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Veterinary Medicine: Drug Approval Process in Europe and USA

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Abstract:

Veterinary medicine ensures a safe food supply for people by keeping the health of food-producing animals. Veterinary medicine has play important role in order to maintain the animal and human health. The regulatory authorities US-FDA and EMA have their own regulations & guidelines for veterinary product approvals and the applicant has to follow strict and stringent procedures to get market-authorization in their countries. The products may be the same but the required documents, timelines and approval procedures are different for US & EU. In US, Center for Veterinary Medicine regulates the veterinary medicine. The New Animal Drug Application (NADA) should be provided to USFDA in e-CTD format. The EU cannot accept the submission in eCTD format; using e-submission is mandatory for all veterinary submissions, i.e., MAA Vet Forms of 1.23.1.1 version and this should be submitted to the CVMP. Regulatory guidelines and other notification for applicants are available in EudraLex-Volume6. Understanding the variations in registration method may leads to deviation in submission approach. This helps us to smooth review process without delays and failures.

Key Words: CVMP, CVM, NADA, Veterinary.

INTRODUCTION

Regulatory approval of veterinary medicinal products is a mandate and rigorous process to safeguard the quality, efficacy and safety of the new drug to both animals and humans which plays an important role in food chain.

The United States of America and Europe are the two primary administrative offices on the planet separated from Japan. US is a solitary nation yet EU is an association of nations. Accordingly, the Drug endorsement process in both the administrative organizations has been fallows the different procedure.

Objective is to understanding the approval procedures to get the market authorization in the EU and US.

This topic gives the information about reviewing reviewing the medication documenting and various parts of getting United States Food and Drug Administration (USFDA) and European Medicines Agency (EMA) endorsement for a medication so as to get a Marketing Authorization in US and Europe and their successful job in improving the guidelines set somewhere near them.

APPROVAL PROCESS IN EUROPE

The Europe Veterinary Healthcare market is estimated to register a CAGR of around 5% during the forecast period, 2018 to 2023. Veterinary medicines are includes the treatment, diagnosis, and prevention of diseases among animals. It covers a variety of animal species, both, in domestic and wild. Based on geography, European veterinary healthcare market is analyzed under various regions namely UK, France, Italy, Spain and Germany. Europe has the dominating share in the global wide market.[1]

ORGANIZATION STRUCTURE (FIGURE: I)

In Europe to get approval for veterinary medicine, marketing authorization application will be submitted to authority (EMA), before that the pre submission meetings are held with applicants, by this applicant will obtain the procedural and regulatory advice from the agency. To consult the agency request form has to be filled and it fallows the content of the guidance “Veterinary pre-submission questions and answers”[2]

The left out information required for the pre-submission meeting are submitted to veterinary application team form, before 6 weeks of the proposed date of meeting.

The regulatory requirement for medicinal products for veterinary use are given in the EudraLex – volume 6, this is very helpful for the applicants. The procedural and other regulatory prerequisites, for renewal processes, dossier necessities for variations of Type IA/IB, product characteristics summary, (SPC), data on package and segregation of product for the supply, label clarity and requirements for the leaflet of package are given in the publications of Volume 6 (The rules governing medicinal products in the European Union").[3]

The procedures for the marketing authorization are given in the volume 6A. This notification to Applicants regarding veterinary drug products. has been set up as per Article 31 of Regulation (EC) 726/20042 and Annex I of Directive 2001/82/EC3 on the Union code.

According to Directive 2001/82/EC of Article 71, the production, importation and usage of immunological veterinary drug products may be precluded.

There are two types of authorizations national and union authorizations.

National authorization: The competent agencies of the Member States are in charge of permitting approvals for veterinary restorative items which are put on their business sectors, aside from veterinary therapeutic items which are approved under Regulation (EC) No 726/2004 ("Union Authorizations").[4, 5]

