013 is an ideal example of secondary legislation which gives detailed provisions of the proclamation no. 661/2009. Ratanwijitrasin and Wondemagegnehu (2002) and OIE (2017) also recommend all regulatory bodies to have all necessary legislations for their activities at all levels of their functional or territorial organization. But in contrast to this, no region has its own legislation to regulate veterinary drug at its administrative territory. Therefore, all regions should adopt their own legislations consistent with the federal legislations to ensure the effectiveness of regulation across the distribution channel.

Veterinary drugs in Ethiopia are regulated by a separate agency VDFACA under the supervision of the Ministry of Agriculture. The world's leading animal raring countries China and Russia have also separate regulatory authorities (Chetana *et al.,* 2012). Even countries with smaller

livestock populations than Ethiopia such as Kenya (Regulations, 2017), Sudan (Omar, 2018), and some Middle East countries (Hassan, 2005) have independent veterinary drug regulatory agencies. Thus, it is appropriate to have an independent agency to ensure effective execution of all regulatory activities as Ethiopia has high livestock population with huge consumption of veterinary drugs. However, strong coordination should be established between the two sister agencies to cooperate and work together on common issues. As having a separate agency by itself is not enough for effective regulation, the authority should be properly structured to effectively implement all legally mandated regulatory functions and to avoid job overlaps identified by this study.

The regulatory functions are vertically distributed between federal and regional regulatory bodies. Even though this decentralization can minimize the cost of regulation and beneficial to nearly cover the geographical territory of the country (Ratanwijitrasin and Wondemagegnehu, 2002), the regulatory system is now highly fragmented. This agrees with the assumption of WHO (2003) on risk of regulatory fragmentation due to lack of unity of command in countries with multiple regulatory bodies of autonomous authority. It also correlates with the problems experienced in India (Chowdhury *et al*., 2015) that there is lack of uniformity in regulatory decision making and limited institutional communication channels between the regulatory bodies. In addition to this gap, no region has veterinary drugs regulatory structure which in turn resulted in high prevalence of illegal veterinary drug handlers and sellers at the lower market chain in Ethiopia as reported by Achenef *et al*. (2017). The VDFACA (2016) survey also indicated high prevalence of illegal veterinary drugs trade at open markets and in other shops with other commodities. The same problem was also reported by Suleman *et al.* (2016) in human medicines regulation in Ethiopia. This may result in to the negative impacts of ineffectively regulated veterinary drugs mentioned by FAO (2004) and Health for Animals (2017). Therefore, systems shall be established for an effective and coherent coordination and concerted efforts between the federal VDFACA and regional regulatory bodies to attain the same regulatory objectives. Inter-agency SOPs could also streamline the regulatory functions as recommended by Ratanwijitrasin and Wondemagegnehu (2002). Ball *et al*. (2016) mentioned that this harmonization improves operational efficiency and maximizes efficient use of resources.

The major factors for employee turn-over and difficulty to hire mentioned by Chejor *et al*., (2018) and Suleman *et al.,* (2016) including low salary and lack of attractive career structure and incentives were also raised by the employees of VDFACA. Cumbersome organizational structure, lack of freedom to make independent decisions, and safety fears are also mention by the study participants. Even though employee turn-over is not currently a problem for the authority, it is inevitable as far as these factors are not solved. The authority may face sever employee turn-over as shown in South Africa (Matsebula *et al*., 2005) which further leads to inefficient regulation of veterinary drugs. Multidisciplinary regulatory experts are essential for effective implementation of the regulatory functions. However, 92.7% of the regulatory experts were veterinary professionals (DVM, DVM+MSc. and BVSc.) (Table 2). Therefore, the regulatory authority should revise its human resource composition in a way to have regulatory experts with variety of qualifications in order to effectively implement the regulatory activities.

