I. INTRODUCTION

The Flea Spot-on Solution 10% w/v products are available for medium dogs (4 kg to less than 10 kg), large dogs (10 kg to less than 25 kg) and extra large dogs (25kg to less than 40 kg), and large cats (greater than 4 kg). These presentations all have identical formulations. The only differences between the presentations are in the fill volume of the pipettes; the three dog products contain 0.4, 1.0 and 2.5 ml and the cat product contains 0.8 ml. This scientific discussion is concerned with Flea Spot-on Solution 10% w/v for Extra Large Dogs. The product is a non-aqueous solution for topical application to dogs at a dose rate of 10 - 25 mg per kg bodyweight (0.1 – 0.25 ml/kg).

Identical products have already been authorised and are being marketed in the UK.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species. The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

Product Development and Composition

Bob Martin Double Action Spot-On Solution 400 mg for Extra Large Dogs is a clear yellow to brownish solution. The choice of the formulation is justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

Detailed consideration is given to some aspects of pharmaceutical development, including choice of formulation and proportion of solvents. Since the formulation contains benzyl alcohol and is presented in a single dose pack, microbial contamination is unlikely to present a problem. However, results of preservative efficacy testing were provided.

Active substance

Although there is no pharmacopoeial monograph for imidacloprid in-house specifications have been developed for the active substance imidacloprid and these are of pharmacopoeial quality. The company's dossier included details of the manufacture and control of the active substance.

This specification is in accordance with current guidelines and ensures that the material is suitable for use in solutions. The methods of analysis have been shown to be valid, and data obtained on several batches show that the specification is consistently met.

Other Substances

Benzyl alcohol and butylated hydroxytoluene are well established excipients and comply with European pharmacopoeial requirements.

Propylene carbonate complies with the USNF[1] monograph which adequately confirms identity and includes tests for specific gravity, pH, residue on ignition, volatile organic impurities and related substances.

Packaging Materials

Bob Martin Double Action Spot-On Solution 400 mg for Extra Large Dogs is packaged in white polypropylene tubes containing 2.5 ml of the product with a white polypropylene cap. Tubes of product are contained in blister packs holding either 2, 3, 4 or 6 unit does tubes. These are packaged in cartons containing either 1, 5, 10 or 20 blisters.

The proposed polypropylene unit dose pack is already approved for use with other similar Bayer products. Compatibility with the proposed formulation has been considered and studies to investigate the volume of overfill required are reported and integrity of sealed tubes is confirmed by routine leak testing.

Manufacture of the Finished Product

All production steps are performed according to pharmaceutical Good Manufacturing Practice (GMP), using conventional techniques. The validation of the process was carried out on three batches of the product. The studies conducted demonstrate that the solution can be produced to a consistent and appropriate quality.

All components of the product have been demonstrated to comply with relevant guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicines.

Finished Product Quality Control

A number of parameters are controlled immediately after the product is manufactured. These include the appearance, identity of imidacloprid, content of the stabilizer, butylated hydroxytoluene, volume, relative density and water content. Data have been provided which indicate the suitability of the methods used in testing the finished product.

Stability of the Product

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

CONCLUSIONS ON QUALITY

The applicant has provided evidence to show that the product is satisfactorily formulated and adequately controlled. A shelf life of 5 years is justified for the product stored in the approved packaging, subject to the following storage warnings:

[1] An official publication, issued first by the American Pharmaceutical Association and now yearly by the United States Pharmacopeial Convention, that gives the composition, description, method of preparation, and dosage for drugs

Store away from food, drink and animal feeding stuffs.

III. SAFETY ASPECTS

Pharmacology

The applicant has provided bibliographical data and studies which show that imidacloprid has novel pharmacological properties. The biological basis of the insecticidal activity of imidacloprid is its high affinity for the nicotinergic acetylcholine binding sites in the insect central nervous system (CNS). The ensuing inhibition of cholinergic transmission in insects results in paralysis and death. Due to the weak nature of the interaction with mammalian nicotinergic receptor sites and the postulated poor penetration through the blood/brain barrier in mammals, it has virtually no effect on the mammalian CNS. The minimal pharmacological activity in mammals is supported by safety studies involving systemic administration of sub-lethal doses to rabbits, mice and rats. In further studies, in addition to the adulticide flea efficacy of imidacloprid, a larvicidal flea efficacy in the surroundings of the treated pet has been demonstrated. Larval stages in the pet's surroundings are killed following contact with a treated animal.