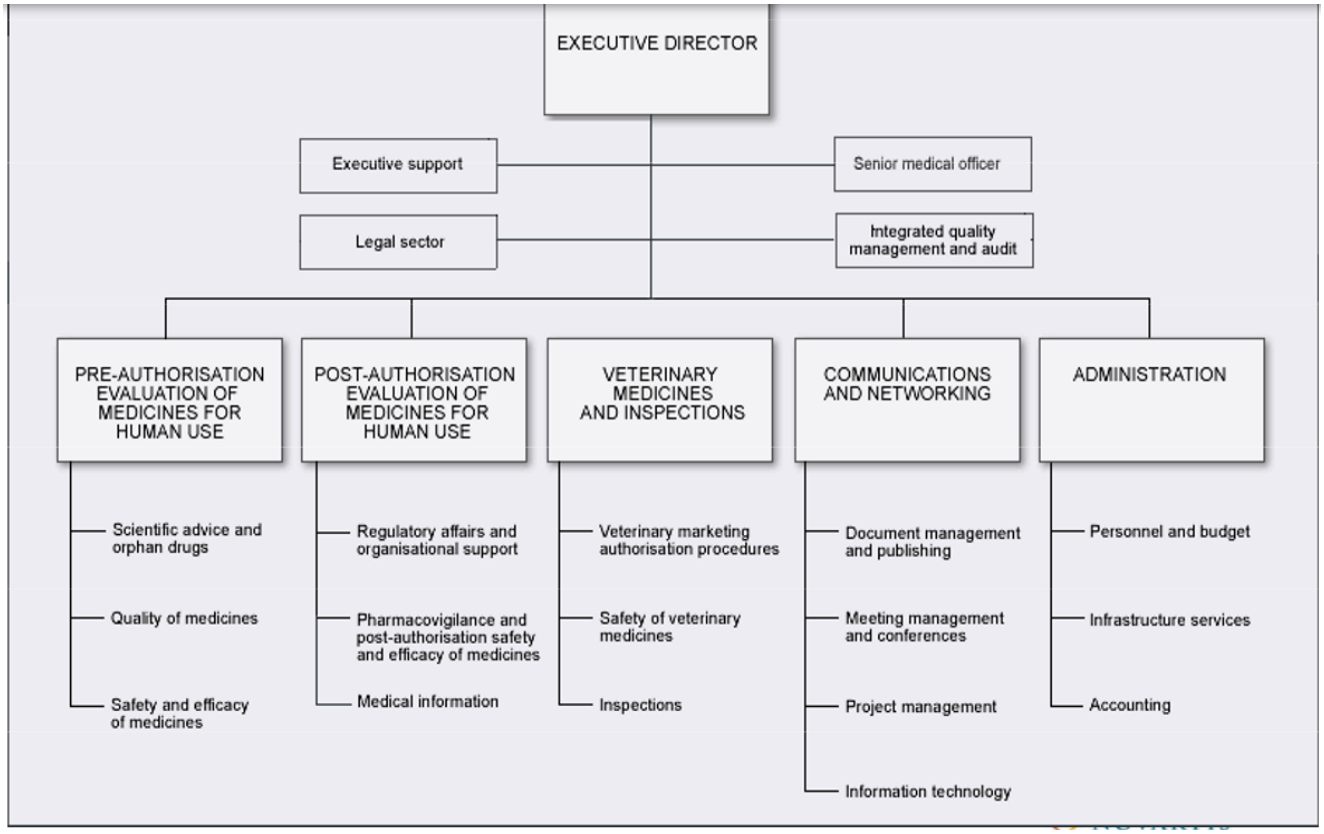


Figure: I : organization chart of EMA

This is the organization structure of the EMA, the head is the executive director, and this consist the 5 division, in that veterinary medicines and inspections is also one of them, veterinary division includes the veterinary marketing authorization procedure, safety of veterinary medicine, and investigation.

By fallowing the mutual recognition procedure, sponsor may submit an application in concerned member states to market their similar veterinary drug products in two or more member states. This procedure can be fallowed, only when national authorization are demanded for the same product in more than two member states.

If the product is not authorized to market in the union, The applicant may submit marketing authorization application through decentralized procedure to get marketing authorization in all member state in a single approach by choosing one of them as reference member state. and according to Directive 2001/82/EC of Article 14 marketing authorization must include product characteristics summary and labelling & package leaflet should be comply with Articles 58 to 61.[5]

Union authorizations: Marketing authorizations conceded in the Union will have an underlying term of five years as per Directive (EC) No 726/2004 of Articles 39(1) & directive 2001/82/EC of article 28(1). After 5 years it should be reestablished based on a re-assessment of the benefit/risk balance.[5]

In Europe the different procedures are fallowed for the submission of application they are

1. Centralized procedure
2. Decentralized procedure
3. Mutual recognition method
4. National procedure

Centralized procedure

The product can be marketed in the entire European union by using this procedure. So it can be marketed in all member states.

