*ejpmr, 2021,8(7), 118-128*

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

# PHARMACEUTICAL DRUG PRODUCT DEVELOPMENT AND ITS ASSOCIATED CHALLENGES IN VETERINARY SCIENCE AND PRECLINICAL RESEARCH – A CRITICAL REVIEW

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**Article Received on 29/04/2021** **Article Revised on 19/05/2021** **Article Accepted on 09/06/2021**

## ABSTRACT

Drug discovery and drug product development has many resemblances for improving human and animal health. In both the cases, innovative research, global existence, high regulations and competitive business are the common goals. While, the research goals are common, there are some noteworthy differences as well. The present review focuses on highlighting and discussing the challenges faced by product development meant for animals during preclinical research as well as veterinary drug delivery. In addition to this, a brief review is provided on the animal health pharmaceutical product with its segmentation, market scenario; as well as special needs in veterinary drug delivery. Lastly, this paper recognizes the further possibilities which can significantly help advance the animal research.

**KEYWORDS:** innovative research, global existence, high regulations.

## 1. INTRODUCTION

The overall goal of a drug product development is to administer the desired dose safely and effectively in the animals for a specific medical condition.[1-4] Surprisingly, the animal health research has equally contributed to the pharmaceutical industry in terms of providing novel drug delivery application, continuous manufacturing and biotech to support overall product development.

Five factors define the requirements of the new technology in veterinary drug product development.

- Enhanced patient (animal) compliance as well as convenience.
- Improved drug pharmacokinetics.
- Proprietary molecules.
- Differentiate the available products for animal use or human use.
- Ensure animal and consumer safety.

Human health and animal health industries share a many common things when it comes to research.[5] Nonetheless, the specific differences should be considered. Out of many considerations, cost, weather, different species, many breeds, weight variability among same species, animal compliance, safety and husbandry practices remain the top challenges during the drug product development.

Drug product development for human use requires a thorough evaluation of safety and efficacy via pre-clinical studies and clinical studies which slows down the process and it can take up to 15 years for a safe and effective drug product for patients.[6] Clinical testing for veterinary drug products typically bypasses pre-clinical studies and phase I clinical evaluations.[7, 8] Therefore, the veterinary drug products can made available for animal use relatively faster as compared to drug products for human use.[9] The challenges that may delay the drug product development activities include a particular therapeutic class, type of therapy, specific species and complex veterinary formulations. These formulation development challenges typically are very rarely known in the pharmaceutical industry and can even more complex due to diversity involved in animal drug products compared to human medicines. Due to the complexities involved the development costs of animal drug product remains high compared to formulations for human use. The burden of selecting a thermodynamically stable form is also investigated for the animal drug products (e.g. fendendazole).[10, 11] These solid forms may include anhydrate, hydrate, solvate, salt, eutectic mixtures and/or cocrystals.[12-15] A physically stable solid form will provide acceptable morphology, physical stability, less hygroscopicity, adequate solubility, high permeability and dissolution rate constant.[16-20] A drug with limited solubility may even need enabling technologies such as lyophilization, amorphous solid dispersion, nanotechnology, lipid-based formulations and similar techniques.[21-25]

Animal studies are a must to investigate the toxicity of a new discovered drug molecule not only for animals, but also for the indirect exposure of an investigational drug substance to human.[26] The animal studies help in understanding the pharmacokinetic profiles and efficacy projections in humans.[27, 28] Similarly, this information also provides an understand to tailor the dosage forms for different animal species in terms of veterinary application.

For example, in livestock sector, it is very important to develop a dosage form rapidly with cost-effective approach to provide the effective treatment in herds.[29, 30] This will allow to achieve an overall goal of animal welfare, hassle-free administration, long term protection along with human safety. The most common approach to administer drug in livestock includes feed additives, topical pour-ons, injections and ruminal boluses. Furthermore, the dosage form selection and route of administration in companion animals is dependent on different aspects, which includes ease of use, pet compliance and dosing flexibility. In pet animals, different dosage forms include medicated collars, sprays, powders, shampoos, and palatable tablets.[1, 31]

The aim of this review work is to: (i) emphasize on the challenges faced during veterinary drug product development; and (ii) recognize the requirements in animal health to keep up recent advances in pharmaceutical industry.