The ultimate financial source to conduct regulatory activities is government budget. Although the authority is collecting money from service charges, the authority couldn't able to reuse this money; which is the same as the problem experienced by FMHACA (Suleman *et al*., 2016) due to the national financial policy. The same is also reported by Ratanwijitrasin and Wondemagegnehu (2002) that in countries with full government budget, such as Cyprus, Malaysia, Tunisia and Venezuela, don't have the power to use the revenue they generate. Unlike the countries mentioned above, drug regulatory authorities in Australia, Netherlands and Zimbabwe are financed entirely by the fees and charges they collect. In these countries the service fees and charges reflect their overall running cost. But, it is difficult for VDFACA to provide its own funding entirely from service fees with the current volume and scope of regulation and the rate of charges for the activities. Charging for each regulatory activity and increasing the rate of existing fees can also have effect on the access of drugs and impose economic burden on the farmers. Therefore, government budget is important but the authority should also have legal power to re-use the revenue generated from service fees to solve the financial shortage the authority may face in the future when it fully implement all the regulatory functions.

Complete absence and/or obsolete regulatory tools are also among the findings of this study. This bucks with the concept of Smith (2013) on the regulatory body's responsibility to establish

and maintain up-to-date regulatory requirements and of ensuring the effective operation of the veterinary drugs regulation system. The registration guideline is in use since 2002; lacking with current scientific and administrative requirements. The products can't be properly evaluated if some assessment criteria are missed and this will allow authorization of unsafe, poor quality or inefficacious products. Guideline on technical requirements for registration of traditional veterinary medicines is not yet issued. Registration applications of traditional veterinary drugs are therefore dropped off that can negatively affect access of these alternative products to animal health care. On the other hand locally produced traditional veterinary drugs are available in the market with unknown quality, safety and efficacy profile where their risk may outweigh to their benefits. This shows poor implementation of the legal provision stated on article 13 of proclamation 728/2011 (FDRE, 2012).

Similar with the problem of lengthy registration time in developing countries reported by Narsai *et al*., (2012), the private sector panelists complained that the registration process is taking long time. This may affect accessibility of essential veterinary drugs. Therefore, the authority must have efficient processes for timely review decisions and effective and timely communications to satisfy the needs of stakeholders. The fast-track registration procedure, similarly reported by EFPIA (2017), is encouraging for the applicants to register minor-use and minor-species products and improve their access. Initial market authorization is not enough to celebrate and consider it as an ultimate and golden tool to ensure products entering the market are safe, efficacious and quality. Registration of products should be supported by strong PMS procedure to ensure that products are entering to the market according to their market authorization specifications. This is also important to screen out products with questionable quality (substandard and counterfeit) from the market (Kang *et al*., 2017). The PMS that VDFACA started is remarkable, but guideline should be developed according to WHO (2016) recommendation to guide officials in conducting the PMS and to avoid confusions and biases.

This study revealed that government owned veterinary drug entities are not properly regulated as privately owned ones though there is no legislation prohibiting regulation of these entities. It is believed that there are at least three veterinary clinics with drug stores and one temporary store house in each woreda. Each region has also a warehouse to hold products before distributing to the woredas. If these storage facilities and dispensaries are not regulated; we can't say quality

products are reaching the end users as this channel is taking huge share of veterinary products supply system. The whole chain of distribution shall be regulated with the aim of ensuring GMP, GDP and rational use of the products, regardless of who is distributing them.

The study participants raised their doubt on the quality of GMP inspections due to unavailability of GMP inspection guidance. Subjective categorization of deficiencies and delayed reporting of findings are among the short comings of the GMP inspection. If there is no guidance how the team of inspectors is established, there may be a bad composition of inspectors in terms of their qualification and experience which in turn results in poor quality of inspection and conflict of interest between the employees may arise. Uniformity of decisions and good governance should also be ensured by harmonisation of the classification of GMP deficiencies. Harmonisation will help ensure that there is a consistent view across inspectorates of what constitutes critical, major and minor deficiencies. If the GMP principles are adopted from international guidelines, the classification guidance should also be adopted at the same time. Guidance like "PIC/S guidance on classification of GMP deficiencies (PIC/S, 2019)" is easily accessible and can be adopted.

VDFACA established a good laboratory and the critical test parameters for drug quality analysis mentioned by IOM (2013) are now operational. However, there are some important tests for some specific products such as bioassay in which capacity is not yet built. Allowing products, requiring these tests, to enter to the market without laboratory quality confirmation may cost the country more than their benefits. Furthermore, although implementation of QMS and securing third party accreditation is among the strategic actions of the animal health strategy and vision of Ethiopia (MOA and ILRI, 2013), test methods are neither validated nor accredited. All higher officials of the authority should give attention to and the laboratory staff should put their legacy by implementing QMS such as ISO: 17025. Implementing QMS will improve credibility and trust of the results generated by the laboratory; and can also attract external customers which will help to generate incomes.

