Title: Prescribing cascade

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- Hello, my name is Donal Murphy. I work for the National Office of Animal Health, or NOAH, as it is more commonly known. I'm going to talk about the prescribing cascade as part of this series of presentations from the RCVS Knowledge Farm Vet Champions project. As a declaration of interest, I want to inform the audience that I am employed by NOAH, which is the trade association for the UK animal health industry. The learning objectives for vets who review this module is that on completion of the module, participants will be able to use correctly and legally the prescribing cascade that must be applied in the UK post-EU exit, and that they will be able to apply appropriate withdrawal periods that must be set when medicines are prescribed under the cascade to food-producing animals.

Cascade use of veterinary medicines. Veterinary medicines are authorised for specific conditions for a specific target species and based on assessed data. And the conditions of use for each authorised veterinary medicine are listed in its Summary of Product Characteristics or SPC. The VMD, the Veterinary Medicines Directorate, has a product information database that contains the SPCs and where those products are authorised for all veterinary medicines that are authorised in the UK. It is important to note now that the EU exit transition period has ended, that these products will be indicated as being authorised in Great Britain only, in Northern Ireland only, or UK-wide, so in both Great Britain and Northern Ireland. So there are differences in authorizations in terms of their geographic scope as a result of the UK's departure from the European Union and the Northern Ireland protocol where Northern Ireland will be following EU regulatory requirements.

Where there is no suitable veterinary medicine authorised for the specific condition in the animal being treated to avoid unacceptable suffering, vets are permitted to use clinical judgement to treat animals under their care in accordance with the cascade. And that last bullet point is the key overriding principle around cascade use of veterinary medicines. There will be differences now between the cascade as it is applied in Great Britain and the cascade as it is applied in Northern Ireland now that the EU exit transition period has ended. I will now address these in the next few slides.

So firstly, the cascade for vets in Great Britain from January, 2021 onwards. Veterinary medicines authorised in other countries anywhere in the world, not just in the EU, now sit higher up the prescribing cascade and are on the same level in the cascade as the UK-authorized human medicines. This means that a veterinary medicine authorised in any country in the world is eligible for import for use under the cascade after the preferred option of the veterinary medicine authorised in the UK. So vets that are based in Great Britain must look to products authorised in the UK in the first instance. If there is a product authorised in Northern Ireland, but not authorised in

Great Britain or UK-wide, vets will need to apply for a special import certificate in order to legally obtain that product for use under the cascade.

I will now go through the different steps in the prescribing cascade that vets in Great Britain should consider when prescribing. The first step is they should consider a veterinary medicine with a marketing authorization valid in Great Britain or UK-wide for the indicated species and condition. If no such product is available or suitable, they should consider step two, which is a veterinary medicine with a marketing authorization valid in Northern Ireland for indicated species and condition. For products not authorised in Great Britain or UK-wide, a special import certificate from the VMD is required. If no such product is available or suitable, they should consider step three, which is a veterinary medicine with a marketing authorization valid in Great Britain, Northern Ireland, or UK-wide for a different species or condition. For products that are not authorised in Great Britain or UK-wide, a special import certificate from the VMD is required. If under step three, nothing is available or suitable, the vet should consider step four, which is a human medicine with a marketing authorization valid in Great Britain, Northern Ireland or UK-wide, or an authorised veterinary medicine from outside of the UK. For products not authorised in Great Britain or UK-wide, a special import certificate from the VMD is required. In the case of a food-producing animal, this medicine must be authorised in a food-producing species. If nothing is available or suitable under step four, they move to step five, which is an extemporaneous preparation prepared by a vet, pharmacist or person holding an appropriate manufacturer's authorization located in the UK. And finally, if nothing is available under those five steps, there is an additional exception, which is that in exceptional circumstances, a human medicine can be imported from outside of the UK.

For products not authorised in Great Britain or UK-wide, a special import certificate from the VMD is required. The VMD have a web page where vets can apply for special import certificates when they need to. The cascade for vets in Northern Ireland from January, 2021. The Northern Ireland Protocol provides for Northern Ireland to remain subject to EU legislation, and the cascade which applies to vets in Northern Ireland is different from the rest of Great Britain as a result of this. Northern Ireland vets must consider Great Britain as being a third country to the EU, and therefore products only authorised for the Great Britain market sit within the last option, which I will explain on the next slide. Preferential consideration must be given to veterinary medicines authorised in the EU over those products authorised on a Great Britain-only basis. If there is a product authorised in Great Britain, but not authorised in Northern Ireland or UK-wide, the vet will need to apply for a special import certificate in order to legally obtain that product for use under the cascade. And vets should also note that the VMD will continue to administer the special import scheme for Northern Ireland because the VMD do remain the regulatory authority with jurisdiction in Northern Ireland. So for vets in Northern Ireland from January, 2021 onwards, the first step they should consider when prescribing is a veterinary medicine with a marketing authorization valid in Northern Ireland or UK-wide for the indicated species and condition. If nothing is available or suitable, they then should consider step two, which is a veterinary medicine with a marketing authorization valid in Northern Ireland or UK-wide for a different species or condition. If nothing is available or suitable, they then should consider step three, which is a human medicine with a marketing authorization valid in Northern Ireland or UK-wide, or a veterinary medicine with a marketing authorization valid in an EU member state.

For products not authorised in Northern Ireland or UK-wide, a special import certificate from the VMD is required. In the case of a food-producing animal, the medicine must be authorised in a food-producing species. If nothing is available or suitable under steps one to three, the vet should then consider step four, which is an extemporaneous preparation prepared by a vet, pharmacist or

person holding an appropriate manufacturer's authorization located in the UK. And then finally, as is the case with Great Britain, there is a final exceptional step which states that in exceptional circumstances, a veterinary medicine with a marketing authorization in Great Britain or outside of the European Union may be imported, or human medicine from outside of Northern Ireland. For products not authorised in Northern Ireland or UK-wide, a special import certificate from the VMD is required.

