

## SCIENTIFIC DISCUSSION

### Analytical

RESPIPORC FLU3 is an inactivated, adjuvanted vaccine intended for active immunisation of pigs against disease caused by Swine Influenza Virus.

RESPIPORC FLU3 is presented as a suspension for injection in vials containing 2 ml per dose. The active substances is inactivated *Influenza A* virus strains /swine/Bakum/IDT1769/2003 hp (H<sub>3</sub>N<sub>2</sub>), /swine/Haselünne/IDT2617/2003 h (H<sub>1</sub>N<sub>1</sub>) and /swine/1832/2000 (H<sub>1</sub>N<sub>2</sub>).

The vaccine is produced by IDT Biologika GmbH, D-06861 Dessau-Roßlau in Germany.

Each dose of 2 ml contains:

#### Active substances:

Strains of inactivated Influenza A virus/swine/

Bakum/IDT1769/2003 (H3N2)	$\geq 10.53 \log_2$ GMNU <sup>1</sup>
Haselünne/IDT2617/2003 (H1N1)	$\geq 10.22 \log_2$ GMNU <sup>1</sup>
Bakum/1832/2000 (H1N2)	$\geq 12.34 \log_2$ GMNU <sup>1</sup>

<sup>1</sup>GMNU = Geometric mean of neutralizing units induced in Guinea pigs after twice immunisation with 0.5 ml of this vaccine

#### Adjuvant:

Carbomer 971 P NF 2.0 mg

#### Excipient:

Thiomersal 0.21 mg

Overall the quality part of the dossier is very detailed and complies with relevant monographs and guidelines.

In general, the description of the production process and methods is clear and detailed. The manufacturing process is considered acceptably validated with pilot scale batches. Validation with production scale batches will be performed after approval, which is acceptable.

The provided information on the choice of vaccine strains and reference to literature data demonstrating the significance of influenza A infections are deemed sufficient. The choice of adjuvant is well-based as powdered Carbopol polymers have been found safe for use in a wide variety of cosmetics, detergents and pharmaceuticals for humans for a long time. A thorough study of 22 adjuvants for their non-virucidal characteristics has clearly demonstrated a low toxic and irritation potential leading only to slight reactions soon replaced by a scar, whereas the commonly used mineral oil adjuvants induce strong inflammatory reactions and muscle necrosis. The choice of antimicrobial preservative thiomersal is acceptable. The efficacy of the preservative has been tested in accordance with European Pharmacopoeia (Ph. Eur.) 5.1.3 and established under simulated in-use conditions. Certificates of analysis were provided for all adjuvants/excipients or their components. These materials were tested according to Ph. Eur. or internal procedures.

The choice of container closure systems is based on well-established use of this type of container for veterinary medicinal products. In particular, the use of plastic containers is reasonable in animal production environments where breakage is a concern.

The starting materials of biological origin comply with the 'Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathies agents via human and veterinary medicinal products' (EMEA/410/01-Rev02). The overall TSE risk associated with the influenza A inactivated vaccine is considered negligible.

The control tests during production are adequately described and validated. Consistency of production has been demonstrated by testing several pilot batches and one batch of maximum batch size. The results are consistent and all results comply with the criteria for the in-process controls. The Marketing Authorisation Holder commits to produce two further full production scale batches following approval with the objective to show comparability in maximum batch size scale.

The methods used for the control of the finished product and the specification are provided. These methods are adequately described and validated.

Batch analysis data are provided for pilot scale batches filled in PET and glass bottles of all sizes. This is considered acceptable; representativeness of pilot scale batches for full production batches has been demonstrated. The applicant commits to provide batch results for two full production scale batches following approval.

The Marketing Authorisation Holder provided an intermediate report on an ongoing real time stability study presenting results for three pilot batches of the final vaccine filled in PET bottles and 3 pilot batches filled in glass bottles stored at 2 °C to 8 °C. Based on the results currently available, a shelf life of 24 months can be granted. The proposed in-use shelf life of 8-10 hours at 2-8°C is satisfactorily supported by stability data. Stability of the virus harvest and deactivated antigens is adequately demonstrated.

To conclude, the quality of RESPIPORC FLU3 is considered acceptably ensured.

