



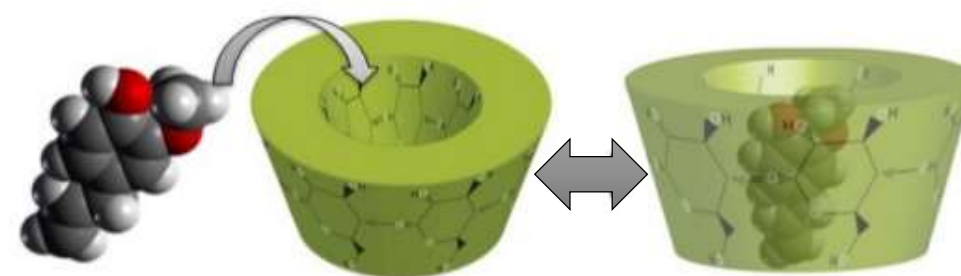
# GETTING THE BEST OUT OF CYCLODEXTRINS

# Cyclodextrins in veterinary use



# What are cyclodextrins?

- Composed of sugars
- Cyclic molecules
- Naturally occurring compounds
- Used in food, pharmaceuticals, drug delivery, chemical industries, agriculture, etc.
- **Sub-nanometer** sized molecular containers with hydrophilic outer phase and hydrophobic interior properties
- Reversible inclusion complex formation



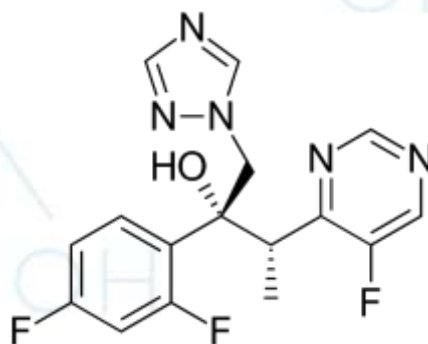
## Why use cyclodextrins? Possibilities

- Significant solubility enhancement (10 to 100,000 fold)
- Improvement of **chemical stability**
- Increased bioavailability, facilitated delivery
- Reduced aggregation
- Moderate irritation or reduced side-effects
- Maximized patient safety, complete renal elimination
- **Enables** formulation of water-insoluble APIs in all dosage forms
- Lower API doses can be achieved

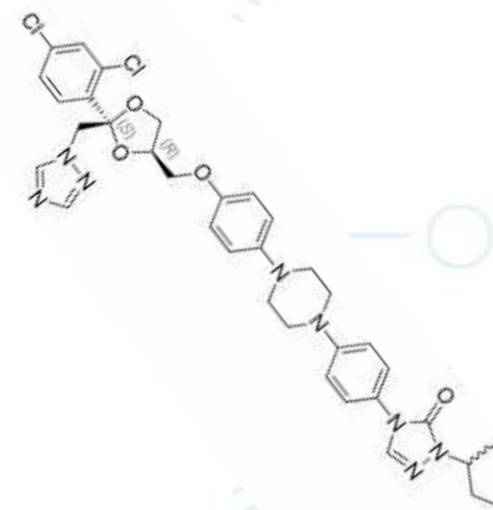


# Examples of CD usages in veterinary formulations/medicine

## Antifungal agents



- **Voriconazole** is an antimycotic drug for both human and veterinary use.
- In the formulation, **sulfobutyl-ether-beta-cyclodextrin (Dexolve™)** is used as an excipient.



- **Itraconazole** (Itrafungol™) is used as antimycotic drug in cats as an oral solution.
- In the formulation, **(2-hydroxypropyl)-beta-cyclodextrin** is used as an excipient.

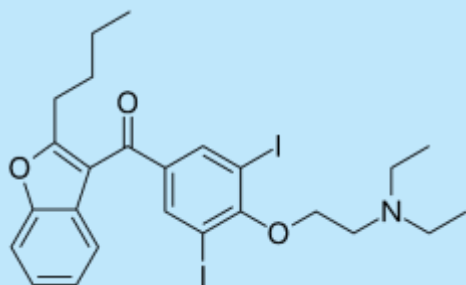
# Examples of CD usages in veterinary formulations/medicine



## Drugs affecting the cardiovascular system

**Amiodarone** is an anthyarrythmic drug with several indications, and it is used both in humans and in veterinary medication.

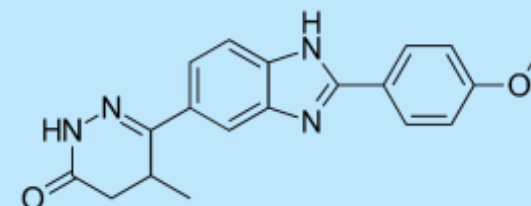
A new formulation (Nexterone™, PM101) contains sulfobutyl-ether-beta-cyclodextrin as a solubilizing agent instead of Polysorbate 80.