The efforts to struggle against AMR are encouraging. In addition to the common national strategy, it would be better to have a separate animal health strategy with specific actions to be implemented by the sector. The strategic objectives could be the same or emanated from the national strategy but with detailed animal health related intervention actions like the EMA

(2016) strategy. In developing the strategy, it would also be better if the strategic actions are in line with FAO (2016) and OIE (2016) action plans. Scientific recommendations and VICH guidelines on AMR should be considered in updating the registration guideline.

The authority couldn't still establish an IT system to enable applicants make online electronic applications and follow their status. Furthermore, access to veterinary drugs information, including registered products, licensed veterinary drug institutions and regulatory decisions, is limited by the absence of appropriate platforms for disseminating information and making it readily available to animal health professionals, consumers, the public and other stakeholders. This challenge is similar to the problem in India reported by Chowdhury *et al*., (2015). Users of products are therefore ill-informed about which products and/or institutions are legal and illegal, which may lead to the purchase and use of illegal and counterfeit products.

Poor coordination of the authority with other stakeholders is also revealed from this study. The same with the report of Suleman *et al*., (2016) dropping off cases are happening due to low awareness of law enforcing bodies (police, prosecutors and judges) on the veterinary drug legislations. Making available these legislations to all stakeholders with further awareness creation platforms could solve this problem. Written legislations and inter-agency standard procedures clearly defining the roles and responsibilities of all stakeholders shall also be established to harmonize the regulatory activities.

8. STRENGTHS AND LIMITATIONS OF THE STUDY

A multi-group expert panel was conducted to include various experts from all technical departments in order to get credible data about each regulatory activity. Private sector representatives were also included in the study to balance the perspectives of the study. Detailed review of regulatory legislations and different documents were also conducted to get full image of the regulatory framework.

However, other data collection methods such as observation of actual activities weren't used. In addition to this, regional experts could not be involved in this study due to unavailability of regulatory structure in the regions. As the research method was also an expert panel and at least five representatives from five regions had to come together and discuss, but there was limited financial and logistics capacity to do so. Institutions considered as stakeholders to the regulatory body such as police, judges and customs were not also included in this study.

9. CONCLUSION

This study showed that Ethiopia does have a regulatory legislation, veterinary drugs and feed administration and control proclamation number 728/2011, and VDFACA is established to execute this proclamation at federal level. Although this proclamation gives a vertical autonomous authority to federal and regional governments, the regions don't have either regulatory legislations and tools or organizational structures to regulate veterinary drugs in their administrative territory where the middle and lower distribution channel is left poorly regulated. In the world of regulatory harmonization in which countries are converging their regulatory requirements to work together, the coordination and harmonization between the two regulatory bodies and with other regulatory and law enforcing stakes was found very poor.

Almost all regulatory functions are available except the limitations on their full implementation. Delayed registration time, negligence in the certification and inspection of public veterinary drug distribution channel, unavailability of traditional veterinary medicines registration platform, unaccredited quality control tests, and poor monitoring of drug residues in food of animal origin are the major limitations in the implementation of regulatory functions.

Poorly structured organogram, obsolete and/or absence of some regulatory tools, unfavorable working environment and poor coordination with other regulatory and law enforcing bodies are shown as the major bottlenecks pulling back VDFACA from conducting its regulatory activities efficiently. Delivery of regulatory information to ensure accessibility of regulatory tools, decisions and veterinary drugs information to all stakeholders and product users is also tarried due to limited use of IT.