## **Safety**

The safety of RESPIPORC FLU3 was evaluated on the basis of the requirements for immunological veterinary medicinal products as described in Directive 2001/82/EC, as amended by Directive 2004/28/EC, the General requirements for the production and control of inactivated mammalian bacterial and viral vaccines for veterinary use, the Guidelines for production and control of porcine live and inactivated vaccines, Ph. Eur. monograph "Vaccinum influenza inactivatum ad suem" (01/2005; 0963) and the relevant monographs of the Ph. Eur., Section 5.2.6: "Evaluation of safety of veterinary vaccines and immunosera" (04/2005:50206).

The safety studies were made in commercial breeds of pigs at the minimum age (56 days old) recommended for first vaccination. Safety studies were also made in pregnant sows at the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> trimester of pregnancy.

The safety studies in piglets were made in a German GLP test facility in accordance with the principles of Good Laboratory Practice laid down in Directive 2001/82/EC, as amended by Directive 2004/28/EC.

Safety in pregnant sows and examination of reproductive performance were made under GLP-like conditions laid down in Directive 2001/82/EC, as amended by Directive 2004/28/EC in a German swine herd.

The vaccine RESPIPORC FLU3 contains three swine influenza-A-virus strains as the active immunological effective ingredients, an adjuvant, thiomersal as a preservative and water for injection. The inactivation of the influenza virus is realized with binary ethyleneimine. The neutralization of the ethyleneimine is carried out with sodium thiosulfate.

In total seven batches were produced for the safety and efficacy trials from which three batches were used in safety testing.

The safety of RESPIPORC FLU3 was evaluated in laboratory studies using a standard experimental design of vaccinated pigs and controls, all piglets being of the minimum age recommended for vaccination and without maternal antibodies to swine influenza-A-virus of the subtypes included in this vaccine (H1N1; H1N2; H3N2). The studies were reported in accordance with the technical requirements as safety after administration of one dose and repeated single dose; safety after administration of two doses followed by one dose; and by repeated administration of a double dose.

In all studies the follow up after vaccination consisted of daily examinations for local reactions and daily examinations for systemic reactions (parameters observed were behaviour, body condition, respiration, coughing, nasal discharge, faecal examinations). Rectal body temperatures were measured from four days before vaccinations, at the day of vaccination and two hours, four hours, eight hours and twelve hours after vaccination and thereafter daily for the next four days. Daily observations on feed intake were also measured, and individual weighing was made from four days before vaccination until seven days after vaccination. Serological examination using haemagglutination test was made before vaccination and regularly after vaccination until euthanasia. After euthanasia and necropsy histological examinations were made of tissue samples from the injection sites.

In none of the above studies any abnormal reactions were recorded in any of the above mentioned parameters. Thus the safety of RESPIPORC FLU3 was adequately documented in the minimum target group of piglets from 56 days of age. There were slight local reactions occurring in some vaccinated animals which are correctly reflected in the SPC.

The studies for efficacy under laboratory conditions were also used to evaluate the safety according to Ph. Eur. monograph 0963. In twelve studies no abnormal increase in the rectal temperature was recorded neither any local or systemic clinical reactions after vaccination. Piglets were 56 or 96 days old respectively when vaccinated. The number of vaccinated pigs and controls were always adequately balanced.

In one of those studies, there was however a high increase of rectal temperature (+ 2.4°C) occurring in one animal immediately after 1<sup>st</sup> vaccination. Also, in two of these studies, there was a significant (although mean differences between groups were mild) increase of rectal temperature immediately after vaccination. These adverse reactions are mentioned in the SPC, Section 4.6.

Examination on the safety in pregnant sows (herd immunisation) were made in three studies as administration of a double dose followed by a single dose in 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> trimester of the pregnancy. The studies each consisted of vaccinates and controls. Parameters included daily examinations for local and systemic reactions, rectal body temperatures from four days before vaccination until four days after vaccination with close follow up just after administration of the vaccine (D0+2h, D0+4h, D0+8h, D0+12h). Furthermore daily observations on feed intake were made as well as pregnancy test using ultrasonic equipment. Serological examinations on sera using haemagglutination inhibition test was made on D0 in order to detect any antibodies to swine influenza virus before vaccination. In none of the three studies were any abnormal reactions recorded.