Decentralized procedure

The candidate may demand more than one Concerned Member States to affirm a draft evaluation report, product characteristics summary, naming and leaflet of package as proposed by the selected Reference Member State if the veterinary products not falling inside the obligatory extent of the centralised procedure.[5]

Mutual recognition procedure

This methodology depends on the shared acknowledgment by Concerned Member State of a national marketing authorisation conceded by the Reference Member State. The Concerned Member State alludes to the Reference Member State that issued the national marketing authorisation on which the shared acknowledgment strategy is based. Toward the finish of the mutual recognition methodology, a national showcasing authorisation will be issued in the Concerned Member State.[5]

National procedure

This is also known as Independent national procedures will continue, but are strictly restricted to veterinary drug products which are not to be approved in more than one Member State.

Directive 2001/82/EC provides the legal requisites for making an application for different purposes, they are as fallows(Table No: 1)

We have to refer the different articles for guidelines, based on the product to be marketed.

After collecting all the information and documents presentation of the dossier and content of the dossier should be arranged as mentioned in the volume 6A. The electronic application form is mandatory for applications, authorizations, variations, and renewals. Then word based application form is replaced by electronic application form with new options like electronic data import/export, data population within the form. The electronic Application Forms (eAF) of version 1.23.1.1 is now available. MAA-Vet Form 04-02-2019 along with this they also released notes which include the differences they have made from the old version.[6]

Submissions for veterinary dossiers in eCTD format cannot be accepted by the Agency. However, in some specific cases, parts of the quality dossier could be accepted by the Agency in CTD format. The dossiers are submitted in the EMA submission gateway, and which is made mandatory from 1 January 2017. The applicant has to register to use EMA e submission gateway and for electronic submissions hard copy of cover letter is not required.[7]

The CVMP members are accepts the dossier in electronic format and MRL applications.

The structure of dossier is as fallows, it contains 4 parts they are

Part 1: Administrative information and summary of the dossier.

Part 2: Quality

Part 3: Safety

Part 4: Efficacy

For centralized procedures, only one submission should be provided, even if the product contains different strengths, pharmaceutical forms or target species which could eventually result in a large number of different presentations. For individual presentations, the strength, pharmaceutical form and/or target species concerned are clearly mentioned in the dossier. The product information files are submitted to the Agency in Word format under “add info”, and should be named as fallows: Product Name-V-Procedure Number-pi-language code. If a dossier fails the technical compliance check it is still possible for an applicant to provide the corrected electronic format during the technical validation period.[7]

As per the Directive 2001/82/EC of Article 1(22), as revised, it ought be noted that the name of the medicinal product “may be either an invented name not liable to confusion with the common name, or a common name or scientific name accompanied by a trade mark or the name of the marketing authorization holder”. It is also understood by legislation that a common name is, according to Article 1(23) of Directive 2001/82/EC, as amended, “The international nonproprietary name (INN) recommended by the World Health Organization, or, if one does not exist, the usual common name”.

DEVELOPMENT OF NEW ANIMAL HEALTH PRODUCT

1. Chemistry
- ✓ Chemical development
- ✓ Pharmaceutical development
- ✓ Analytical development

2. Preclinical studies

- ✓ Pharmacology
- ✓ Toxicology
- ✓ Pharmacokinetics
- ✓ Residue studies

3. Clinical studies

4. Registration phase

REVIEW OF APPLICATION

The Agency will send a compilation of the written QRD comments to the applicant at the latest by Day 155.

Initial (Full) Marketing Authorization application assessment timetables (table No: 2)[8]

LABELLING: Member States would not accept use of an alternative mutually-agreed language (other than the official language of the Member State) for the immediate and secondary packaging. And this rule is amendment of article 61.

Pictograms and standard abbreviations are used on packaging and labelling of veterinary medicines to decrease the wording that translation requirements, [9]to enable the use of multi-lingual packaging, to facilitate the improved availability of animal drug products in small markets.

FEES

Marketing-authorization application (single strength, one pharmaceutical form, one presentation) From €143,700[10]

In order to obtain approval we should give the justification for the drug will be safe for using in animals, environment, and humans also. The justifications are like how the drug is used, how does it works, what are the benefits of the drug have been shown in studies, the risks associated with the drug, the precautions for the person who gives the medicine or comes in contact with the animal, the withdrawal period in food producing animals, and other information about the drug should be submitted to the agency. Dossier contains the summary of the product characteristics, this document includes the different annex.

- Annex I - Product characteristics Summary
- Annex IIA - Manufacturing-authorization holder responsible for batch release
- Annex IIB - The marketing authorization Conditions
- Annex IIIA - Labelling
- Annex IIIB - leaflet of Package[11]

The Committee for Medicinal Products for Veterinary Use (CVMP) is the committee that is responsible for preparing the Agency's opinions on all questions concerning veterinary medicines.