Some further points to consider when using the prescribing cascade in food-producing animals. It should only be on a case-by-case basis. It should not be a standard or routine practise. It must be under specific veterinary direction. The vet responsible for prescribing the medicine must keep specified records. The details of these records go beyond the scope of this presentation, but they can be found on the VMD's website. And the vet responsible for prescribing the medicine under the cascade must specify an appropriate withdrawal period. And I will cover that in more detail on the following slides.

The following conditions apply when a vet prescribes a product under the cascade for use in a food-producing animal. The active substance in the medicine must have a maximum residue limit or MRL, but this does not necessarily need to be in the species for which you are going to prescribe the product under the cascade, too. So when checking this, vets should also consider the other provisions for the MRL. For example, some substances are allowed to be used in animals producing products for meat, but not allowed to be used for animals producing eggs or milk for human consumption. For use in Northern Ireland, the allowed substances that are permitted to be used under the prescribing cascade in food animals are listed in Table One in the Annex to EU Regulation Number 37/2010.

For use of products under the prescribing cascade in food-producing animals in Great Britain, substances with an MRL are listed in the Great Britain MRL Register as established under Article 14A of retained Council Regulation 470/2009. This register will be incorporated into the VMD Product Information Database from May, 2021 onwards. Obviously accessing this information is difficult for practising vets. And if in doubt, I would urge you to contact either the Veterinary Medicines Directorate or the Marketing Authorization Holder for the product which you were considering using to obtain further information.

The withdrawal period is the length of time that must pass between the final administration of the medicine and the point the animal can be slaughtered to enter the food chain, or when produce is taken for human consumption. When products are used in food-producing animals under the cascade, minimum withdrawal periods must be specified by the prescribing vet. For eggs and milk, this is a minimum of seven days. For meat, it is a minimum of 28 days, and 500 degree days for fish meat. As the prescribing vet, you must satisfy yourself that the minimum withdrawal periods are sufficient, and you should consult more widely if you need to obtain more information about what minimum withdrawal period should be set. And once again, I would recommend that prescribers contact the technical department of their animal medicine company to seek further advice on what the minimum withdrawal periods should be used.

Responsible use of antibiotics under the cascade. This requires vets to consider not only the most appropriate active substances, but also the most appropriate formulation, the dosage, the current pattern of resistance in your locality or on the farm, an awareness of how to reduce selection pressure and other related factors, such as good biosecurity and husbandry and hygiene. If vets can demonstrate that these steps have been taken and are being considered, then cascade use of antibiotics is supported. To minimise the development of antibiotic resistance, where a particular

antibiotic has shown to be effective against a bacteria, for example, through culture and sensitivity testing, vets can prescribe a narrow spectrum antibiotic under the cascade instead of a broad spectrum antibiotic that has an authorised indication for the condition being treated.

When considering the prescribing cascade, the terms the cascade or off-label use often feature. Which should be used? The term off-label use is regularly used, but there are different interpretations as to what it means. Actually, there is no definitive legal definition for the term off-label. It is best to refer only to authorised use and cascade use. With authorised use, a product is used in accordance with the clinical advice given on the Summary of Product Characteristics, which is agreed by the regulatory authorities. For example, the indications, dosage regime, contraindications, target species safety warnings are all followed exactly for it to be considered authorised use. Any alterations to dose regime, duration of treatment, use for a condition other than specified on the SPC, use in another species, all of these are considered to be cascades use.

Cascade use should only take place under the authorization and direction of the prescribing vet. It is very important that prescribers note that increases in dose rate, dose frequency, et cetera, all constitute cascade use. Therefore, when used in this way in food-producing animals, then cascade use minimum withdrawal periods must be applied. If you are in doubt, contact the technical department of the Marketing Authorization Holder for advice.

Any deviation from the marketing authorization without authorization or direction from the prescribing vet or without the vet following the cascade correctly is illegal use. Some examples of illegal use would include a farmer treating mastitis with an extended course of tubes without veterinary authorization and direction, or using medicines to treat an animal for which it was not prescribed, such as using a leftover antibiotic to treat another animal. That is an example of illegal use of veterinary medicines.

Use of combinations of veterinary medicines. When combinations of medicines are used for treatment, for example, an antibiotic injection plus a nonsteroidal anti-inflammatory drug injection, or two vaccines administered at the same time, neither of these examples would be considered to be cascade use as long as each medicine is used as per its own SPC, and there is no contraindication stating that these two products could not be given at the same time. The longest of the two product withdrawal periods should be used. However, a note of caution and care is needed if combinations of antibiotics are used. For example, I would recommend that vets should consult the technical department of the Marketing Authorization Holder if in doubt, for example, if both an injectable antibiotic and an intramammary antibiotic were being used.

So in conclusion, cascade use should only take place under strict veterinary control. This is a legal requirement. Changes to dose rate, frequency and duration all constitute cascade use. Different cascades use rules apply in Great Britain and in Northern Ireland now that the EU exit transition period has passed. If prescribers are in any doubt, I would recommend they consult VMD cascade use guidance and consult the technical department of the MA Holder or the animal health company.

If you have any questions following this presentation about use of the prescribing cascade, please feel free to contact me. I have included my email address. Some useful references for you to refer to for further information. The first link is some VMD guidance regarding the prescribing cascade. The second link is to the VMD's Special Import Scheme, which I referred to on numerous occasions during the presentation today.