**Pimobendan** (Vetmedin™), is a calcium sensitizer and a selective inhibitor of phosphodiesterase 3 (PDE3) with positive inotropic and vasodilator effects, used for the treatment of heart failure in dogs.

A new patent by Boehringer Ingelheim describes a formulation that consists of modified **cyclodextrins**.

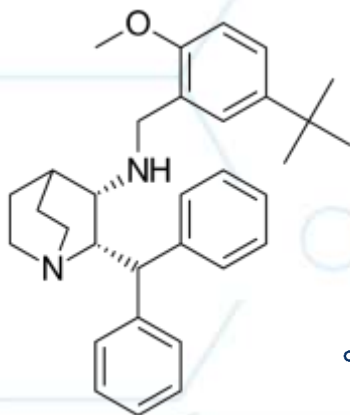
Boehringer Ingelheim  
Vetmedica GmbH, Liquid  
preparation comprising  
pimobendan, 2015,  
US9107952 B2





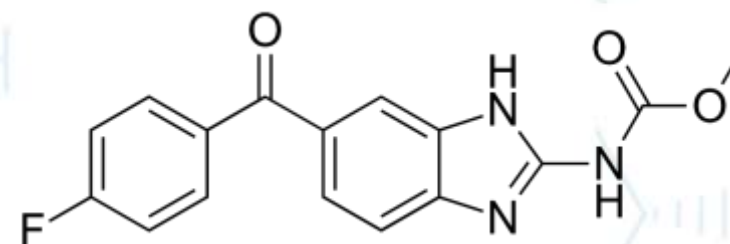
## Examples of CD usages in veterinary formulations/medicine

- **Maropitant** (Cerenia™), a drug used for the treatment of motion sickness and vomiting in dogs.
- In the formulation, **sulfobutyl-ether-beta-cyclodextrin** is used as a solubilizing agent.



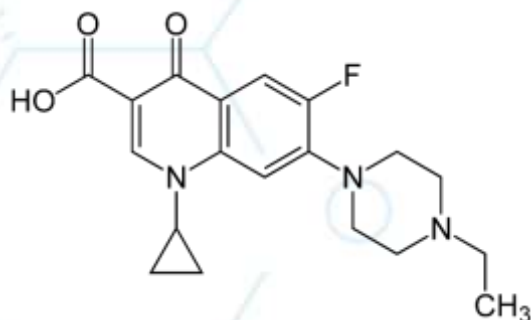
L. Ceballos et Al., Pharmacokinetic comparison of different flubendazole formulations in pigs: A further contribution to its development as a macrofilaricide molecule, International Journal of Parasitology: Drugs and Drug Resistance, 5(3):178-184

- **Flubendazole** is an antihelmintic drug, used both in veterinary and human medication.
- **(2-hydroxypropyl)-beta-cyclodextrin** can be used as a solubilizing agent, to improve water solubility.



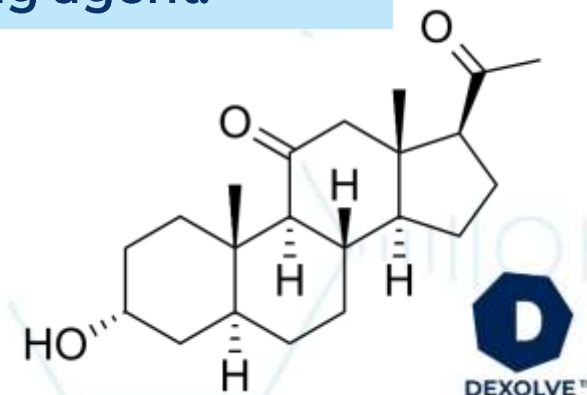
## Examples of CD usages in veterinary formulations/medicine

- **Enrofloxacin** is a fluoroquinolone antibiotic widely used for microbial infections in cats and dogs.
- Its complex with **(2-hydroxypropyl)-beta-cyclodextrin** showed improved solubility and bioavailability.



Ding, Y et Al., Formation of inclusion complex of enrofloxacin with 2-hydroxypropyl- $\beta$ -cyclodextrin, Drug Delivery, 27(1):334-343

- **Alfaxalone** (Alfaxan<sup>TM</sup>), is a neuroactive steroid molecule with general anesthetic effects. It is used only in veterinary practice.
- In the formulation, **(2-hydroxypropyl)-beta-cyclodextrin** is used as a solubilizing agent.



## Examples of CD usages in veterinary formulations/medicine

Cyclodextrins are also used in vaccines

- Suvaxyn PCV™ contains inactivated recombinant Porcine Circovirus type 1, expressing the Porcine Circovirus type 2 ORF2 protein. This vaccine is used for the active immunization of pigs over the age of 3 weeks against Porcine Circovirus type 2 (PCV2)
- **Sulfolipo-cyclodextrin (SLCD)** is used as an adjuvant.