THE STABILITY TESTING

This reports also should be included in the dossier, To understanding the effect of environmental factors on the drugs quality varies with time, stability testing are used. Environmental factors are like temperature, moistness, and light, are considered to find out the re-trial for the medication substance or a time span of usability for the restorative item and suggested stockpiling conditions. The guidelines on the stability testing are available in the VICH (Veterinary International Committee on Harmonization) GL3 guideline, this guideline comprises the fallowing information:

- Defines new drug's stability data on package
- It explains the content of the registration application for new chemical entity and related medicinal product
- Information regarding abbreviated application, variation, etc.. are not included.[12]

BIOEQUIVALENCE STUDY

Bioequivalence study requirements are very essential to confirm the efficacy & safety of the veterinary medicines, During advancement of an item containing a NCE or a known dynamic substance, bioequivalence ponders or other similar pharmacokinetic information might be required as crossing over investigations between various plans for example among essential and early clinical preliminary definitions. Examinations identifying with the restorative item ought to guarantee prompt discharge properties and demonstrate comparability between the insightful items, for example test and reference veterinary therapeutic item ought to have a comparative in-vitro disintegration considering physiologically important test pH conditions.[13]

The primary accomplishments of naval Regulation (EU) 2019/6 on veterinary medicinal products are as fallows

- contemporary, advanced and fit for legal framework purpose are provided
- provides incentives to encourage the new innovation
- to make, use of veterinary medicine by giving incentives
- strengthens the action of EU to encounter antimicrobial resistance

VOLUME 7 - SCIENTIFIC GUIDELINES ON VETERINARY MEDICINAL PRODUCTS

The CVMP prepared the scientific guidelines to governs the veterinary medicinal products in the European union, these guidelines helps to applicants to prepare the marketing authorization application for medicinal products for the veterinary use.[14] By this applicants understood that basis for practical harmonization of the manner in which the EU member states and EMA interpret and apply the detailed requirements for the demonstration of quality, safety, efficacy contained in the community directives. This also tells that in such a manner that will be recognized as valid by the EMA.

At the time of submission the applicant should justify the deviations from the guidelines if any, before that they should seek the scientific advice to discuss the propose deviations during medicine development.

CLINICAL TRIAL

The clinical trials are conducted to determine the impact of veterinary drugs on the animal subjects which are taken for the study, during the study safety, effectiveness, ADME (Absorption, Distribution, Metabolism, Excretion) and product residue in target species will be assessed. adequate pharmacological, toxicological and pharmaceutical/immunological information should be present on the product to justify the product is accessible.

APPROVAL PROCESS IN USA

Over the past 5, the veterinary services in the US industry has grown by 5.4% to reach revenue of 49 billion dollar in 2019. In the same timeframe, the number of business has grown by 1.6% and the number of employees has grown by 2.3%.

In USA also we need to fallow certain procedure to get authorization from the authority to market the veterinary drugs in the USA. The requirements for approval process are given in the code of federal regulation (CFR) tittle 21, part 514.1.[15]

In USA to get market authorization for the veterinary medicinal products we need to apply New Animal Drug Application ie.,NADA and for the generic veterinary products Abbreviated New Animal Drug Application (ANADA).

The types of information should be included in the NADA application are as fallows

1. **Chemistry, manufacturing and controls**: This section includes the information on manufacture of new animal drug active ingredient. It also includes information on personnel, facilities, containers, components and composition, manufacturing procedures, GMP compliance.
2. **Effectiveness:** this section involves the studies which are conducted by the sponsor that they ensure the effectiveness of the product. Dose validation, dose determination & dose titration informations should be present in the effectiveness section of an application.
3. **Safety to the target animal species**:. The toxic syndrome related to the drug & the boundary of safety use of the product in the treated animal are included in this section

   This section also assure the safety of humans because while administer they may come into contact with the drug.
4. **Human food safety:** The human food safety section may include short and long term toxicology studies, total residue and metabolism studies, analytical method validation studies, and tissue residue depletion studies. This is especially for the food producing animals, these studies shows that whether the drug is present in the food or any other unwanted growth in the food. Also provides the quantity of drug present in it.
5. **Labelling:** The NADA sponsor must give the Labeling. Blue bird labels submitted by sponsor of the

type A article as apart of the NADA application. This includes the final copies of the container labels, package and all other labelling components i.e. associated with the product.

