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Review Article

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Comparative study of Regulatory requirements for preparation of Dossier for Registration of Veterinary Drug in US, EU and Canada

Swati Raysing*, Pankaj Nerkar, Siddhesh Sanghavi, Shewta Jogdand, Atul Patil

R. C. Patel Institute of Pharmaceutical Education and Research, Karwand Naka, Shirpur, Maharashtra 425405

Abstract

The main purpose of this article is to research the requirement of the veterinary drug dossier submission in the three countries is US, EU, and Canada and the procedure of all the three countries are different for the submission of the veterinary drug dossier and their rules and regulation are different but all the three countries follow the VICH guidelines in these articles all the information available like necessary documents timeline approval procedure are different for US, EU, and Canada.

Keywords: Veterinary Drug, Registration, CTD, eCTD, CVM, REP, SMPC, CVMP, VDD

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*Corresponding author

1. Introduction

The field of Drug Regulatory Affairs is one that is always evolving and growing, the veterinary market is expanding to make evolving changes in the field of veterinary medicines. To ensure the new drug's quality, effectiveness, and safety for both animals and humans, veterinary medicinal products must go through a mandated and demanding regulatory approval process. The two major administrative centres in the world, aside from Japan, are in the United States of America, Europe, and Canada. This article gives the information about submission of dossier and dossier requirement for all the three countries US, Europe, and Canada. (1)

2. Drug Approval process in US

In the past five years, the veterinary services sector in the US has increased by 5.4%, bringing in 49 billion dollars in sales in 2019. The number of organizations has increased by 1.6% over the same period, while the total number employee has increased by 2.3%. In US the New Animal Drug Application (NADA) and the Abbreviated New Animal Drug Application (ANADA) are required in order to obtain market authorization for veterinary medical products.

According to the Federal Food, Drug, and Cosmetic Act (the act), a new animal drug may sold into interstate commerce after an approved new animal drug application (NADA), abbreviated (ANADA), or there is a conditional approval (CNADA) in effect for the detail procedure we go through the 21 CFR part 511. (1)

Organization Structure of USFDA for Approval of Veterinary drug.

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

- FFDCA: Federal Food, Drug and Cosmetics Act.
- FDA: Food and Drug Administration
- CVM: Centre for Veterinary Medicine
- ONADE: Office of New Animal Drug Evaluation s
- OMUMS: Office of Minor Use and Minor Species
- Animal Drug Availability Act of 1996

The terms "approved new animal drug" denotes that the medication has passed the NADA inspection and been given the CVM seal of approval. When conducting the NADA process, CVM also takes into consideration. (2)

Environmental consequences of drugs:

Ensured safety of those who give drugs to animals

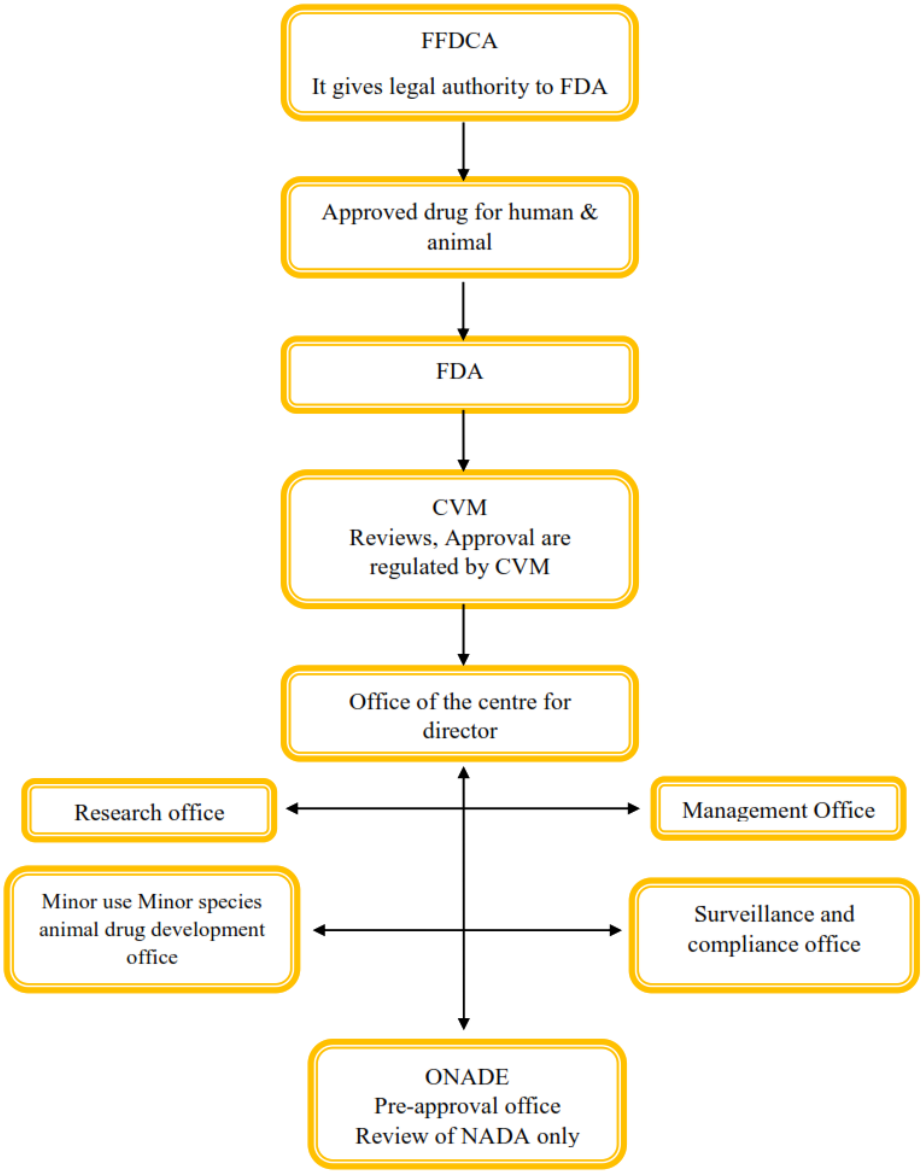

Figure 1. Flow Chart of US Approval Process of Animal Drug Application (3)

3. Drug approval process in Europe

The market for veterinary healthcare in Europe is anticipated to reach a value of USD 10.37 billion in 2022 and USD 14.15 billion in 2027, expanding at a compound annual growth rate (CAGR) of 6.4% during those years.

Veterinary healthcare includes the market for identifying, treating, and preventing illnesses in both wild and domesticated animals. The centralised marketing authorisation applications (MAA) are opened to a scientific inspection by the European Medicines Agency (EMA) (4) The EudraLex volume 6 contains the regulatory requirements for pharmaceuticals intended for veterinary use, which is particularly beneficial to applicants. The publications of Volume 6 (The rules governing medicinal products in the European Union) provide information on the procedural and other regulatory requirements, for renewal processes, dossier requirements 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. (5)

There are four procedures for MAA application is

a) Centralized procedure

b) Decentralized procedure

c) Mutual recognition procedure

d) National procedure

a) Centralized procedure

The pharmaceutical product may be marketed in all Member States with the help of a centralised procedural marketing authorization, which is valid for the entire EU market. When it comes to veterinary pharmaceuticals that must follow the centralized procedure in accordance with the application is filed to the EMA in accordance with Regulation (EC) No. 726/2004's Annex. (6)

b) Decentralized procedure

For veterinary medicines that do not fall under the mandatory context of the centralized procedure, the applicant may ask one or more Concerned Member State(s) to approve a draft assessment report, summary of product characteristics, labelling, and package leaflet as suggested by the selected Reference Member State. The Reference Member State's and the Concerned Member State's (s) competent authorities receive an application**.** (7)

c) Mutual recognition procedure

A national marketing authorization issued by the Reference Member State is mutually recognized by the Concerned Member State as the framework for this process. The Reference Member State is the state that granted the national marketing authorization on which the Mutual Referral Agreement was issued, and the Concerned Member State is based through a recognition process. A national marketing authorization will be provided in the Concerned Member State following the completion of the mutual recognition process**.** (7)

d) National procedure

Standard national procedure is not for the veterinary drug submission due to one-time authorization for only one member state.

It is not possible for the applicant to make a reference to a European reference medicinal product if a medication with the same active ingredient(s) and pharmaceutical form as the generic medication that is the subject of the application is already authorized in the reference Member State. No matter who is the marketing authorization holder for the proposed reference medicinal product is in the reference Member State. (7)