10. RECOMMENDATIONS

Strengthening the veterinary drugs regulatory system has dual purpose in improving animal health and protecting the public from zoonotic diseases and drug residue hazards from consuming poor quality animal products. Unreserved efforts are therefore required to strengthen the regulatory system by solving the current challenges at this infant stage before much more complex problems happen. The following recommendations are therefore forwarded:

- Organizational structure (organogram) of VDFACA should be re-structured in a suitable way to conduct all functional activities efficiently.
- Regional states should be initiated to draft their own regulatory legislations and to establish regional regulatory bodies.
- Systems and platforms shall be established to harmonize the regulatory activities and improve the level of communication and cooperation between the federal and regional regulatory bodies. Awareness creation programs on the legislations and regulatory importance of veterinary drugs are also important to pull all stakeholders to work together with the regulatory bodies.
- Detailed legislations and regulatory tools that can help to implement all regulatory functions such as implementing regulation and guidelines for registration, GMP and PMS should be developed and maintained up-to-date.
- Good work environment including attractive salary, incentives and freedom of independent decision making should be created to sustainably hold regulatory experts and to attract new ones.
- The regulatory authority should have efficient and predictable registration timeline to satisfy the stakeholders and customers need and to promote access of veterinary medicines.
- The quality analysis laboratory should fully implement QMS and be accredited to ensure that the laboratory is compliant with international standards.
- It is also better if the regulatory authority can have its own website and databases to disseminate regulatory information and all professionals, users and other stakeholders can easily access this information. Registration and licensing applicants can also save their time and money if an e-application system is introduced.

10.1. New Proposed Organogram of VDFACA

New organizational structure of VDFACA is proposed based on the findings of this study (annex II). In this organogram, related regulatory activities are organized in the same directorate. For example, Veterinary drugs institutions licensing and inspection activities are organized in the same directorate. Product surveillance team is also proposed to accommodate both quality and safety surveillance activities. New import and export directorate is proposed in order to handle all import and export related activities which were led by branch offices coordination directorate. This organizational structure can solve the conflicts of interest that have been experienced between different directorates. The laboratory structure is also changed from test method to sample based arrangement. The current branch offices were established following regional arrangements. But it was difficult to establish branch offices at each region and not cost effective. On this new organogram five new branch offices are proposed re-structured based on geographical directions of the country.

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ANNEXES

Annex I: Adverse drug event reporting form

Veterinary Drugs Adverse Event Reporting Form

1. Animal Information							
Species/Breed	Sex	age	weight	Physiological condition (eg. Pregnancy)	Number of animals treated on this	Number of animals reacted	Number of deaths

2. The Adverse Drug Event		
Date of onset of an adverse event		**Description of the adverse event:**
Duration of the event		

laboratory findings (if done)			**Postmortem findings (if any)**
Lab test	Result	test date	

3. Drugs suspected to have caused the adverse event

Trade and Generic Name:	Manufacturer:	Batch Number:	Expiry Date:

Route of Administration	Dose and Frequency	Date Started/Given	Date Stopped	Reason for use