6. **Environmental assessment:** The environmental information should be comply with the National Environmental Policy Act (NEPA). The potential effect of the product on the environment is important for the approval of drug. Environment assessment is performed to determine the the environmental impact statements (EIS) or the EA document is used for the justify the finding of no significant impact (FONSI).
7. **Freedom of information (foi) summary (food-producing animal species):**
   This section includes the studies which are considered by the agency for the approval of drug and summary of the environmental assessment. These information should be made available to the public after the approval of drug.[16]

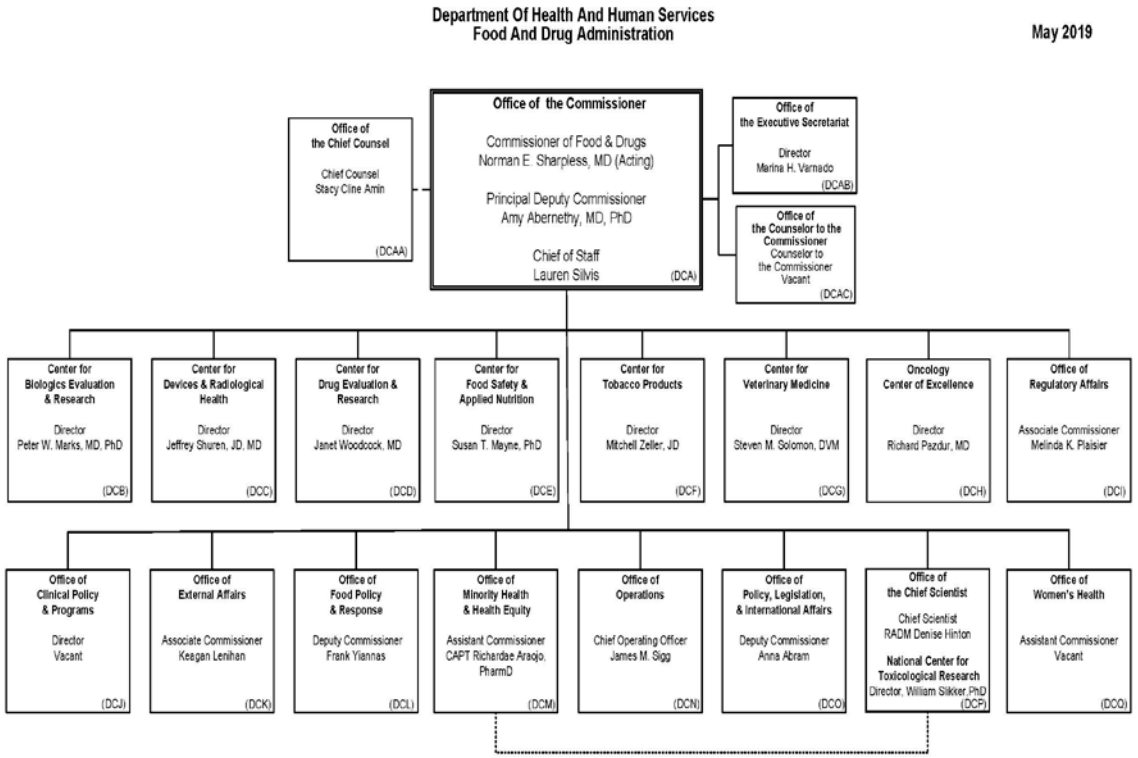


Figure No: II : Organization chart of the USFDA
This is the organization structure of the USFDA, Office of the commission is head of the organization this includes the 16 division and centre for veterinary medicine handles the approval process of the veterinary drug products

ORGANIZATION STRUCTURE (FIGURE NO: II)

The laws and authorities which governs the approval process in the USA are the

1. FFDCA: Federal Food, Drug and Cosmetics Act (figure No: 3)
2. FDA: Food and Drug Administration
3. CVM: Centre for Veterinary Medicine
4. ONADE: Office of New Animal Drug Evaluation
5. OMUMS: Office of Minor Use and Minor Species
6. Animal Drug Availability Act of 1996

Approved new animal drug means the drug should undergone the NADA process and has received CVM'S stamp of approval. The two more things CVM consider when NADA process are

1. Drug impact on environment
2. The safety of people who administer the drug to animal

Dossier format for submission in USFDA for the submission of dossiers is electronic common technical document. (figure No:

TIME FRAME: 180 day from the date of the application to approve the application.

SUBMISSION OF APPLICATION**:** The dossiers are submitted electronically through the electronic submission gateway. electronic system helps to optimize the timeliness and accurate submissions. Extensible markup language (XML) files in a SPL format adopted by the FDA for submission files. These are the steps involved in the registration process

1. The applicant has to register with CVM Electronic submission system by sending original signed paper registration letter to CVM.
2. Form FDA 3538 i.e. CVM ESS Manage form is submitted to CVM
3. Electronic & paper acknowledgement received from CVM

4. Digital signature created by adobe is submitted by registered sponsor in FDA Form 3538
5. Electronic submission gateway of FDA is established by the agency for regulatory electronic submissions.
6. FDA ESG allows the review of regulatory information.
7. After completion of all the registration process the CVM ESS account will be activated.
8. Then sponsor can start sending electronic data to CVM by using ESG.