The applicant has also conducted acute dermal studies in rats and target animal overdose and serum kinetic studies have established that systemic absorption is very low, transient and not relevant for the clinical efficacy. This has been further demonstrated by a study in which fleas were not killed after having fed on previously treated animals once the animal's skin and fur had been cleaned of all active material.

The product is indicated for cutaneous administration. Following topical application in dogs, the solution is quickly distributed over the animal.

Toxicology

Single Dose Toxicity

Rats and mice were exposed to imidacloprid via oral or intraperitoneal administration. Toxic signs were similar for each method of administration and included behavioural abnormalities (apathy), decreased motility, staggering gait[2], respiratory disturbances, piloerection[3], narrowed palpebral[4] fissures, transient trembling, spasms and convulsions. Following either route of administration, signs commenced shortly after administration and reversed by one day (mouse, oral) 4 days (rat, intraperitoneal) or 6 days (rat, oral). In one study a no observed effect level (NOEL) of 150 mg/kg body weight was determined for oral administration in rats. In another study toxic signs were observed in 100% of rats recieving oral doses of 100 mg/kg body weight.

No adverse signs were recorded in rats following dermal application of 5000 mg/kg body weight or an aerosol of 69 mg/m^3 air. Toxic signs were observed following high inhalation exposure levels (4 hours inhalation exposure to dust at levels at or above 2577 mg/m^3 air), these were slightly laboured breathing, decreased motility, piloerection and slight tremor.

Imidacloprid (500 mg/animal) was a non-irritant to the shaved skin of rabbits in a 4 hour exposure under semi-occlusive conditions. When introduced to the conjunctival sac of rabbits Imidacloprid caused no eye irritation when exposed for 24 hour exposure model.

[2] A **gait** is a particular way or manner of moving on foot
[3] The reflex of producing goose bumps
[4] means relating to the eyelids.

Diluted imidacloprid was tested for dermal sensitisation potential in guinea pigs. No evidence of sensitisation was found.

Acute toxicity of the formulated product

The toxic signs observed in a group of rats dosed for up to 2 days following oral administration were similar, but not identical to those observed following oral administration of the active substance. The lowest dose tested was 495 mg/kg body weight.

An additional acute oral toxicity study in rats was presented. A group of rats were orally dosed with Imidacloprid Spot-on 10% at 450 or 600 mg/kg body weight in polyethylene glycol 400:water (1:1) and observed over a period of 14 days. No effects were observed at either dose level. A NOEL of 600 mg/kg formulated product is therefore proposed.

Dermal exposure to Imidacloprid Spot-On 10% was for 24 hours under occlusion. No treatment-related toxic signs were observed but in both treated and control groups, there was a high incidence of red nasal stain in both sexes and urine stain in female animals. Exposure to aerosol was nose-only exposure to particle in the respirable range for 4 hours. No clinical signs were observed in the male rats. Oral staining was observed in the female rats at the only exposure level tested (2145 mg/m³ air).

Sensitisation potential of the formulated product to the skin and eyes was also investigated. Imidacloprid Spot-on 10% (0.5 ml/animal) was found to be a mild irritant to rabbit skin when exposed for 4 hours under occlusion. Imidacloprid Spot-on 10% (0.1 ml applied into the conjunctival sac) was assessed as a moderate irritant to the rabbit eye. All signs of eye irritation had resolved by day 14. Also no evidence of skin sensitisation was found.

Repeated Dose Toxicity

A number of studies were carried out whereby groups of rats were given a diet comprising different concentrations of imidacloprid for a range of different days, (minimum length of time being 13 weeks, maximum 2 years). In each study a group of rats acted as a control group and received no imidacloprid. The reversibility of any effects were also observed. Main observations were decrease in body weight gain, and changes to organ weights and function. It is considered that these aspects have been adequately addressed in the dossiers.