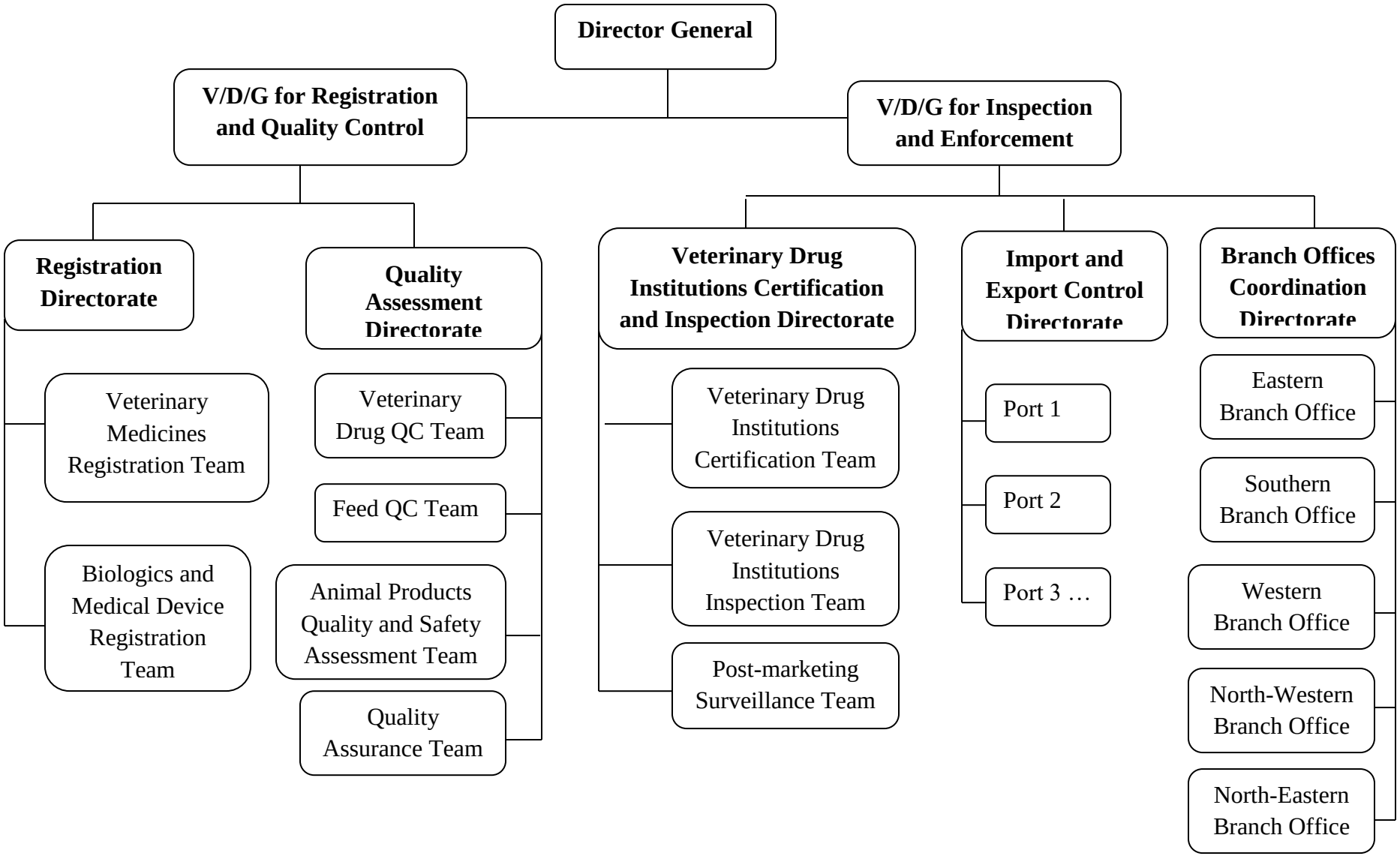
Details of products given concurrently		Drugs given after onset of the adverse event	

4. Product Quality Problems (Color change, change of odor, caking, precipitation, incomplete packs, poor packaging/labeling, etc.)	

5. Lack of Expected Efficacy	

6. Reported by:					
Name		E-mail		Phone No.	
Profession/Qualification					

Annex II: New Recommended Organogram for VDFACA



Annex III: Ethical Clearance Letter

በ ፋርማሲ ት/ቤት
የኢቲካል ሪቪው ቦርድ

አዲስ አበባ ዩኒቨርሲቲ
Addis Ababa University

School of Pharmacy
Ethical Review Board

ቀን Date: November 05, 2019

ቁጥር Ref. No.: ERB/SOP/125/11/2019

To: **Hailu Zeru**

School of Pharmacy

Re: Ethical Clearance

It is to be recalled that you submitted a study proposal entitled ***"Assessment of veterinary medicines regulatory framework in Ethiopia"*** for ethical approval by the School's Ethical Review Board (ERB). The Board thoroughly reviewed the proposal based on its operational guidelines and found it to fulfill all ethical requirements stipulated in the guidelines. This is, therefore, to inform you that the proposal is ethically approved for implementation.

With best regards,

Arebu Issa

Chairperson, ERB

☎ 00251156 02 12 ✉ 1176 ቴሌክስ Telex: 21205 ፋክስ Fax: 00251(11)1558566 ቴሌግራም Cable: AAUNIV

Annex IV: Expert panel participants' registration form

S/N	Name (Coded)	Gender	Age	Qualification	Job Position	Total work experience (Years)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

Annex V: Expert Panel Data Collection Tool

1. Regulatory Policy, Legislation, Structure, and Resources

1.1. Are the functions/job responsibilities of core departments of the regulatory authority clearly defined and there is no overlapping of responsibilities among the departments?