   The general reason for the FDA ESG is to give an incorporated, Agency-wide interchanges point for safely getting electronic submissions.[17]

   The steps involved in drug establishment are

   1. Drug listing data & establishment registration of drug are provided for electronic submission by the sponsor to establish their drug
   2. SPL standard format is used for the submission of data
   3. Data is based on the HL7, CDA & Reference data model

   The code & code sets are used fro the easy review & archive the submissions, these codes can be easily recognized by the computer system. such as unique ingredient identifiers and data universal numbering system (DUNS) Number.[18]

   FEES: The ADUFA (Animal Drug User Fees Act) gives fees for the veterinary drug application $449348.[19]

LABELLING:

Labels and labeling for drugs sold in the United States must be in English, labelling requirements are mentioned in the 21 CFR 501. The product label must contain the following: - The proprietary and established name of the drug; - lot control number; - name of manufacturer, packer (if any) or distributor, country of origin (if applicable); - expiration date; - statement to refer to any accompanying leaflet for use of the product; Complete drug use information must be provided in an accompanying leaflet or insert.

ASSURANCE FOR SAFETY OF THE VETERINARY DRUG:

The sponsor has to ensure the quality of the veterinary medicinal products in the two phases, in the first phase the product should be manufactured under the GMP compliances, and other conditions which influences has the suitable quality and standards of the resulting drug product. In the second phase continued monitoring of the drug when the drug product is entered into the market, they are supervised by pharmacovigilance, examining and testing of items available in the market, & manufacturing site inspection. Residue limits in the veterinary products alos may affect the quality of the product.

STABILITY GUIDELINES

Section 512(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 360b) establishes the requirements for new animal drug approval. 21 CFR 514.1 specifies the proper form and the information required to be submitted. As per the section 514.1(b)(5)(x) that an applicant has submit data from completed stability studies as well as information regarding studies that are ongoing to validate the request for a exact expiration date and give data on the stability of the medication items.

BIOEQUIVALENCE STUDIES

These studies are used in different situation, these studies are required for the generic, new animal as well as supplemental NADA application, even it is also need for for the change of route of administration & dosage form because these also may affect the bioavailability. These studies should comply with the GLP guidelines as mentioned in the 21 CFR part 58. The general principles of these guidance is applicable for both ANADA & NADA's.

VICH

VICH (Veterinary International Committee on Harmonization) is multinational programme. It was established in April 1996. The function of this VICH is to harmonize information & studies required by the regulatory authorities involved in the VICH. The European Union, USA, Japan are the members of the VICH.

The main goals of VICH are:

- To meet the quality, wellbeing and viability measures, VICH implemented the harmonized technical information needed for the veterinary products in VICH regions. This also reduces the use of animals for the study and expenditures of product development.
- Basis for registration necessities for international harmonization is given by VICH
- Monitor and keep up existing VICH rules, taking specific note of the ICH work program and, where essential, update these VICH rules.[20]

The VICH has given certain guidelines related to the veterinary medicinal product approval process and studies and other requirements. Out of these guidelines few guidelines were adopted USA and Europe. (refer table:3)

Table No:1 Prerequisites for making an application

Articles	
13	Applications for generic veterinary medicinal product, "hybrid" veterinary drug products and Biosimilar veterinary drugs.
13a	applications depend on on well established veterinary use supported by bibliographic literature
13b	novel fixed combination products applications
13c	Informed consent from a MAH for an authorized veterinary drug products
13d	regarding the derogation for immunological veterinary products