## 2. Veterinary drug delivery challenges and special considerations

Drug product development for veterinary use faces the similar research challenges as that pharmaceutical companies that manufactures drug product for human use. The factors that further complicates the veterinary drug product development includes variability in the species, different animal breeds, external weather fluctuations, geographical differences, bodily metabolism, varied biology and economic factors.[32, 33] Pharmacokinetic as well as pharmacodynamic differences play a critical role in this type of research activities. The drug elimination can very different among species.[34, 35] One research work showed that the half-lives of six different drugs tested in cattle, horses, dogs, cats and humans were significantly different.[36] Similarly, the absorption of the drug can be very different among different species. The rate of absorption post intra-muscular administration for kanamycin was six-fold lower in dogs compared to horses.[37] These differences can lead to different therapeutic level as well as associated bioavailability, especially if the drug substance has a narrow therapeutic index.[18] The bioavailability of amoxicillin was observed to relatively higher in cats compared to other species.[37] The reasoning for this is unclear however, one plausible reason may include the metabolism in cats.[38] Inter-animal or inter-species variability in animal variability may also pose a challenge during veterinary product development. The animals weigh in the range of as low as 1 kg and as high as 700 kg. To provide an overview on the impact of animal, a new chemical entity to be administered on mg/ kg dose basis, the final dose can vary by 12-fold among the different dog breeds and by 700 fold among small and large animals. The weight variation among animals can lead to either under-dosing or over-dosing.[16] This can be directly associated with the safety and efficacy of potent drugs. For example, levothyroxine sodium, a low dose narrow therapeutic index drug to cure hypothyroidism in animals as well as humans can have a significant effect in terms of therapeutic efficacy.[19]

The pet animals drug delivery requirements are usually similar to those of human drug products in terms of dosage forms to treat a particular ailment. As compared to livestock animals, cost-effectiveness may not be a rate limiting criteria for drug product development.[39] The therapeutic agents are typically small molecules dosed chronically. Once-a-day oral or topical dosing is the preferred dosing regimen and mode. Overall safety and drug tolerance are also important factor in addition to the ease and safety for the pet owners or animal care takers.[40]

On the other hand, the therapy for farm animals is required to be cost effective due to multiple reasons. One of the reasons include high doses for both small molecules as well as some cases large molecules (biologics) administered for acute, sub-chronic or chronic uses. The length of treatment is often long ranging from 2 weeks to 6 months. Parenteral dosage forms are often preferred; however, major apprehensions include local toleration and residues at injection site.[41, 42]

Formulation challenges with pet animals and farm animals are very similar with the only different in the therapeutic and safety implications. In pet animals, the administration compliance is largely dependent on the pet owner's acceptance.[43] However, in livestock animals, the administration of a drug in animal may have a direct business impact as in case of dairy, poultry farm or similar cases.[44] Again, the dosage form varies not only in size and shape but also route of administration. Parenteral dosage forms are common for farm animals, but, oral medications are preferred for pet animals. Sometime, controlled release dosage forms may become a challenge for pet animals due to eating habits and diet.[45]

All the animals require vaccination, which can be a completely different area of research. In the US, vaccines follow an exclusive regulatory approval process to maintain high quality standards.[46] Large molecules are generally used to prepare vaccine. The cost involved in vaccine production can be very sensitive due to additional manufacturing steps required to ensure the sterile environment as compared to oral medications. In

most cases, a single shot therapy is preferred, but in some cases subsequent booster shots may be required in cases such as COVID19 given the current pandemic.

### 3. Application of research knowledge from human medications: prospects and limitations

The drug products with common ailments have substantial similarities among veterinary, especially pet animals, and human dosage forms. Majority of the pharmaceutical companies benefitted from utilizing a combined strategy of using approved drug candidate meant for human use in animals and vice versa.[47] Importantly, it should be recognized that any drug candidate has to undergo animal studies to determine the toxicity, safety and therapeutic efficacy of a drug candidate and "proof of concept" is generated before its clinical use in human patients. This can serve as an added advantage, wherein, if needed, the drug product can be approved for animal use even before its further research investigations for human use.