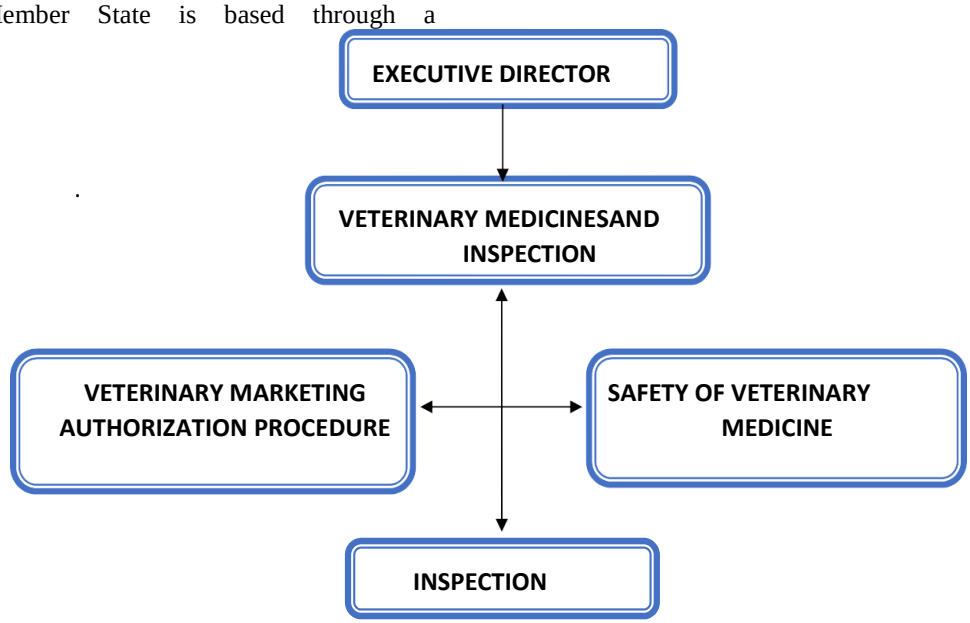

Figure 2. Organization Chart of EMA for Veterinary Section (3)

4. Drug approval process in Canada

The market for veterinary healthcare in Canada is primarily driven by expanding adoption rates for animals, the prevalence of animal diseases, and rising expenditures for animal health. The high levels of awareness of companion animals and livestock among Canadians have led to an increase in the adoption of these animals for social well-being and a healthy lifestyle, which has led to the market's expansion. Analgesics, antibiotics, anti- inflammatory medications, and anaesthetics have also seen an increase in demand, followed by biologics and vaccinations for veterinary services such as those for dogs and cats. (8)

The Veterinary Drugs Directorate (VDD) of Health Canada adheres to for the management of regulatory submissions and associated information supplied by submission applicants (hence referred to as sponsors). This procedure complies with the Food and pharmaceuticals Act and the Food and Drug Regulations, which provide that all pharmaceuticals must receive authorization before being marketed or imported for sale in Canada, unless they are specifically exempted. The VDD is responsible for enforcing rules governing the sale of medications designed for use in animals as well as the administration of the Food and Drugs Act. (9)

There are six divisions in VDD

- Director General Office
- Human safety division
- Manufacturing and chemical evaluation Division
- Clinical evaluation Division
- Submission and knowledge management Division
- Policy planning and International affairs Division

A drug must have a valid DIN to be sold or imported for sale (referred to as sold hereafter) in Canada. The regulatory enrolment process (REP), which permits the filing of submissions via the common electronic submission gateway (CESG), is strongly recommended

by the VDD for submissions that fall under its preview. Regulatory enrolment process review@hc-sc.gc.ca

These are the veterinary drug submission process which we go through for the various types of submission of drugs in Canada.

The following veterinary drug submission types are (10)

- New drug submission (NDS)
- Supplemental new drug submission (SNDS)
- Abbreviated new drug submission (ANDS)
- Supplemental abbreviated new drug submission (SANDS)
- Notifiable change (NC)
- Drug identification number (DIN) application and change to DIN

Drug submission process has different information according to countries and their regulation & guidelines for all the three countries are US, EUROPE & CANADA

Table 1. Comparison requirement for US, Europe, Canada

PARAMETERS	US	EUROPE	CANADA
Regulatory authority	food and drug administration act (USFDA)	European medical agency (EMA)	health Canada (HC)
Dossier format	CTD,ECTD	ECTD,VNEES	CTD
Changes approval	changes in approved drugs filed in pas cbe-30/CBE annual report	changes in approved drugs filed in Type i variation Type ib variation Type ii variation	changes in approved drugs filed in level changes from1 to 8
Types of application	IND, NDA, ANDA, BLA	MAA	NDS , SNDS, ANDS SANDS , INDS ,NOC, DIN

Drug submission process general requirement which is mandatory but different changes in requirement which is mention in these table 2

Table 2. Comparison of various countries of drug submission process requirement

Sr. No	Requirement for Nada for(US)	Development for New Animal Product for (EUROPE)	Requirement for NDS for (CANADA)
1	Chemistry manufacturing & control	Product characteristics Summary	Mater volume
2	Effectiveness	Manufacturing-authorization holder responsible for batch release	Manufacturing and quality control
3	Safety to target animal species	The marketing authorization Conditions	Animal safety
4	Human and food safety	Labelling	Efficacy
5	Labelling	leaflet of Package	Human safety
6	Environmental assessment	Environmental impact	Environmental impact
7	Freedom of information summary		

These are the compulsory documents which is attached with submission of dossier these documents information is available on FDA website.