Repeated dose dermal toxicity studies were carried out on rabbits. Diluted imidacloprid was applied as a paste to the unabraided shaved skin of rabbits under semi-occlusive dressings at doses of 0 or 1000 mg/kg body weight for 6 hours a day on 5 consecutive days/week for 3 weeks. There was no evidence of treatment-related effects on appearance, behaviour, feed consumption, body weights, clinical chemistry, haematology, organ weights, gross pathology or histopathology and no local effects on the treated skin. The NOEL for the study was 1000 mg/kg body weight.

Inhalation toxicity studies were carried out in rats. Rats were exposed to air containing 0, 20, 109 or 505 mg/m³ imidacloprid as a dust for 6 hours and on 5 successive days. The NOEL in this study was 20 mg/m³. Observed effects were decreased body weight gain and hepatic[5] function disturbances. In a similar study rats were exposed to a dust of imidacloprid (purity 95.2%) at mean concentrations of 0, 5.5, 30.5 or 191.2 mg/m³ during 6 hours per day, 5 days per week for 4 weeks. The percentages of particles within the respirable range (< 5 µm) were

[5] related to liver

95, 53 and 43 % respectively for the three concentration levels. The design of the exposure chamber resulted in head and nose exposure. The NOEL for the study was 5.5 mg/m^3. Observed effects also related to hepatic function disturbances.

Reproductive Toxicity, including Teratogenicity:

A group of rabbits were given diluted imidacloprid orally at 0, 8, 24 or 72 mg/kg body weight on gestation days 6 - 18. Maternal toxicity was evident at doses from 24 mg/kg body weight. This was shown by decreased feed intake and body weight gain at this or higher doses. Ab increased mortality was shown at 72 mg/kg body weight. Increased post-implantation losses were also recorded at 72 mg/kg body weight with a corresponding decrease in the litter size. Foetal body weight (not statistically significant) and the extent of skeletal ossification[6] were reduced at the high dose. These effects are considered likely to result from primary maternal toxicity. The NOEL for maternal toxicity was 8 mg/kg body weight per day based in reduced body weight and food consumption at ≥24 mg/kg body weight per day. The NOEL for embryo- and foeto-toxicity was 24 mg/kg body weight per day based on resorptions, decreased body weight and delayed skeletal development at 72 mg/ kg body weight per day. There was no evidence of teratogenicity.

In a similar study rats were given diluted imidacloprid orally at doses of 0, 10, 30 or 100 mg/kg body weight per day on days 6-15 of gestation. The appearance, behaviour and mortality of the rats were not affected at any dose level. Food intake and body weight gain were depressed at 30 and 100 mg/kg body weight per day. No treatment-related changes were observed in the incidence of gravid females, the incidence of females with viable foetuses, rates of implantation, numbers of viable foetuses and resorptions, foetal weights or sex ratios, external appearance or appearance of viscera[7] at any dose level. The incidence of wavy ribs was increased at 100 mg/kg body weight per day. This is likely to be the result of maternal toxicity. The NOEL for maternal toxicity was 10 mg/kg body weight per day. The NOEL for foetal toxicity was 30 mg/kg body weight per day. There was no evidence of teratogenicity.

Mutagenicity

Mutagenic potential has been tested in a wide range of *in vitro* and *in vivo* test systems. Most of the *in vitro* studies and all of the *in vivo* studies all gave negative results. It is therefore concluded that imidacloprid presents no mutagenic or clastogenic[8] hazard to users.

Carcinogenicity

Given the proposed use of the products and the lack of mutagenic activity, carcinogenicity studies in rodents would not normally be required for authorisation. However, studies in rats and mice have been provided and provided no indication that imidacloprid is a potential carcinogenic.

Other Studies

The applicant has conducted additional studies on immunotoxicity[9] and neurotoxicity[10]. The immunotoxicity study concluded that there was adequate information to show that the product is

[6] Ossification is the process of bone formation
[7] Internal organs
[8] Clastogenic effects are damages to chromosomes, such as breaks in or change in the of amount of proteins
[9] Immunotoxic chemicals that can cause immune system malfunction with exposure

unlikely to present an immunotoxic risk to users. Similarly, results from the neurotoxicity study concluded that imidaclioprid is unlikely to be a potential neurotoxin.