Tablets and injectables are among the most common formulations administered in both human as well as animal health.[5] However, transforming either formulation is not a simple task as it may appear. The factors that need attention include multiple strength, low dose drug products, mg/kg doses based on weight and taste-masking or taste improving are important in design animal formulations which makes it even complicated during the drug product development stage.[48]

In humans, the drug product design and therapeutic dose decisions are relatively simple as average weight of humans is considered to be 70 kg. As in case of animals despite the availability of dose information on mg/kg basis, the same animal group may have a huge weight variability, so multiple strengths, at least three or four, become necessary for the treatment of a particular animal group to ensure accuracy in the dosing.[49] In few cases, the formulation optimization may not always require change in the formulation components, a simple change in processing can also improve physico-mechnical properties of a drug product.[50] If lower dose is required for human population, then the tablets can be manufactured as scored tablets, which can be split into half and the need for additional strength can be avoided but scored tablets may not be a best alternative for animal formulations.[49] Similarly, if the dose strengths are in the multiples of a number, the best approach is to prepare a common blend and manufacture smaller tablets, however, this may not be always feasible. Typically, the tablets for animal use even for a lowest strength have to be big in size for easy administration. To achieve this, it may be required excess excipients will be required. Drug formulations with low drug loading can potentially exhibit instability issues. Therefore, it is important to consider the drug load and possible drug-excipient interaction for animal health purposes as well.[51] This may further increase complications like degradation and impurities during drug product development to ensure safety and quality of a drug product.[52, 53] Summary of ICH guidelines are reported in Table 1, which suggests the slightly flexible impurity levels for animal health formulations compared to human health products.[53] Furthermore, high drug dose due to very high animal weights lead to an increase in the tablet dimensions. In animal, it may not be an issue, however, if the tablet is relatively big in size, the animal patients may be able to recognize the drug product which may lead to unacceptability issue among animal patients. In such situations, an alternative which is explored in human drug products can also be applied and extended to the animal formulation, wherein, a particular polymorph or a cocrystal can be used to reduce the optimize the size of the tablet formulation.[54-57]

**Table 1: ICH guideline on impurity level.**

| | Individual impurities as per cent of parent drug | |
|---|---|---|
| | **Human health** | **Animal health** |
| Report | 0.1 | 0.3 |
| Identify | 0.5 | 1.0 |
| Qualify | 0.5 | 1.0 |

Typically, the oral dosage forms developed for animals comprise of taste enhancing agent. Similar to pediatric patients, the dosage form compliance can be improved in animals also.[58] Yeast-based or meat-based flavors are most common to develop the tablet blend.[59] These flavoring agents may react with the active ingredient and/or alter the tablet dissolution. The flavoring systems may further complicate the analytical method development due to interference of the flavoring agents which typically includes flavonoids or any other naturally occurring ingredients used to improve palatability. Addition of only flavor may not always help in all the animal species due to different taste perception in different species. In case of dogs, simple addition of flavor has led to 80 % acceptance rate. If a drug substance has a strong odor then a simple flavor addition may not work. Unlike human drugs wherein taste enhancement is a primary criterion, in animal formulations odor of a drug product is important.

Among dog species odorous drug has a minimum acceptable rate of 20 %, while bitter tasting and bland drug were reported to be acceptable in 40 – 60 % cases.[5] The odorous drug products did not improve the acceptance rate by a simple addition of flavor in dogs. Odorous drugs were even challenging in cats with an acceptance rate of only 50 %, despite the addition of a flavoring agent. The formulation scientists face major challenges in order to develop a palatable oral formulations for pet animals. Few of the many important factors include drug-flavoring agent compatibility, global regulatory acceptance, receptiveness by dogs and cats, analytical characterization of the flavoring agent and physico-chemical stability of the flavoring agent.[60]

Like humans, "effect of food" also affects the drug absorption and thereby *in vivo* bioavailability of the drug.[61] The interaction between food and drug substance can lead to either a positive or negative effect on the bioavailability.[62, 63] Watson et al reported no food effects when chloramphenicol palmitate tablets were administered to cats, however, suspension did show an interaction with food and there by affecting its physico-chemical properties.[64] Therefore, the effect of food in animals becomes quite more challenging and may not be easily embraced by the animals. The main goal of a formulator while designing a robust drug product for animals, wherein the dosage form function is independent of food and does not require plenty of water.

