



The American Chamber of Commerce in Japan
在日米国商工会議所
Animal Health Subcommittee



EUROPEAN BUSINESS COMMUNITY
欧州ビジネス協会
ANIMAL HEALTH COMMITTEE

農林水産省消費・安全局
衛生管理課
課長
栗本まさ子 殿

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非食用動物用の動物用医薬品における生殖・発生毒性試験の必要性に関する要望事項

ACCJ及びEBCの合同動物薬小委員会は、犬、猫などの非食用動物用の動物用医薬品について、催奇形性試験（げっ歯類及び非げっ歯類）が必須資料とされていることに関して下記の規制緩和をご提案します。

現在の状況

我が国においては、動物用医薬品のための毒性試験等ガイドライン（平成12年3月31日付け12-32畜産局衛生課薬事室長通知）のなかで、生殖・発生毒性試験として新動物用医薬品については原則的にげっ歯類及び非げっ歯類（通常、ウサギ）を用いた催奇形性試験が要求されております。このことは犬、猫などの非食用動物用の動物用医薬品についても同様であり、妊娠動物への適用を想定していない場合でも例外ではありません。

VICHにおいては、食用動物用の動物用医薬品を対象にした「ヒト食品中残留動物用医薬品の安全性を評価する試験」（VICH GL32）のなかで生殖毒性試験及び発生毒性試験のガイドラインが提示されており、ヒトへの影響を慎重に評価する内容となっております。つまり、食用動物用の動物用医薬品では生殖毒性試験及び発生毒性試験は必須となっております。このことについては異論を挟む余地はないと考えられます。一方で、非食用動物用の動物用医薬品における生殖・発生毒性試験の必要性については、各規制当局の判断に委ねられているところであり、EMEA及びFDAでは、非食用動物用の動物用医薬品にはそれらを要求しておりません。ただし、繁殖用動物あるいは妊娠動物に使用することが予定されている場合には、その限りではなく、対象動物を用いた生殖毒性試験が必要であります。つまり、生殖・発生毒性試験の必要性は、妊娠動物への使用の有無如何によるものとしています。この判断は科学的に矛盾のないものであり、妊娠動物への適用は使用上の注意で規制することが可能であります。また、過剰に動物実験を行うことで動物福祉に配慮していると考えられます。

我が国においても、非食用動物用の動物用医薬品については一律に生殖・発生毒性試験を要求するのではなく、妊娠動物への使用を検討していない場合においては、催奇形性試験の必要性はないものと思われれます。

ACCJ/EBCからの意見

ACCJ及びEBCの合同動物薬小委員会は日本の薬事行政当局に対して、非食用動物用の動物用医薬品については、妊娠動物への適用を想定していない場合には、催奇形性試験を不要とするように要望します。

このご提案を前向きにご検討いただければありがたく存じます。

敬具

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ACCJ Animal Health Subcommittee

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Ms. Masako Kurimoto
Director
Office of Animal Health and
Animal Products Safety Division
Food Safety and Consumer Affairs Bureau
Ministry of Agriculture, Forestry and Fisheries

July 30, 2004

Subject : Teratogenicity study requirement for non-food producing animal products

ACCJ and EBC Joint Animal Health Sub-Committee would like to propose the following deregulation concerning the Teratogenicity study requirement for non-food producing animal products

Current situation:

VICH guidelines on the testing of developmental toxicity for veterinary medicinal products used in food-producing animals (VICH GL32: "Studies to evaluate the safety of residues of veterinary drugs in human food: developmental toxicity testing") require comprehensive studies in order to evaluate the effects of the residue of concerned compound in food on human health. It is mandatory in the US, EU and Japan to conduct developmental toxicity tests for any products intended for use on food producing animals, a requirement that is well accepted by the scientific community.

The necessity of conducting developmental toxicity tests for non-food producing animals, on the other hand, depends on the regulatory body. The EMEA and FDA do not require studies for non-food producing animal products unless the product is to be used on pregnant animals. Here they are only concerned with target animal safety. The VICH Guidance on target animal safety (currently in development) states that developmental toxicity studies will be required for products intended for use in breeding animals. These would be specific studies in the target species. The Guidance includes dogs and cats. This proposal is scientifically accepted and the target animals can be protected by a contraindication on the label.

In Japan, the guideline of toxicological evaluation for veterinary products (Notification 12-32 on March 31st, 2000) requires applicants of new animal health products to submit teratogenicity studies from rodent and non-rodent species, respectively. This requirement applies to non-food producing animals, such as dogs and cats, regardless of whether or not the product is intended for use on pregnant animals.

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The EBC and ACCJ feel that this requirement is unreasonable. Japan should consider abolishing the requirement for developmental toxicity tests for all new veterinary products intended for use in non-food producing animal products, so long as the products concerned are not intended for use on pregnant animals. This requirement does not have any basis in science and does nothing to protect the safety of the target animals. It also adds an unnecessary burden on producers of animal health products. Companies have even reported being asked to supply teratogenicity studies for compounds that have already been used in humans worldwide (including Japan) for over 30 years without any reported adverse effects (see attached). Also, it is a matter of animal welfare, which suggests not killing laboratory animals more than is required or needed.

ACCJ/EBC recommendation:

ACCJ and EBC Joint Animal Health Sub-Committee requests that the Japanese Animal Health Administration consider omitting the requirement to test for developmental toxicity for products intended for use on non-food producing animal so long as the products concerned are not intended for use on pregnant animals.

Your positive consideration to our above proposal will be greatly appreciated.

Yours sincerely,
Yoshihiro Shimizu
Chairman
Animal Health Subcommittee
The American Chamber of Commerce in Japan

Dr. Gerhard H. Roth
Chairman
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Attachment

A company recently tried to register a combination drug with three active ingredients for treatment of *otitis externa* in dogs. One of the components "C" was approved for human use in the 1970s, just before the introduction of new guidelines requiring rabbit teratogenicity and was approved based on rat and mouse teratogenicity studies only. The original manufacturer conducted a non-GLP study in rabbits and published the result in 1974 (Postgrad Med J, July Suppl. 1974, pp17-20). The report stated: "no teratogenicity was observed in rabbits up to 200 mg/kg", but the original data is not available now. PDR also describes that the drug is not teratogenic in rabbits up to 200 mg/kg.

This drug has been used for humans including a considerable number of pregnant women for 30 years without any problem worldwide, *including in Japan*. After the first approval in Japan, this drug has since been subsequently authorized as an over-the-counter product and a number of generics are now available in the Japanese market. None of the license holders have ever been requested to conduct additional teratogenicity studies using rabbits.

It is accepted worldwide that this drug has no teratogenicity. According to the FDA pregnancy category, topical use is graded "B" and the Australian Drug Evaluation Committee's "Prescribing medicines in pregnancy" 4th edition graded it as "A". Both of these categories mean that no evidence of teratogenicity has been reported. (Please refer to the websites.)

As part of the application dossier to have this new drug approved for use in dogs, the company submitted rat and mouse data as well as all of the above comments and published epidemiological reports concerning pregnant woman (e.g. Czeizel AE, Toth M, Rockenbauer M.: No teratogenic effect after clotrimazole therapy during pregnancy. *Epidemiology*. 1999 Jul;10(4):437-40). The company also proposed that this drug not be used in pregnant dogs.

Despite its long history of safe use in humans (including pregnant women) and its intended use on non-pregnant dogs, the Ministry of Agriculture Fisheries and Forestry still insisted that a teratogenicity study for this product be conducted on rabbits.

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