Observations in Humans

The applicant has provided information stating that no adverse effects have been reported among employees who may have been exposed to imidacloprid during production or formulation of the product.

Studies on Metabolites, Impurities, Other Substances and Formulation

The applicant has provided information regarding impurities in the active substance and metabolites which showed that any of the impurities present were of limited toxicity and of no cause for concern. It is considered that these aspects have been adequately addressed in the dossiers.

Many of the excipients are commonly used in veterinary medicines.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the proposed use of the product dose not pose a risk to users. .
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

This product contains benzyl alcohol and may cause skin sensitisation or transient skin reactions (for example, irritation, tingling). Avoid contact between the product and skin, eyes or mouth. Do not eat, drink or smoke during application. Wash off any skin contamination with soap and water. If the product gets into eyes accidentally, the eyes should be thoroughly flushed with water. If skin or eye irritation persists, obtain medical attention. If the product is accidentally swallowed, obtain medical attention immediately. Wash hands thoroughly after use. After application, do not stroke or groom animals until application site is dry.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product would appear to present minimal risk to the aquatic environment. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASPECTS

Clinical Pharmacology

[10] This occurs when the exposure to natural or manmade toxic substances, which are called neurotoxins, alters the normal activity of the nervous system.

Pre-Clinical Studies

Pharmacology

Imidacloprid has a high affinity for the nicotinergic acetylcholine binding sites in the central nervous system. This produces in an inhibition of cholinergic transmission in insects and results in paralysis and death. There is only a weak interaction with mammalian receptor sites and this, coupled with the postulated poor penetration through the membranes of central nerve cells in mammals, means that there is virtually no effect on the mammalian CNS. Imidacloprid thus has a minimal pharmacological activity in mammals.

The applicant has referred to studies with radio-labelled imidacloprid in laboratory animals. These have indicated that the compound is rapidly and almost completely absorbed from the gastrointestinal tract. It is also extensively metabolised and rapidly excreted following both oral and intravenous administration. There appears to be no accumulation in any specific organs.

Following topical application of a 10% solution as proposed for marketing, imidacloprid is quickly distributed over the body in dogs.

Acute dermal studies in the rat and tolerance studies in the target species, indicate that systemic absorption is negligible after topical application.

It is considered that these aspects have been adequately addressed in the dossiers and that the information provided in the Summary of Product Characteristics is accurate and helpful

Tolerance in the Target Species of Animals

The applicant has conducted controlled target animal tolerance studies using multiples of the recommended dose in the target species. All doses were administered topically. The highest dose rate used represented 8 times the maximum recommended dose and this was applied on a single occasion to a group of dogs.

Throughout these studies only one adverse reaction was recorded. This was in a dog treated with 200 mg/kg which managed to lick off some of the product as the large dose volume resulted in run-off. This animal vomited shortly after application and it is suggested that this was due to the bitterness of the product rather than any toxic effect. The dog was reported to be normal when examined 3.5 hours later. The only other effects noted were 'crystals' on the skin of two dogs after application of 3 ml of product at a single site and slight, transient, yellow discoloration around the application site on the coats of 2 out of 3 white dogs treated with 3 ml of the product. This effect had disappeared 3 days after application.

In addition to the above, further tolerance studies were also carried out in pregnant/lactating bitches and their offspring. No abnormalities were observed in the offspring which were examined from birth up to 1 and 7 weeks of age. A number of these bitches were treated twice during lactation with 18-30 mg/kg imidacloprid. No adverse effects were observed in either the bitches or the offspring. In two other studies, a group of bitches their offspring were treated before the offspring were weaned. No adverse effects were observed in any of the offspring or bitches. Further studies in weaned offspring aged 8 to 10 weeks did not cause any observable adverse reactions with doses of imidacloprid of 18-40 mg/kg.

Therefore the data provided on tolerance of the product in dogs indicate that it should have a wide safety margin when used as recommended. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

The product is bitter tasting and salivation may occasionally occur if the dog licks the application site immediately after treatment. This is not a sign of intoxication and disappears within some minutes without treatment

Clinical Efficacy

Laboratory Trials

In all of these studies, dogs were artificially infested with at least 100 fleas of the species *Ctenocephalides felis* and untreated/placebo groups were included. Some special case trials were also conducted to simulate the effects of rain and to determine flea control on young dogs when only the bitch was treated. Dose rates of 1-20 mg/kg imidacloprid were tested in these studies.