From the above described three studies the reproductive performance was recorded. Parameters recorded were litter size, stillborn and crushed piglets, average body weight of newborn and live born piglets, number of live piglets on D1 after farrowing and number on weaning, average body weight of piglets at weaning, percent losses of piglets from farrowing to weaning. In none of the studies any reproductive parameters were affected by vaccination.

In field trials RESPIPORC FLU3 was tested as a single dose vaccination and as repeated administration of a single dose in the minimum target group of piglets. In one field trial the piglets were sero-negative to H1N2 but positive to H1N1 and H3N2 while piglets in the two other field studies were sero-negative to all serotypes included in this vaccine. The trials were balanced including vaccinated pigs and controls in each study. The parameters recorded included local and systemic reactions prior to vaccination and four hours after vaccination and on the two first days after vaccination. Rectal temperatures were recorded on the same occasions, and necropsy was made if injection site reactions occurred. In none of the field trials were any abnormal reactions recorded.

Safety field trials also were made in sows during pregnancy (1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> trimester) and in gilts before insemination. Parameters recorded included local and systemic reactions prior to vaccination, four hours after vaccination and on the two first days after vaccination. Rectal temperatures were recorded on the same occasions, and necropsy was made if injection site reactions occurred. In none of the field trials in sows or gilts were any abnormal reactions recorded. Local reactions were, however, observed in some vaccinated animals, and these are correctly reflected in the SPC.

RESPIPORC FLU3 will not give rise to residues which will be harmful to the consumer. No withdrawal periods are considered to be necessary before vaccinated pigs are slaughtered for human consumption. The used adjuvant Carbomer 971 P NF is falling not within the scope of Regulation (EEC) No. 2377/90. The preservative thiomersal is included in Annex II of Regulation (EEC) No. 2377/90.

The vaccine is unlikely to harm the user except in the case of accidental self-injection where a minor local reaction may be expected. The use of this inactivated vaccine will not damage the environment.

### **Efficacy**

The Marketing Authorisation Holder has provided a good overview of the development over time of swine influenza in Europe. Vaccines are on the market with claims for protection against H1N1 and H3N2, which are the strains that have been circulating in most swine producing countries for decades. In 1994, H1N2 arose in Great Britain due to a triple reassortment where some HA genes were of human influenza virus origin, some NA genes were of swine H3N2 origin and some internal protein genes were of avian-like swine H1N1 origin. H1N2 has now spread to a number of European countries with variable prevalence. References 7 and 17 show that there is insufficient protection against challenge with H1N2 in pigs vaccinated with H1N1 and H3N2. This was the reason for developing RESPIPORC FLU3, which contains those three swine influenza types.

The target species is pigs and the recommended route of administration is by intramuscular injection behind the ear. This has been used in all trials. Pigs of youngest recommended age and pregnant sows have been included. The proposed vaccination scheme for pigs from eight weeks of age (56 days) is two doses of RESPIPORC FLU3 to be given with a three week interval (primary vaccination). Duration of immunity is claimed to be four months for pigs vaccinated between the age of 56 and 96 days, and six months for pigs vaccinated after 96 days of age. Pregnant sows should be revaccinated with a single dose 14 days prior to farrowing to develop colostral antibodies, which will clinically protect piglets for at least 33 days after birth. The vaccination scheme used in the laboratory and field trials was always in line with the proposed vaccination schedules.

An acceptable justification of choice of strains has been provided. However, the isolates for the vaccine come from one area in Germany and the first challenge trials were performed with German field viruses. As there may be a high diversity between isolates in other regions of Europe, the Marketing Authorisation Holder performed five additional challenge studies (among others, using field isolates from Denmark and France) and investigated the *in-vitro* cross reactivity with many different field virus isolates. The vaccine showed good protective capacity with all tested strains, including a new H3N1.