5. General Requirement & Administration Document for US

- Cover letter
- Table of Contents
- Declaration by the applicant
- Screening checklist
- Payment proof
- Certificate of pharmaceutical Product (COPP)
- Good Manufacturing Practices License
- Summary of product characteristics (SMPC)
- Labelling (primary and secondary packaging)
- Package insert and patient information leaflet
- Quality information summary (QIS)
- Proof of Approval
- Authorization Letters
- GMP Certification/Proof of GMP Compliance
- Patent declaration

These are the compulsory documents which is attached with submission of dossier these documents information is available on EMA website.

6. General Requirement & Administration Document for Europe

- Cover letter
- Table of Contents
- Declaration by the applicant
- ATP code
- Screening checklist
- Payment proof
- Certificate of pharmaceutical Product

(COPP)
- Good Manufacturing Practices License
- Summary of product characteristics (SMPC)
- Labelling (primary and secondary packaging)
- Package insert and patient information leaflet
- CEP Certificate
- Proof of Approval
- Authorization Letters
- GMP Certification/Proof of GMP Compliance
- Patent declaration
- GMP inspection evidence from EEA

These are the compulsory documents which is attached with submission of dossier these documents information is available on health Canada website.

7. General Requirement & Administration Document for Canada

a. Cover letter
b. Table of contain
c. Submission certification
d. Authorization letter
e. Drug submission application form
f. Veterinary drug submission fee application form
g. Animal ingredient form
h. Draft product label
i. Patent form/ documents
   - Form IV patent list (notice of compliance)
j. Form V declaration form (notice of compliance)GMP status information and licence information
k. Prior submission
l. Submission and product summary
m. Summary of 3 batches information
n. Information Package for the Canadian Food Inspection Agency (CFIA)

A) Drug premix product

Comparative study of the administrative part in which there is detail information of the requirement which is different for all the three countries is mention in these table No.3

Table 3. Comparison of administrative part

Sr No.	US	EUROPE	CANADA
1	Debartment certificate is required	Debartment certificate is required	Debartment certificate is not required
2	Numbers of 3copies required	Numbers of 1 copies required	Numbers of 3 copies required
3	Approval time line 18 months	Approval time line 12 months	Approval time line 18-20 months
4	Fees for administration is 0/-	Fees for administration is 10-20 lakhs	Fees for administration is 20-25 lakhs
5	Presentation is done on paper and eCTD format	Presentation is done on eCTD format	Presentation is done on paper and eCTD format
6	Appointment letter from agent is applicable	Appointment letter from agent is applicable	Appointment letter from agent is applicable
7	Environmental Assessment Report is required.	Environmental Assessment Report is required.	Environmental Assessment Report is required.
8	Reports of Pharmacovigilance are not applicable	Reports of Pharmacovigilance are applicable	Reports of Pharmacovigilance are applicable

These is the information regarding to technical part like dimension of the format pages, stability batches, climatic zones which is also different for the all the three countries is mention in these table no.4

Table 4. Comparison of technical administrative part

Sr No.	US	EUROPE	CANADA
1	Dimensions for CTD are A4 paper size, font size is 12 and font style is Times NewRoman	Dimensions for CTD are A4 paper size, font size is 12 and font style is Times New Roman	Dimensions for CTD are A4 paper size, font size is 12 and font style is Times New Roman
2	Number of batches required for stability studies are 3	Number of batches required for stability studies are 3	Number of batches required for stability studies are 3
3	Climate zone is zone 1	Climatic zone is zone I& II	Climatic zone III & IV
4	Quality overall summary	Quality overall summary	Quality overall summary
5	Quality overall summary	Quality overall summary	Quality overall summary
6	Appointment letter from agent is applicable	Appointment letter from agent is applicable	Appointment letter from agent is applicable
7	Environmental Assessment Report is required.	Environmental Assessment Report is required.	Environmental Assessment Report is required.

8. Conclusion

In this article the comparison between general registration procedure and requirements of US, EUROPE and CANADA have been discussed. In US, EUROPE eCTD format of dossier is used while in Canada CTD format is used for the drug registration

process. This article differentiates the basic differences between regulatory requirements for the dossier filling. And the regulatory authority of Authority of US is (USFDA) and the Europe is (EMA) and for the Canada (HC) this article list out all the differences between these three regulatory authorities.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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