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Legal constraints in EU product labelling to mitigate the environmental risk of veterinary medicines at use

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Abstract

This paper summarises what possibilities and obligations are created by the EU Directive 2001/82/EC on the registration of veterinary medicines to mitigate the environmental impact of the use of a veterinary medicinal product. More specifically, an identified environmental risk may be mitigated to an acceptable level by special precautions in the information that accompanies the product in labelling and packaging. These precautions can address the fate of contaminated slurry and treated animals, but are only acceptable under the EU Directive if their effect can be demonstrated using the risk assessment methodology. Next, all possible keepers of the animals or the manure, including third parties, should be addressed, either in the precaution, or in the national regulation that should enforce the precautions. A number of examples illustrate that some precautions used are not quantifiable in the risk methodology, and that others are legally inadequate. To render risk mitigation measures effective, hence suitable for labelling and packaging, it is imperative that the risk assessment methodology is further developed and applied adequately, and that the legality of precautions is established in national regulation, harmonised between Member States.

Keywords: Environmental risk assessment; Risk mitigation; Labelling; Packaging; Precautions

1. Introduction

European and national regulators are involved in managing environmental risks of veterinary pharmaceuticals from two perspectives. One is the registration of pharmaceutical products (Blasius and Cranz, 1998), and the other is the management of good environmental quality (Montforts and De Knecht, 2002). The framework of the registration procedure for veterinary medicines consists amongst others of the European Community legislation, Member State legislation, case law, as well as global (trade) agreements. In this paper, we investigate what possibilities and obligations are created for applicants and authorities within this framework to assess the environmental impact of the use of a veterinary medicinal product, to take the results of the risk assessment into account in decision-making, and to bind users and third parties to precautions in the labelling and packaging. The objective of this article is then to investigate methodological and legal restraints that render the precautions in the labelling and packaging ineffective as risk mitigation measures within the European Union. For further reading on the legal context in the US the reader is kindly referred to Daughton and Jones-Lepp (2001); Haskell et al. (2003a,b); and Nidel (2003).

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2. The obligation to take environmental risk into account at registration of veterinary medicinal products

The codified EU Directive 2001/82/EC lays down rules for, amongst others, placing products on the market, labelling, and package leaflet. Placing on the market evolves around the permit to market the product, the so-called marketing authorisation (MA), the procedures for granting the marketing authorisation, and procedures for mutual recognition of marketing authorisations within the EU. The Directive addresses both regulatory authorities and applicants, but not the consumers of the marketed products. The recently adopted Directive 2004/28/EC amends the 2001/82/EC Directive. In this new Directive, any risk of undesirable effects on the environment is included in the definition of risks relating to the use of the product [worded in Article 1(19)]. Article 12(3)j requires the applicant 'to provide tests assessing the potential risks posed by the medicinal product for the environment. This impact shall be studied and consideration shall be given on a case-by-case basis to specific provisions seeking to limit it.'

The risk assessment is to be examined by the registration authority. This examination is performed by a scientific committee, since the European Court of Justice (ECJ) ruled in case C212-91 (Angelopharm) that "the Scientific Committee is the only party involved in the policy-making process that is competent to make those scientific and technical assessments on which the legal validity of the measures depends" (Heyvaert, 1999). At the European level Regulation (EC) 726/2004 (re)installed the Committee for Veterinary Medicinal Products (CVMP) to provide these risk-based opinions in the centralised procedures. The CVMP is also involved in decentralised procedures, where a marketing authorisation obtained in one Member State is taken for mutual recognition to other member states. When disputes between member states about public health or environment remain unsolved, the case is also referred to the CVMP, which will provide for a binding opinion on the matter (Blasius and Cranz, 1998).

The framework of the registration procedure for veterinary medicines thus generates a scientific opinion on the environmental risk. There are two possible options for the authority in response to an identified environmental risk. The first option is to eliminate the risk by denying marketing authorisation. This option is based in the articles 30 and 33 to the Directive. In the Directive 2004/28/EC, amending the 2001/82/EC, Article 30 states that marketing authorisation is denied if the risk-benefit balance of the product is, under the authorised conditions of use, unfavourable. A risk/benefit balance is defined as 'an evaluation of the positive therapeutic effects of the veterinary medicinal product in relation to the risks.' In Article 33, it is stipulated that a mutual recognition of a marketing authorisation can be denied if there are concerns for a potential serious risk to human or animal health or for the environment.