Yes ☐

No ☐

Please mention if there are overlapping responsibilities_____

_____

1.2. What is the source of budget for the regulatory functions?

Source of Budget	**Yes/No**
Government	
From internal revenue e.g. regulatory service fees	
Financial supports from non-governmental organizations	
Others; specify _____	

1.3. Is the regulatory authority fully independent of any political influence in making decisions on the regulatory activities given by the proclamation 728/2011?

Yes ☐

No ☐

1.4. If the answer to #1.3 is No, why, what and from whom are the influences? _____

_____

1.5. If the authority is not fully independent of decision making, what are the impacts of such interferences in the regulatory system? _____

_____

1.6. Is there an established system to allow exchange of regulatory information between veterinary medicines regulatory bodies, to harmonize activities and facilitate appropriate cooperation and collaboration between federal and regional regulatory bodies?

Yes ☐

No ☐

1.7. What are the structural and functional problems being seen between veterinary drug and animal feed administration and control authority (VDFACA) and regional regulatory bodies? _____

_____

1.8. Is there an agreement signed with regulatory bodies of other countries for cooperation and harmonization of regulatory system?

Yes ☐

No ☐

Please specify the regulatory bodies if there is an agreement _____

_____

1.9. What are the legislative, organizational structures, regulatory personnel and infrastructure related problems challenging the regulatory system?_____

_____

_____

1.10. What do you recommend to solve these problems? _____

_____

2. Product Registration (Market Authorization)

2.1. Are there written guidelines for evaluation and registration of different types of applications?

Yes ☐

No ☐

Type of application	**Availability**		**Last update of the guideline** (*if available*)
	Yes	No	
New chemical entity			
Generic products			
Biologics			
Medical devices			

Traditional veterinary medicines			
Re-registration			
Variation			
Fast-track			
Others (*specify*): _____			

2.2. Do you use international and/or other countries guidelines to support evaluation of applications?

Yes ☐

No ☐

2.3. If yes, which country guideline or standard is adopted and why? _____

_____

_____

2.4. Is there a fast-track registration system?

Yes ☐

No ☐

2.5. If the answer for #2.4 is yes, what are the criteria for the product to be processed through fast-track procedure? _____

_____

2.6. What is the average time taken to evaluate and register each product indicated below?

Category of products	**Average time taken for registration (days)**
Generic products	
Products containing a new active pharmaceutical ingredient	
Fast-track products	
Medical devices	

2.7. Is there an electronic system (data base, software, e-application system) to manage registration applications?

Yes ☐

No ☐

2.8. Are updated list of all products granted market authorization and their summary of product characteristics (SPC) regularly published and publicly available? If Yes, discuss how and if Not, why?_____

_____

2.9. What procedures are being followed to minimize the time between application submission and product authorization, improve quality of assessment and ensure the fairness of the registration system? _____

_____

_____

2.10. What are the major challenges related to product registration/market authorization? _____

_____

_____

2.11. What do you think are the possible solutions to improve the registration/market authorization system? _____

_____

3. Certification of Institutions

3.1. Is there a guideline for importers, exporters, wholesalers and distributors on the content of the application, the format and the procedure to follow in order to submit an application for certificate of competence? _____

3.2. Who is issuing certificate of competence for importers, exporters, wholesalers, and retail outlets? _____

_____

3.3. Do you think the federal and regional regulatory bodies are issuing certificate of competence in a uniform standardized format? If No, what are the peculiar differences and why? _____

_____

3.4. Are all regional regulatory bodies frequently reporting list of retail outlets certified to VDFACA and are centrally retained and accessible to the public? _____

_____

3.5. Are government owned and run veterinary drug entities (manufacturers and distribution channels) well regulated?

Yes ☐

No ☐

3.6. If the answer for 3.5 is No, why? _____

_____

3.7. Is updated list of veterinary medicines premises/establishments certified, and those suspended and revoked their certificate of competence regularly published and made publicly available? If Yes, how? If No, why?_____