As an excipient, **(2-hydroxypropyl)-beta-cyclodextrin** is used.





## Examples of CD usages in veterinary formulations/medicine

### Dietary supplements

- Feluro™ is a palatable oral suspension to support the maintenance of a healthy urinary tract in cats. The active ingredients are hibiscus, N-acetyl-D-glucosamine and green tea extract. It also contains **gamma cyclodextrin**.



Anxitane® chewable tablets help pets keep calm and relaxed. Containing L-theanine, an amino acid naturally found in green tea leaves, Anxitane tablets are a palatable option that both cats and dogs will enjoy and a great option to use in conjunction with a behavior modification program. It also contains **gamma-cyclodextrin**.



## Other possibilities for cyclodextrin usage

### Vitamins and cyclodextrins

- **$\beta$ -cyclodextrins** improve pharmacokinetics of  $\alpha$ -tocopherol in heifers.
- Cyclodextrin encapsulated vitamin K (K1, K2) can reduce osteochondral effects in animals.

### Cryopreservation

- Cholesterol-loaded cyclodextrins can prevent cryosurvival of animal sperms.
- Cholesterol/cholestanol-loaded cyclodextrins improve quality of stallion spermatozoa.

### Essential oils and cyclodextrins

Several patents are about essential oil formulations with cyclodextrins, e.g.:

- Camphor oil (respiratory stimulant)
- Lemon oil (flavor enhancer)
- Cinnamon oil (flavor enhancer)
- Garlic oil (antimicrobial)

### Effects of cyclodextrin complexes on methane production in heifers

- The  **$\beta$ -cyclodextrin** complexes appear to be a promising solution to mitigate methane emissions without reducing energy intake.

Who are we at CycloLab?



The world's only all-round **CYCLODEXTRIN** company with experience  
in **CD-technology** since 1991

in pharmaceutical-, cosmetics-, food-, environmental- and analytical  
applications

### Experience

Over 540 technical/scientific papers and 950 technical reports  
to customers

200 different cyclodextrin derivatives

130 patents/applications

40 products on the market

Drug Master Files (USA type IV) and eCTD

Over 20,000 citations to CYCLOLAB's papers

### Expertise & Technology

Custom synthesis

Drug solubilization and stabilization

Further industrial applications

Cyclodextrin-related analytics

Stability testing

GMP-conform manufacturing

Feasibility studies



# CycloLab service portfolio

## Related services – R&D



### Early phase drug development

Customization of CD enabled formulations

Investigation of changes in physico-chemical properties

Life cycle management

### IP services and consultation

### Custom cyclodextrin synthesis

Exclusive manufacture, unique synthetic routes

Self-tailored products and characteristics

Experience in the compilation of CD-related patents (synthesis, application, etc.), patent claim analysis, and consultancy in CD-related projects since 1991.

Over 62.000 CD related papers

### In vitro bioequivalence studies

Design and performance of in vitro studies to support bioequivalence of a CD enabled formulation

### Analytical services

Method development, validation; cGMP release testing of pharma grade CDs

HPLC, GC, CE, UV, MS, NMR, IR, Micro and BET content methods

Stability studies

CD-guest interaction studies

CD-based chiral separations

Assay, impurity tests

Bioanalytical investigations

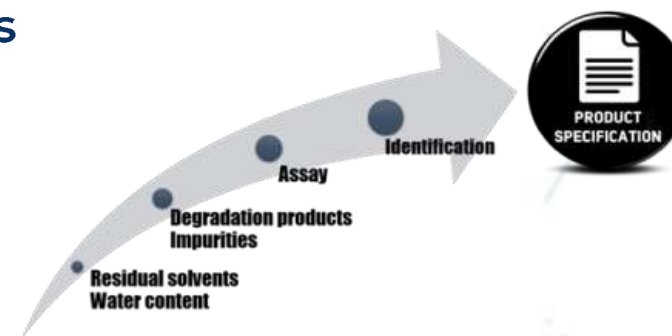


## About CycloLab Service portfolio



### GMP SYNTHESIS

Regulatory license for manufacture of APIs and  
clinical investigational products





## CycloLab service portfolio

### Related services – R&D



#### Feasibility study

Running a short feasibility study with your molecule free of charge

Proof of concept to consider CD based formulations



#### CycloLab Grant

CycloLab offers a unique possibility to collaborate on creating novel and interesting cyclodextrins under the terms of the CycloLab Grant

The proposal after application is thoroughly evaluated by CycloLab

If the application is approved, the cyclodextrin is provided free of charge for the beneficiary



**CDs in veterinary use**

## **COMPANY CONTACTS**

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