The second option is to mitigate the predicted risk to an acceptable level by addressing the user of the veterinary medicine through the information that accompanies the product (Koschorreck et al., 2002). This option has the intention of establishing a code of conduct that is reaching further than the Good Agricultural Practice taken as a starting point in the risk assessment. This option is held in high esteem, since it is explicitly worded in Article 12.3.j of the 2004/28/EC Directive and the recital. This option is further investigated in this article, by examining the requirements set in the Directive towards the risk assessment methodology and the obligations towards the user of the medicinal product.

3. The structure of the environmental risk assessment

The EU Directive and the Notes for Guidance provide for a methodology for assessing environmental risk following the use of the product under representative conditions. It is stated in Annex I, Part 3, Chapter 1.5, to the EU Directive 2001/82/EC that:

'The assessment shall normally be conducted in two phases. In phase I, the investigator shall assess the potential extent of exposure to the environment of the product, its active substances or relevant metabolites, taking into account:

- the treated animal species, and the proposed pattern of use (for example, mass-medication or individual animal medication),
- the method of administration, in particular the likely extent to which the product will enter directly into environmental compartments,
- the possible excretion of the product, its active substances or relevant metabolites into the environment by treated animals; persistence in such excreta,
- the disposal of unused or waste product.

In phase II, taking into account the extent of exposure of the product to the environment, the investigator shall then consider whether further specific investigation of the effects of the product on particular ecosystems is necessary. The available information about the physical/chemical, pharmacological and/or toxicological properties of the compound which has been obtained during the conduct of the other tests and trials required by this Directive have to be taken into account. As appropriate, further investigation may be required of:

- fate and behaviour in soil,
- fate and behaviour in water and air,
- effects on aquatic organisms,
- effects on other non-target organisms.'

Thus the Directive has specified the scope and boundary conditions for the environmental risk assessment to be performed. Article 33(2) of the recent Directive 2004/28/EC coerces the Commission to adopt guidelines defining a potential serious risk for human or animal health or for the environment. This is essential to make the risk/benefit-based decisions (Di Fabio, 1994). The European Medicines Agency (EMEA) and the CVMP have published guidance on the environmental risk assessment, that was implemented in 1997 in the European registration process (EMEA, 1997). A revised guidance document on Phase I has been implemented by July 1st 2001 (VICH, 2000). For Phase II, the 1997 guidance is still leading, but a new Phase II guidance is under preparation that is expected to come into force in 2005 (VICH, 2003). The guidance documents consider the use stage of the products. The waste stage of the products is, however, not guided by these guidance documents, and neither it will be considered here.

The Notes for Guidance identify acceptable risks of applications: generally when the level of exposure is below a predicted no-effect concentration. If the predicted exposure level were to be greater than the predicted no-effect level, the assessment proceeds to a next tier where the Note for Guidance requires more data and more advanced methods to refine the risk assessment. Regarding the exposure assessment, the identified and consolidated emission routes are direct emission to the environment, emission through dung of grazing animals, emission of contaminated water, and emission through spreading of slurry from treated animals. The assessment is performed taking codes of conduct according to Good Agricultural Practice into account. Good Agricultural Practices to the use of manure on land may differ between members states and are amongst others set by the EU Nitrate Directive 91/676/EC for vulnerable areas, advisory standards for crop fertilisation, and tolerance of crop for excessive manuring (Montforts and Tarazona, 2003). This allows for the use of generalised data on animals, manure production, storage, handling, and spreading, under worst case conditions. A second important assumption is that spreading of manure is a given fact, and that the contamination by the veterinary medicinal products does not restrict the spreading of the slurry.

The EU Directive 2001/82/EC as amended by the EU Directive 2004/28/EC and the Notes for Guidance provide thus for a methodology for assessing environmental risk following the use of the product under representative conditions. The most important conclusion is that risks arising from direct exposure, at treatment, or from exposure to treated animals, and indirect exposure, by the spreading of contaminated materials such as dung and manure, are within the scope of the registration assessment. Further details on the risk model and the available methodology will be addressed below, where relevant. We will now investigate what the possibilities are for risk reduction by provision of instructions to the user of the veterinary medicine.

4. Risk mitigation by labelling and packaging

Together with the marketing authorisation, several documents and particulars with relevant information are issued at registration. These entail a summary of product characteristics (SPC) and an assessment report, as stipulated in Articles 14 and 25, the containers and outer packages (Article 58), and a package leaflet (PL, Article 61). All of these particulars should contain 'precautions (as a special class of prescriptions) for disposal of unused medicinal products or waste material from medicinal products, if any.' The SPC should also contain explanations of these precautions together with an indication of any potential risk to the environment. All these precautions shall conform to the particulars and documents pursuant to Article 12 of Directive 2001/82/EC. Precautions should therefore *demonstrably* reduce the environmental risk. We will now consider these documents and particulars in greater detail. It will be investigated what the subject of the measures can be, who the addressee is (the object of the precaution), and what the disposition of the precautions is (precept, prohibition, or recommendation).