_____

3.8. What are the major challenges related to certification of veterinary medicines premises? _

_____

_____

3.9. What do you recommend to solve the above challenges? _____

_____

4. Inspection and Enforcement

4.1. Are there directives or guidelines for inspection of distribution channel on the periodicity for inspection, categorization of noncompliance, follow-ups on deficiencies, procedure for administrative measures and legal prosecutions? _____

_____

4.2. What is the average frequency of inspection of domestic manufacturers, importers and wholesales? _____

4.3. Do inspectors have adequate powers and authority to carry on their inspection and are independent to make decisions? _____

4.4. Are there formalized structural and functional relationships between regional inspectors and inspectors at VDFACA? _____

_____

4.5. Is inspection of products at consignment and warehouses supported by technologies to identify falsified products? If Not, why?_____

_____

4.6. Does the inspectorate have GMP guidelines? _____

4.7. Do you use external GMP guidelines (such as WHO, PIC/S, OIE) to inspect manufacturing facilities? _____

4.8. Is there guidance on the selection criteria of GMP inspectors, reporting of findings, categorization of deficiencies and follow-up of corrective measures to the findings? _____

4.9. Is there documented procedure to accept GMP certificates issued by external bodies such stringent regulatory authorities? _____

4.10. What is the validity period of the GMP certificate issued? _____

4.11. Is there a written guideline or procedure for disposal of expired and defective products? _____

4.12. What is the regulatory enforcement procedure followed and which organizations/institutions are key players in the enforcement? _____

4.13. What are the major coordination problems between the internal law enforcing directorates and with external stakeholders in enforcing laws? _____

4.14. What are the major challenges in the inspection and enforcement activities? _____

4.15. What do you think the possible solutions for the above challenges to strengthen the inspection and enforcement? _____

5. Post-Marketing Surveillance

5.1. Is there a structure and designated experts to conduct post-marketing surveillance (PMS)? _____

5.2. Is there a written PMS guideline indicating the procedure, criteria for selection of products to be included in the surveillance, sampling procedure, and regulatory actions following surveillance reports? _____

5.3. What are the criteria to categorize products in PMS and which products are categorized as high risk products to be surveyed frequently? _____

5.4. Is a pharmacovigilance system (guidance, structure, personnel, and tools) established? Is it functional, if not why? _____

5.5. Is there an online adverse drug event (ADE) reporting system? _____

5.6. Is ADE reporting forms easily accessible to animal health professionals and the public? __

5.7. Is it a mandatory requirement for a marketing authorization holder to conduct pharmacovigilance and submit reports to a regulatory authority? _____

5.8. How is the product defect identified by PMS communicated to stakeholders and the community? _____

5.9. What are the major challenges in the PMS system of veterinary medicines? _____

5.10. What do you think of the possible solutions for the above challenges? _____

6. Quality Analysis Laboratory

6.1. Which standards are used as a reference for the analysis of products?

- ☐ USP
- ☐ Eu.Ph./BP
- ☐ IP
- ☐ Manufacturer Method
- ☐ In-house Method
- ☐ Other,(specify):_____

6.2. Does the VDFACA laboratory implemented and certified for quality standards (ISO)? Which standard(s) are implemented and granted certificate? _____

6.3. Are all analytical methods validated? If not, how many and which test methods are validated? _____

6.4. How many tests are accredited by the national accreditation office? _____

6.5. Which products are being analyzed in the laboratory?

Product	**Yes/No**	**Remark**
Veterinary drug		
Vitamins and minerals		
Veterinary medical equipment		
Vaccines		
Residue in animal products		

6.6. Which tests and methods are performed by the laboratory?

Tests	**Yes/No**	**Analytical technique used**
Appearance		Visual inspection Other(s)
Identification		☐ HPLC ☐ GC ☐ TLC ☐ FTIR ☐ Spectrophotometer ☐ Chemical test ☐ Other(s)
Assay		☐ HPLC ☐ GC ☐ TLC ☐ Titration ☐ Spectrophotometer ☐ Biological assay ☐ Other(s)
Physical tests		☐ Disintegration test ☐ Dissolution test ☐ Friability test ☐ pH ☐ Weight/content uniformity ☐ Other(s)
Microbial limit test		☐ Culture media

		☐ Other(s)
Sterility test		☐ Culture media ☐ Other(s)
Potency test (for vaccines)		☐ Titration ☐ Other(s)
Other (specify)		