The efficacy of RESPIPORC FLU3 was evaluated on the basis of the requirements for immunological veterinary medicinal products as described in Directive 2001/82/EC, as amended. The Ph. Eur. monograph 01/2008:0963 Porcine Influenza Vaccine (Inactivated) describes the immunogenicity tests that the Applicant has used as a basic model for all laboratory studies. It requires at least ten vaccinated and ten controls of minimum age to be vaccinated with a minimum potency vaccine. Challenge is performed with each strain three weeks after end of recommended vaccination schedule by intratracheal administration of virulent field virus. Half of the pigs are euthanized after 24 hours and the rest after 72 hours. The quantity of influenza virus is measured in two pools of lung tissue from the three lobes of left and right side, respectively. The test is invalid if any control pigs have antibodies prior to challenge, and the vaccine complies if there is statistically significant lower mean

virus titre in the vaccinated pigs on both days. The virus harvest is incubated in embryonated hens' eggs for four days and investigated by hemagglutination assay.

The Marketing Authorisation Holder has deviated in the time to challenge (seven days in stead of 21 days), which is acceptable. Also, the rationale for developing a challenge method, which resembles the natural infection better than the method required by Ph. Eur., is accepted. In studies provided, it is shown that both methods give satisfactory results.

The laboratory efficacy studies were performed with batches of minimum antigen content or potency, although the batch potency test did not always reflect the antigen content completely.

The vaccines used in the efficacy trials were made in accordance with the method of preparation described in the dossier. Two batches were used in the trials; one of these had a minimum input of antigen and a minimum potency in the guinea pig test for H3N2 and H1N2, but a medium potency for H1N1. This batch was used for all laboratory trials except one. The other batch was blended to have a titre that would be considered representative for future batches for marketing but had minimum potency for H1N1 and medium potency for H1N2 and H3N2. This batch was used for all the field trials and for the laboratory trial mentioned above (H1N1 challenge). The Duration of Immunity study for H1N1 was repeated using a new vaccine batch of minimum potency.

Three studies have been provided as documentation for onset of immunity for the three vaccine components. All studies were conducted in accordance with GLP and were blinded, randomised and placebo-controlled. They are well performed and reported and support the efficacy of the vaccine.

The vaccine complies with the Ph. Eur. monograph for swine influenza, 0963, for all three serotypes when batches in the range of minimum potency are used. The pigs were of minimum age, 56 days, at first vaccination. Virulent field challenges were given seven days after last vaccination. Both intratracheal and aerosol challenge were used in parallel studies. The aerosol challenge is less stressful for the animals and seems to mimic the natural disease better as demonstrated by the distribution of lesions in the lungs. Reduction in viral load in the lungs, reduction in dyspnoea scores and in some cases absence of fever and lung lesions in the vaccinated pigs compared to placebo-treated pigs was shown in the studies. Onset of immunity was demonstrated by challenge to be seven days after 2nd vaccination, but increased antibody levels could be seen already from four days after 2nd vaccination in the study where blood samples were taken more frequently.

The Marketing Authorisation Holder originally provided nine studies in support of the Duration of Immunity of the vaccine. The protocol was similar to the immunogenicity test described in Ph. Eur. monograph 0963, except for the use of aerosol challenge and time to challenge. Because there may be interference of maternally derived antibodies until approximately eight weeks (56 days) of age, the pigs were vaccinated at 56 or 96 days of age, and challenged after four or six months. Subsequently the Marketing Authorisation Holder performed a long term study of maternally derived antibody kinetics and reanalysed the serological reactions in the studies already performed. It became clear that maternally acquired immunity is more complex than what has so far been known and the Marketing Authorisation Holder defended the recommended vaccination scheme based on the new knowledge.

#### Viral load in lungs:

For all three serotypes based on viral load in lungs, the duration of immunity for pigs first vaccinated at 96 days is shown to be 6 months, and for pigs first vaccinated at 56 days it is shown to be at least four months.

For H1N2 and H3N2, the duration of immunity for pigs first vaccinated at 56 days is just exactly shown at 6 months, whereas for H1N1 in pigs first vaccinated at 56 days, the duration of immunity is four months. The H1N1 study was repeated because a number of seronegative pigs were born from sows that had been vaccinated early in life and despite the immeasurable Maternally Derived Antibodies (MDAs) their response on early vaccination had a shorter duration. The new study in combination with the new knowledge of MDA kinetics, led to the recommended vaccination schedule where the documented duration of the basic immunisation is 6 months for pigs older than 96 days at

first vaccination and 4 months for pigs older than 56 days and younger than 96 days at first vaccination. The decline of maternally derived antibodies varies considerably between pigs; even between litter-mates from the same sow. The vaccination schedule is therefore based on an average of the data presented. The intention is to vaccinate pigs after the decline of MDA, which in most cases occurs before eight weeks of age. Depending on the sows contact with antigens via vaccination or field infections, this period may be extended to after twelve weeks of age for one or more antigens. The SPC contains advice, which is useful for the vet/farmer in the decision of vaccination age/timepoint in the light of MDA levels.