Table No:2 Marketing Authorization Application assessment timetable

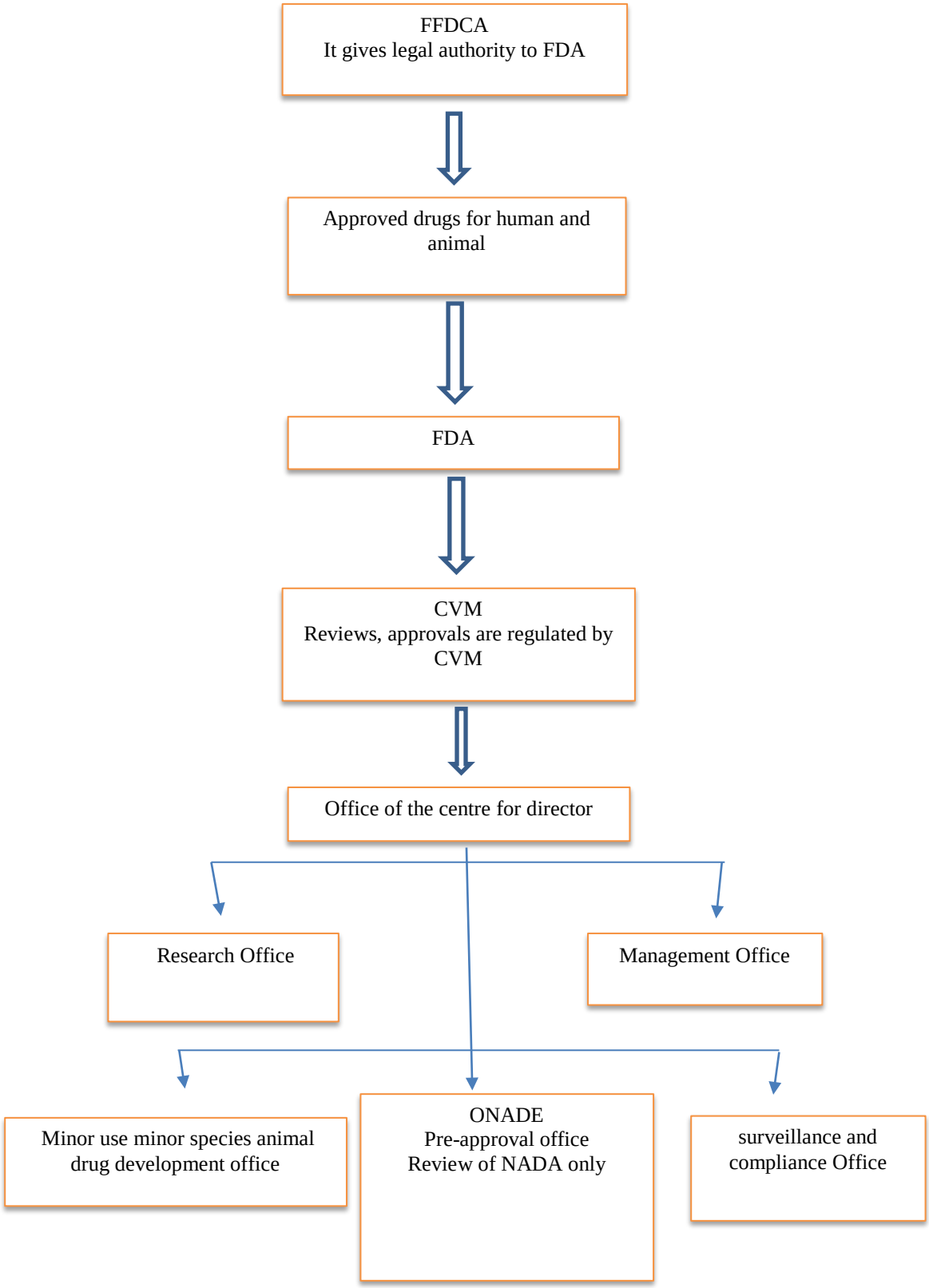
Assessment of initial submission	120-day timetable
Assessment of responses to List of Questions	60-day timetable after clock-stop for submission of responses
Assessment of responses to List of Outstanding Issues	30-day timetable after clock-stop for responses
Assessment of responses to List of Outstanding Issues	30-day timetable after immediate responses
Assessment of Outstanding Issues following Oral Explanation	30-day timetable