The minimum effective dose rate selected (10 mg/kg) was found to offer >99% efficacy against flea challenge at 24 hours after treatment and >90% at 28 days. The recommendations on treatment given in the Summary of Product Characteristics and product literature provide imidacloprid dose rates of 10 to 25 mg/kg in most dogs and the data available indicate that this will offer a high level of protection against flea infestation for at least 28 days after treatment.

The special situation of large dogs and the larger dose volume required was investigated in one study. In this it was found that dividing the dose equally and applying it at two sites resulted in slightly better efficacy at all time points up to 7 weeks post-treatment. At 28 days, the efficacy rates following application at two sites and one site were 99.4% and 91.6% respectively. The two sites selected were on the skin between the shoulder blades and the skin between the iliac crests.

The choice of the 10 mg/kg dose rate and 10% formulation means that even the largest dog would receive only 2.5 ml of the product at one site. Such a volume was observed to disappear rapidly into the coat and never to 'run off'.

Field Trials

Three field studies were carried out with the final formulation of imidacloprid presented in pipettes containing 0.4, 1.0 or 1.5 ml and applied at dose rates of 10 - 20 mg/kg between the shoulder blades, and also on the rump in the case of dogs >25 kg. The details were as follows:

Trial 1

This was conducted at a number of sites and the performance of imidacloprid was compared with that of an authorised Marketing Authorisation (MA) against natural flea infestations with *Ctenocephalides felis* or *C. canis*. This included one group of dogs being treated with imidacloprid at the recommended dose rate and the other being treated with the authorised MA according to the manufacturer's recommendations. Many breeds of dogs were included so that a good variety of coat lengths and dose ranges were represented Efficacy was calculated by comparing flea counts at each examination time to the values pre treatment

Although the results in the group treated with the authorised MA were slightly better, there were no statistical differences between groups. In addition to the effects on fleas, there was a significant decrease in pruritus, alopecia and Flea Allergy Dermatitis in animals treated with imidacloprid. Again, there were no significant differences between the treatments with regard to clinical signs. Tolerance was good in both groups.

Trial 2

In this study a group of dogs naturally infested with *Ctenocephalides felis* or *C. canis* were treated with imidacloprid at the proposed recommended dose rate. Again, the dogs were of a wide variety of sizes, breeds and hair type.
Some of these dogs were assessed one week post-treatment when 81% were found to be free of fleas. In a further 12%, the degree of infestation was markedly reduced at this time point. Of the dogs examined during the 3 week period post-treatment, 92% were free of fleas at one examination. At 4 weeks after treatment, 77% of dogs were flea-free, 21% had from 1-3 fleas and 2% had 4-10 fleas. No adverse effects of clinical relevance were reported, nor were any interactions noted in dogs treated concomitantly with other pharmaceutical products and/or vaccines.

Trial 3

This was a trial conducted at a greyhound kennels with a serious flea problem due to *C. canis*. A number of greyhounds were treated with imidacloprid at the recommended dose rate whilst a smaller group of dogs remained as untreated controls. An efficacy rate of 92% was recorded by day 1 after treatment and this remained at >95% up to day 32 when the study was concluded.

It is considered that these studies confirm that imidacloprid is very effective at treating and controlling flea infestations of dogs for up to 28 days when applied as a spot-on at dose rates of 10 to 25 mg/kg under typical field conditions

CONCLUSIONS ON CLINICAL ASPECTS

It can be concluded that the studies carried out in dogs and cats under both laboratory and field conditions confirm that the product should be effective at treating and controlling flea infestations for up to 28 days after treatment when applied as recommended at a dose rate of 10 - 25 mg/kg.

PART V. OVERALL CONCLUSION ON THE PRODUCT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(WWW.GOV.UK/CHECK-ANIMAL-MEDICINE-LICENSED)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(WWW.GOV.UK/CHECK-ANIMAL-MEDICINE-LICENSED)