Oral drug products meant for administration in the animal patients also require an extensive characterization. The drug product analysis includes assay, disintegration, *in vitro* drug release, long term and accelerated studies as well as in-use stability studies.[65-68]

The development of parenteral formulations for animals are far more complication as compared to humans. Firstly, the tolerance at injection site. Tolerance at injection site is largely a common issue in both humans as well as animals. In humans, if the site of injection is not well tolerated other site may be preferred, however, this may not be an option in farm animals or even the pet animals. Due to cost of care-taker and management practices the ideal expectations are to not include a therapy require intravenous or multiple injections. "One-shot" therapy with either intra-muscular or sub-cutaneous administrations are the most preferred choice in animals. This would minimize the tolerance at injection site issue as well as ease for care-takers to administer a medication to numerous animals with further complications. One of the commonest side effects with injections are the local tissue reaction with negatively impacts the drug absorption. [69-71] Pain and swelling are generally observed in pet animals, whereas farm animals may impact the quality of meat and safety of human food. These factors play a critical role in determining the success of the animal formulations.

As a cost effective approach, a multi dose vials for parenteral delivery are manufactured for animal health. Similar to humans, the parenteral formulations involve same challenges while developed a multi-dose vial. The pareteral formulations require selection of a stable and compatible preservative, formulation's ability to succeed preservative efficacy test as required by most regulatory agencies, a robust stopper for multiple dose withdrawal and the in-use stability data for the given product. In addition to this, any possible interaction of the drug substance in the injectable solution with packaging components may also lead to a decreased potency drug product.[72, 73]

In-use stability is the most important set of information as it may be easy to control the environmental conditions for the formulations meant for pet animals, however, for farm animals, the controlled conditions may not be available and pose challenge while administering the medication in open environmental conditions. A formulation may have demonstrated the desired stability in the ICH recommended stability conditions, it may undergo oxidative degradation in open conditions and small amounts of oxidative degradant might deem the formulation toxic or ineffective for further use.[74]

## 4. Recent animal drug products approval in United States

The advances in the research and development for animal drug products can be evidenced by 24 approvals of new drug products as well as generic drug products within last six months in the US market (Table 2).[75]