Table No:3 VICH guidelines adopted by USA & Europe

VICH guidelines	**USFDA**	**EMA**
VICH GL53: Electronic exchange of documents	✓	✓
VICH GL1: Validation of analytical procedures methodology	✓	✓
VICH GL2: Validation of analytical procedures definitions & terminology	✓	✓
VICH GL10 : Impurities in new veterinary drug substance	✓	✓
VICH GL11: Impurities in new veterinary medicinal products	✓	✓
VICH GL8: Stability testing for medicated premixes	✓	✓
VICH GL4: Stability testing requirements for new dosage forms	✓	✓
VICH GL3: Stability testing of new veterinary drug substance and medicinal products	✓	✓
VICH GL5: Photostability testing of new drug substance and products	✓	✓
VICH GL51: Statistical evaluation of stability data	✓	✓
VICH GL39: Test procedures and acceptance criteria for new veterinary drug substance and new medicinal products	✓	✓
VICH GL6: Environmental impact assessment for VMP'S Phase-I	✓	✓
VICH GL38: Environmental impact assessment for VMP'S, Phase-II		✓
VICH GL46: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food producing animals: metabolism study to evaluate the quantity and identify the nature of residue.	✓	✓
VICH GL23: Studies to evaluate the safety of residues of veterinary drug in human food: Genotoxicity	✓	✓
VICH GL43: Target animals safety for pharmaceuticals	✓	✓
VICH GL27: Pre-approval information for registration of new veterinary medicinal products for food producing animal with respect to antimicrobial resistance.	✓	✓
VICH GL9: Good clinical practice	✓	✓
VICH GL7: Efficacy of Anthelmintics: general requirements	✓	✓
VICH GL12: Anthelminitics: Bovines	✓	✓
VICH GL15: Anthelminitics: Equine	✓	✓
VICH GL14: Anthelminitics: Carpines	✓	✓
VICH GL16: Anthelminitics: Swine	✓	✓
VICH GL52: Bioequivalence: Blood level bioequivalence study	✓	✓

Table No: 4 Comparison Between USA and Europe

CRITERIA	**USA**	**EUROPE**
Regulatory authority	USFDA	EMA
Application	NADA	MAA-Vet Form
Submission type	Electronic	Electronic
Procedure	Single procedure	Multiple procedure
Dossier format	eCTD Format	EU CTD Format
Timeline	180 Days	120 Days
Labelling	21 CFR 501	Volume 6C
Review	CVM	CVMP
Fees	$449348	€143,700
Submission guidelines	21 CFR part 514.1	Volume 6A
Stability studies	VICH	VICH
Bioequivalence studies	VICH	VICH
Standards required	GMP	GMP
Environmental Impact Assessment	Required	Required



FigureNo: III: divisions involved in approval process USA: flow chart gives the picture of step by step processing of review of the animal drug application, Federal food, drugs and cosmetics act gives authority to FDA, under FDA CVM is situated, and this includes the 6 offices.

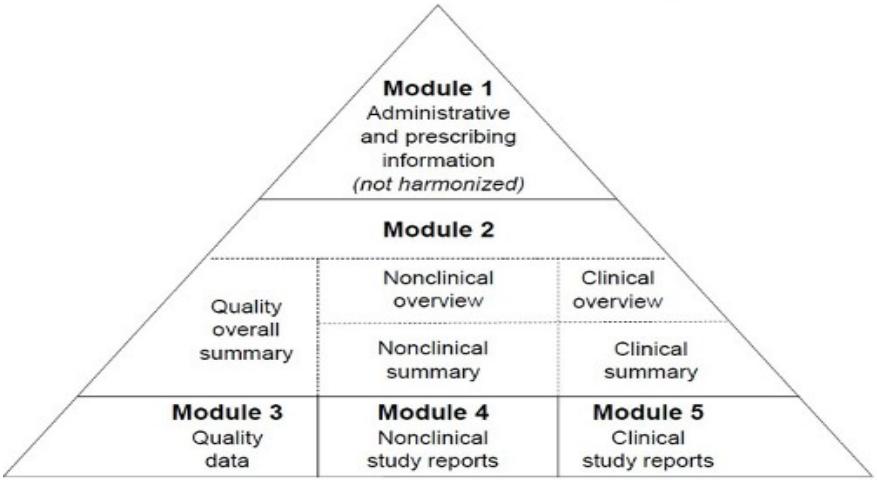


Figure No: IV ; CTD Structure

This is the CTD structure, this involves the 5 modules, and the administrative data, quality data, quality overall summary, clinical and non clinical data should be in CTD format.

RESULTS AND DISCUSSION

The comparison of veterinary drug approval process between the USA & EU is done for clear understanding table 4 comparison between USA and Europe. The VICH guidelines which are adopted by the USA & EU are mentioned in (table:3).

CONCLUSION:

Approval process plays a very important role in safeguard the animal health by ensuring the safety & quality of the drug product, then only it will be approved. The safety of the drug according to label on the product should be ensured by the company. Another benefit of the drug approval process is monitoring of drug product after they entered into the market. Sometimes it reveals the safety & efficacy issues that were not observed during the approval process. The primary purpose of the rules governing veterinary medicinal products in USA, & EU is to safeguard animal health as well as public health. The pharmaceutical companies should comply with regulations and that is ensured by the regulatory authorities. Some legislation that expect medications to be created, tried, trailed, and manufactured in accordance to the rules, by this public's wellbeing is protected.

Acknowledgement:

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