6.7. In which animal products is drug residue level monitored? Meat ☐ Milk ☐ Honey ☐ Egg ☐ Others _____

6.8. Which maximum residue limit (MRLs) standard is used in testing drug residues?

MRLs Standard	**Yes/No**
National standard	
CODEX	
EU standard	
US standard	
Other(s)	

6.9. Do you outsource tests that can't be tested in your laboratory? Which tests and to which laboratory are you outsourcing?_____

_____

6.10. What are the major legislative, organizational structure, equipment and supply and personnel related challenges in the laboratory? _____

_____

6.11. What are your recommendations to solve the above challenges? _____

_____

Annex VI: Data Collection Tool for Private Veterinary Drug Actors

1. What are the major regulatory gaps/challenges with regard to the following regulatory functions?
    a. Registration of products _____
    _____
    b. Certification of institutions (institutional certificate of competence) _____
    _____
    c. Inspection of premises and products _____
    _____
    d. Post-marketing surveillance _____
    _____
    e. Quality control laboratory _____
    _____
2. What problems do you face related to the regulatory structure and human resource (skill, knowledge and attitude)?
    _____
    _____
3. What are the challenges related to legislations (proclamation, directive, guideline, etc.)
    _____
    _____
4. Can you mention the strengths of the regulatory system?
    - _____
    - _____
    - _____
5. Any other issue you want to forward/add _____
    _____
    _____

Annex VII: Archival Review Tool

I. Regulatory Legislations, Regulations, Organizational Structures and Resources

1. Legislative history of veterinary drugs regulation (title(s) and date(s) of enactment of the different veterinary drugs legislation/regulations previously and currently used to regulate medicines in the country).
2. Legislative provisions on regulatory functions (registration, inspection, certification, post-marketing surveillance, pharmacovigillance and product quality analysis)
3. Organizational structure (Organogram) of VDFACA and Regional regulatory bodies
4. Number of staff working in the regulatory authority
5. Financial resource of the regulatory authority and five year trend of annual budget and its consumption.

II. Product registration (Market authorization)

1. Number of registration applications, evaluated applications and registered products in the last five years

Activities	**2014**	**2015**	**2016**	**2017**	**2018**	**Total**
Total number of applications						
Number of evaluated applications						
Number of authorized products						

2. Types of products registered in the last five years

Types of products	**Number of registered products**
Veterinary drugs	
Biologicals (vaccines and hormones)	
Medical equipments	
Traditional medicines	

3. Number of products suspended and revoked their market authorization because of quality, safety and efficacy issues in the last five years.

Measures	2014	2015	2016	2017	2018
Suspended					
Revoked					

III. Certification of veterinary drug institutions

1. The number of certificate of competence (CoC) issued in the last five years?

CoC		2014	2015	2016	2017	2018	Total
Issued	Manufacturers						
	Importers						
	wholesalers						
	Retail outlets						
	Traditional medicine producers and dispensers						

IV. Inspection and Enforcement

1. cGMP compliance status of manufacturing facilities inspected by VDFACA in the last five years

	#
Total number of facilities inspected	
Compliant and GMP certified	
Non-compliant facilities	
Number of companies accepted their cGMP certificate from SRA countries	

2. Violations registered and administrative measures and judiciary sanctions applied in the last five years

	2014	2015	2016	2017	2018
Total number of violations registered					
Number of administrative measures implemented by the regulatory authority					
Number of legal sanctions implemented by a judicial body/court					

3. Number of enforcement measures taken in the last five years

Enforcement measures	2014	2015	2016	2017	2018
Written warning					
Fine					
Imprisonment					
Suspended certificate of competence					
Revoked certificate of competence					

V. Post-Marketing Surveillance (PMS)

1. Number of samples collected by PMS and their compliance status in the last five years

	2016/17	2017/18
Total number of samples collected		
Number of products found non-compliant		

2. Available pharmacovigillance tools (guidance, reporting form, human resource, etc)

VI. Quality Analysis

1. Quality certificates such as QMS and accreditation certificates

VII. AMR and Residue Monitoring

1. National AMR strategy
2. Legislative provisions and national standards on AMR and veterinary drug residues