The effect of a booster vaccination given eight months after basic vaccination was provided in a new challenge study, which showed that revaccination can be performed even later than six months after basic vaccination with good results.

Rectal temperatures showed only minor differences after challenge depending on serotype. i.e., a significant difference can be seen in some studies approximately 24 hours after challenge.

Clinical respiratory signs showed more pronounced differences between vaccinated and control animals. For H1N1, there were significantly more respiratory signs in controls at 24 hours after challenge, except for the pigs vaccinated at 56 days and challenged after six months, which corresponds to the lack of difference in viral load in the lungs, as described above. For H1N2 and H3N2, the clinical respiratory signs were highly significantly different after challenge, except for one study, where results were disturbed by very warm weather conditions.

Serology: There seems to be a reasonable steady development of antibodies after vaccination, and there is no clear indication that 96-day old pigs develop higher antibody responses than 56-day old pigs. The SPC contains a warning about the influence of maternally derived antibodies on the serological response induced by vaccination.

The protection of piglets that received MDA via colostrum was shown in a challenge study where piglets born from sows having received the primary vaccination scheme and then a booster approximately six months later at one week before farrowing were challenged simultaneously with a combination of three influenza strains (H1N1, H1N2 and H3N2) at 33 days of age. The controls consisted of seronegative piglets born from unvaccinated sows. The seronegative piglets showed clear clinical signs of influenza for many days and high virus load in the lungs, whereas the MDA-positive pigs remained healthy. This study did not show an effect on the amount of virus present in the lungs after challenge.

A comprehensive number of laboratory experiments have been performed and taken together these studies document the efficacy of the vaccines in protecting against field isolates of the three subtypes.

The Marketing Authorisation Holder has provided seven field studies in support of the laboratory studies. Three studies were conducted in pigs vaccinated at youngest age, 56 days. Three studies were conducted in sows during first, second and third trimester of pregnancy. One study was conducted in gilts vaccinated prior to insemination and revaccinated during pregnancy prior to farrowing. The studies also evaluated the safety of the vaccine. The efficacy parameters consisted of serological examination at study start, at seven days after primary (two dose) vaccination and at study end. In the studies with sows and gilts, the antibody level of colostrums at farrowing and in piglets four weeks after birth was also investigated. There was no outbreak of clinical swine influenza disease during the studies, but in some of the studies there was evidence of circulating virus. The efficacy in the field trials is therefore based on the serological measurements.

The vaccine was able to induce antibodies in the same levels that were seen in the laboratory studies and the results were in general statistically significantly different between vaccinated animals and controls. In the only field trial where maternally-derived antibodies were present at the time of primary vaccination at the youngest age, a clear interference with the induction of a Haemagglutination Inhibition (HI) response against the respective influenza subtypes was evidenced. In farms where there were circulating infections, the immunological response on the vaccine was, as expected, decreased

for the serotypes where active immunity already existed. The vaccine was able to induce antibodies against H1N2 in farms where active immunity against H1N1 and H3N2 existed.

The antibody titres induced in sows by vaccination strongly depended on the levels of antibodies present at the time of vaccination: i.e., vaccination induced higher antibody levels in animals having pre-existing low to medium level of antibodies than in seronegative animals (booster effect). When the antibody titres were very high at the time of vaccination, the vaccination had no detectable effect. Overall, harmonization of the antibody levels was however achieved. There was good correspondence between the levels of antibodies in the sows, the level in colostrums and in general the level in piglets born to the individual sow.

Overall, the MAH has provided good documentation of the efficacy of the vaccine and documented or justified the outstanding issues.