**Table 2: Recent drug approvals for US market meant for veterinary use.**

| Date of Approval | NADA / ANADA | Manufacturer | Drug Product Name | Animal Species | Active Ingredient | Dosage Form | Therapeutic Dose | Therapeutic Indications for Use |
|---|---|---|---|---|---|---|---|---|
| April 26, 2021 | NADA | Intervet, Inc. | Safe-Guard® | Beef cattle | Fendendazole | Medicated Feed Block | 750 mg | Anthelmintic used against gastrointestinal parasites |
| April 23, 2021 | ANADA | Cronus Pharma Specialities India Private Ltd. | Amoxicillin and Clavulanate Potassium Tablets | Dogs and cats | Amoxicillin and Clavulanate Potassium | Tablets | 6.25 mg/lb of body weight | Antibiotic to treat infections |
| April 12, 2021 | NADA | Elanco US Inc. | Credelio™ CAT | Cats | Lotilaner | Chewable Tablet | 12 mg / 48 mg | Treatment and control fleas and ticks |
| April 5, 2021 | ANADA | Accord Healthcare, Inc. | Enrofloxacin | Dogs | Enrofloxacin | Injectable solution | 22.7 mg/mL (2.27%) | Anti-bacterial |
| March 24, 2021 | NADA | Intervet, Inc. | Safe-Guard® Panacur® 10% Paste | Cattle/Beef and Dairy Cattle | Fenbendzole | Paste | 10 % | anthelmintic used against gastrointestinal parasites |
| March 22, 2021 | ANADA | Bimeda Animal Health Ltd. | KetoMed™ | Horses | Ketoprofen | intravenous injection | 1 mg/lb (1 mL/100 lbs) of body weight | Anti-inflammatory for musculoskeletal disorders |
| March 19, 2021 | NADA | Zoetis Inc. | MGA® and Bovatec® and Aureomycin® | Growing beef heifers fed in confinement for slaughter and replacement beef and dairy heifers | Chlortetracycline<br>Lasalocid<br>Melengestrol Acetate | medicated feeds | 50/90/100 g<br>150/90.7 g/lb<br>200/500 mg per pound | For increased rate of weight gain, improved feed efficiency, suppression of estrus (heat), for control of coccidiosis |
| March 15, 2021 | NADA | Zoetis Inc. | MGA® and Aureomycin® | Growing beef heifers fed in confinement for slaughter and replacement beef and dairy heifers | Chlortetracycline HCl<br>Melengestrol Acetate | Dry Formulation Liquid Formulation Granular | 50/90/100 g<br>200/500 mg per pound | For increased rate of weight gain, improved feed efficiency, suppression of estrus (heat), and treatment of bacterial enteritis |
| March 11, 2021 | ANADA | Akorn Operating Company LLC (dba Akorn Animal Health Inc.) | Dexmedetomidine Hydrochloride Injection | Dogs and cats | Dexmedetomidine Hydrochloride | Injectable solution | 0.5 mg/mL | Sedative and analgesic |
| February 26, 2021 | NADA | Pharmgate, Inc. | Pennitracin MD® and Coban™ | Growing turkeys | Bacitracin Monensin | Medicated Feeds | 50 g/lb<br>90.7 g/lb | Increased rate of weight gain and improved feed efficiency, and for the prevention of coccidiosis |
| February 18, 2021 | ANADA | Bimeda Animal Health Ltd. | MACROSYN™ | Beef cattle, non-lactating dairy cattle, suckling calves, dairy | Tulathromycin | Injectable solution | 100 mg/mL | Treatment of respiratory disease and against infectious bovine keratoconjunctivitis (IBK) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | calves, veal calves, and swine | | | | associated with *Moraxella bovis*. |
| February 18, 2021 | ANADA | Elanco US Inc. | Increxxa™ | Beef cattle, non-lactating dairy cattle, suckling calves, dairy calves, veal calves, and swine | Tulathromycin | Injectable solution (Subcutaneous, Intramuscular) | 2.5 mg/kg (0.25 mL/22 lb) BW | Treatment of respiratory disease and against infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis*. |
| February 16, 2021 | ANADA | Chanelle Pharmaceuticals Manufacturing Ltd. | Animec™ Plus® | Cattle | Ivermectin<br><br>clorsulon | Injectable solution (Subcutaneous) | 10 mg<br><br>100 mg | Treatment and control of parasites |
| February 8, 2021 | ANADA | Sparhawk Laboratories, Inc. | SparMectin Plus Clorsulon | Cattle | Ivermectin<br><br>clorsulon | Injectable solution (Subcutaneous) | 10 mg<br><br>100 mg | Treatment and control of parasites |
| February 1, 2021 | ANADA | Huvepharma EOOD | CycleGuard® and Monovet® | Heifers fed in confinement for slaughter | Melengestrol Acetate<br><br>Monensin | Medicated Feeds | 500mg/lb<br><br>90.7 g/lb | Increased rate of weight gain, improved feed efficiency, suppression of estrus (heat), and prevention and control of coccidiosis |
| February 1, 2021 | ANADA | Huvepharma EOOD | Optigrid® and Monovet® and CycleGuard® | Heifers fed in confinement for slaughter | Melengestrol Acetate<br>Monensin<br>Tylosin | Medicated Feeds | 500mg/lb<br><br>90.7 g/lb<br>40g/lb | Increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis |
| January 15, 2021 | NADA | Neogen Corp. | ThyroKare™ | Dogs | Levothyroxine Sodium | Tablet | 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, or 1.0 mg | For replacement therapy for diminished thyroid function in dogs. |
| January 14, 2021 | NADA | Pegasus Laboratories, Inc. | KBroVet®-CA1 | Dogs | Potassium Bromide | Tablet | 200/500 mg | Anti-epileptic |
| January 11, 2021 | NADA | Anivive Lifesciences, Inc. | LAVERDIA™-CA1 | Dogs | Verdinexor | Tablet | 2.5 mg, 10 mg, or 50 mg | Treatment of lymphoma |
| January 7, 2021 | NADA | ECO LLC | Aivlosin® | Swine intended for slaughter | Tylvalosin tartrate | Granules for solution | 62.5 % w/w | This supplement provides for the addition of *Mycoplasma* control of swine respiratory disease. |
| December 16, 2020 | ANADA | Bimeda Animal Health Ltd. | SelaSpot™ | Dogs and cats | Selamectin | Topical solution | 60 mg/mL and 120 mg/mL | prevention and control of flea infestations, kills adult fleas and prevents flea eggs |
| December 14, 2020 | NADA | Revivicor, Inc., a wholly owned | pPL657 rDNA CONSTRUCT IN | Domestic Pigs | pPL657 rDNA construct | Large molecule injectables | N/A | Biological derivatives of the homozygous GalSafe® lineage |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | subsidiary of United Therapeutics Corporation | DOMESTIC PIGS | | (Undetectable endogenous galactose-alpha-1,3-galactose sugar residues) | | | that are intended to be used as sources of food or human therapeutics |
| November 25, 2020 | ANADA | Dechra Veterinary Products LLC | Tzed™ | Dogs | Tiletamine Hydrochloride Zolazepam Hydrochloride | Intravenous injection | 1–2 mg/lb | Supplement inhalant anesthetic for maintenance |
| November 16, 2020 | NADA | QBiotics Group Ltd. | STELFONTA® | Dogs | Tigilanol tiglate | Injectable solution | 1 mg/mL | For use in dogs for the treatment of:<br>1) non-metastatic cutaneous mast cell tumors<br>2) non-metastatic subcutaneous s mast cell tumors located at or distal to the elbow or the hock. |