## **RISK-BENEFIT BALANCE**

RESPIPORC FLU3 is an inactivated virus vaccine intended to provide protection against porcine influenza. The target species is pigs and the recommended route of administration is by intramuscular injection. The proposed vaccination scheme for pigs from 8 weeks of age (56 days) is two doses of RESPIPORC FLU3 to be given with a 3 week interval. Duration of immunity is claimed to be 4 months for pigs vaccinated between the age of 56 and 96 days, and 6 months for pigs vaccinated after 96 days of age. Pregnant sows should be revaccinated with a single dose 14 days prior to farrowing to develop colostral antibodies, which will clinically protect piglets for at least 33 days after birth.

### **Benefit assessment**

#### **Direct benefits**

Swine influenza virus of serotypes H1N1 and H3N2 has been circulating in most swine producing countries in Europe for decades. In 1994, H1N2 arose in Great Britain due to a triple reassortment where some HA genes were of human influenza virus origin, some NA genes were of swine H3N2 origin and some internal protein genes were of avian-like swine H1N1 origin. H1N2 has now spread to a number of European countries with variable prevalence. It has been shown that there is insufficient protection against challenge with H1N2 in pigs vaccinated with H1N1 and H3N2. No other H1N2-vaccine is available on the market. The main benefit of RESPIPORC FLU3 is that it contains all three swine influenza types.

A comprehensive number of well performed laboratory and field experiments have been performed in animals of youngest age and in sows before and during pregnancy and these studies document that the vaccine protects against virulent challenge of swine influenza. Active immunization of pigs with the vaccine reduces clinical signs and viral lung load after infection caused by the subtypes H1N1, H3N2 and H1N2. The vaccine was able to induce antibodies against H1N2 in farms where active immunity against H1N1 and H3N2 existed. Cross reactivity between the subtypes of the vaccine and several circulating strains in Europe has been shown *in-vitro* or by challenge trials.

The onset and duration of immunity and the efficacy of a booster vaccination have been clearly documented in well performed studies. The efficacy of vaccination in presence of maternally derived immunity has been further clarified.

There was good correspondence between the levels of antibodies in the sows, the levels in colostrum and in general the level in piglets born to the individual sow.

Clinical protection of piglets by maternally derived antibodies has been sufficiently demonstrated by a challenge trial at the age of 33 days.

Because there may be interference of maternally derived antibodies until approximately 8 weeks (56 days) of age, the pigs in the studies were vaccinated at 56 or 96 days of age, and challenged after 4 or 6 months. The influence of MDAs was further clarified with regards to the age of vaccination and duration of immunity. The protection by maternally derived antibodies was investigated until 33 days of age, whereas the interval from 33 days of age until the recommended vaccination age of 56 days has been less well characterised. The recommended age of first vaccination was chosen based on studies of the decline of MDAs. The interference of maternally derived immunity on the efficacy of vaccination has been clarified but there is a large inter-individual difference in the time-point where the MDA disappear and full response to vaccination can be achieved. The recommended vaccination schedule is therefore based on an average of the data presented.

### **Additional benefits**

The vaccine has an adjuvant system, which is shown to be safe in both young and pregnant animals with very minor local reactions at the injection site and occasional transient increase in body temperature.

The quality part of the dossier is detailed and complies with relevant monographs and guidelines, and the description of the production process and methods is clear and detailed.

### **Risk assessment**

No major risk for target animals has been identified for this inactivated vaccine.

RESPIPORC FLU3 will not give rise to residues which will be harmful to the consumer. No withdrawal periods are considered to be necessary before vaccinated pigs are slaughtered for human consumption.

The vaccine is unlikely to harm the user except in the case of accidental self-injection where a minor local reaction may be expected. The use of this inactivated vaccine will not damage the environment.

### **Evaluation of the benefit risk balance**

### **Discussion**

The vaccine provides protection against a novel serotype of swine influenza virus. The diversity and duration of protection was further clarified, as well as the vaccination schedule, the efficacy of vaccination in presence of MDAs and the passive protection of piglets born of vaccinated sows. No major risks were identified for the target animals, the user, consumer or the environment.

### **Conclusion**

Based on the review of the data on quality, safety and efficacy, the CVMP considers that the application for the vaccine RESPIPORC FLU3 can be approved.

## **OVERALL CONCLUSIONS**

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of RESPIPORC FLU3 were considered to be in accordance with the requirements of Directive 2001/82/EC, as amended, and that the benefit-risk balance was favourable.