## 5. Global market and regulatory constraints

The total sales of animal drug products were reported to be around $22 billion globally in 2019.[9] The vaccines, medicines and medical devices for pet animals and livestock animals were determined to be $ 8 billion and $ 14 billion, respectively. Zoetis, Merck Animal health, Merial, Elanco Animal Health, Bayer Healthcare Animal Health, Boehringer Ingelheim Animal Health, Novartis Animal Health and Virbac Group produced sales in the billions for animal pharmaceuticals.

Furthermore, Animal Health Institute, an industry trade group reported that animal medicines account for about 2.5 % of the total pharmaceutical market. The innovations for animal health is expected to benefit about 27 billion animals worldwide (24 billion chickens, more than 1 billion cattle and sheep, 750 million pigs and goats, 500 million dogs and 400 million cats).[76]

Like human health products, animal health products are also guided by the guidance for industry to obtain approval from regulatory agencies (e.g United States Food and Drug Administration).[77] The approximate time to bring a new animal drug product ranges from 10 – 15 years with an estimated investment of $100 million before drug product approval.[78] Vaccines for pet animals as well as livestock animals are also major contributors to the animal pharmaceutical market. The development of vaccine can range from three to five years with an estimated investment of $80 million.[79]

Drug product approval may require additional user fees (e.g. Animal Drug User Fees Act (ADUFA) and the Animal Generic Drug User Fee Act (AGDUFA) by USFDA) to support the regulatory approval process. [77]

## 6. CONCLUSION

To summarize, the animal drug product development can become challenging sometimes despite the availability of the developmental challenges from the human drug products, if already approved on market. The timeline for a new animal drug from discovery to approval may range from 10 to 15 years, which relatively shorter as compared to human drug product lifecycle. Due to physiological difference and numerous animal species, the decision making for dose strengths can be difficult and ultimately as high as ten strengths may be required for a single drug product. The stability of the drug substance and drug product is very critical due to the varied environmental conditions and use of the inactive components in the drug product. In some countries, user fees may be required as a part of approval process which may increase the total cost of the animal research and development prior to approval of a drug product. Innovations in animal research have geared up recently with the increased understanding of animal health and the potential risks of spreading infections to the human population, if left untreated. This review paper identified and discussed three major areas of drug delivery needs in animal health such as convenience of delivering a drug product in pet animals and livestock animals, potential use of biologic drug products and injectable products.

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