A precaution is not a mandatory enactment under the Directive 2004/28/EC. The Directive does neither elaborate on obligations to consumers to obey the documents and particulars nor on supervision and sanctions. Precautions are hence not legally binding through the Directive. Although it can be expected that the precautions will have their intended effects in a certain number of instances, the reasonable worst case situation remains the one where the precautions are not followed. In that sense, the precautions are merely recommendations. Paradoxically, all precautions should therefore be considered as ineffective risk reduction measures, unfit for inclusion in the labelling. However, national legislation concerning the veterinary practice should turn these prescriptions into legal injunctions. The situation in the Netherlands is presented here as an example.

In the Netherlands, rules on precautions have been laid down in the Veterinary Medicines Act (Diergeneesmiddelenwet) (Anon., 1985). It is established in Articles 7 and 40 that it is forbidden to act against the prescriptions in the documents and particulars issued at registration. This prohibition applies to the users of the veterinary medicine, provided that the prescriptions are stated in the Package Leaflet, the container, or the outer packaging. Information in the SPC alone is, however, not legally binding, but may assist the veterinarian in selecting the appropriate treatment. Ignoring the prescriptions issued at registration is a penal offence, super-

vised and sanctioned, under the Economic Offences Act (Wet op de economische delicten) (Anon., 1950). The Veterinary Medicines Act also controls the availability of veterinary medicines. There are three classes of veterinary medicines: freely available products, products under prescription that can be administered by the keeper of the animals, and products that can only be administered by the veterinarian.

The subject of instructions (the 'what' question) in the labelling may be the product (e.g., dosage and posology), the treated animals, or animal products such as eggs and milk (e.g., withdrawal times). Likewise, the excreta of treated animals can be addressed by special instructions, since these are under control of the keeper of the treated animals. The addressee of these precautions (the 'who' question) may be the veterinarian or the keeper of the treated animals. Other persons or subjects are not the users of the products and cannot be addressed.

It is also very important that the precaution addresses the right addressee with reasonable demands. Unreasonable demands will not only be ineffective, but may also delay the registration procedure. An illustration of unreasonable demands can be found in the precautions concerning the application of biocidal products for the impregnation of wood. The precautions of concern addressed the person that impregnates the wood with instructions on the selection of the product for certain types of wood. The precaution distinguished between the different final destinations of the wood: use in contact with soil and water, or not. A Netherlands Court, the Board for the Appeal of Private Enterprise (CBB) ruled that restrictions on the use of wood preservation products should only have bearings on destinations (of the treated wood) that were to be determined reasonably clear and objective at the time of use of the product (CBB, 2000). Restrictions bearing on the anticipated use of the wood in contact with soil or water were considered not to meet this requirement. It was taken into account, that the person applying the product for impregnation was not the person who determined the destination of the treated wood. When deciding on using the product on a given batch of wood, the destination of the wood would not be reasonably clear for him to make the right decision. The precaution that distinguished between contact with water and soil or not, was unreasonable and the authorisation was nullified.

If precautions refer to the handling of treated animals or manure that has been contaminated with residues of the medicinal product, such precautions only should have legal force if the user of the product also controls these animals or this manure. Such precautions would have no legal force if another person than the user of the product actually determines the destination of the animal or the manure. Without legal force, the precaution cannot be considered to mitigate the risk. There are two situations where this applies. First, regarding the products that are to be administered by the veterinarian only, the precautions cannot instruct him or her on the destination of the treated animals or the manure, since the farmer controls these. Second, for products that are administered by the keeper of the animals, the precautions do have binding force. However, once the animals or manure have been sold to a third party, the precautions are no longer binding. For these open ends a solution must be developed.

All precautions should be based on factual information provided in the dossier and generated in the risk assessment. To what extent the effect of the precaution is demonstrable by the risk assessment methodology will be explored in the next section.

5. The demonstration of the effect of risk mitigating precautions

In European Member States, several medicinal products have been registered after decentralised procedures, with special precautions contained in the SPC, Package Leaflet, container and outer packaging. All these precautions shall conform to the particulars and documents pursuant to Article 12 of Directive 2001/82/EC. Precautions should therefore demonstrably, i.e., quantifiably, reduce the environmental risk. This means that the impact of the precaution should be expressed in the risk assessment, in conformity with the dossier and the risk assessment methodology. The methodology available typically targets realistic worst case conditions of use that cover all possible situations in the field. Special precautions should apply without exemption to the worst case conditions.

Below some examples of special precautions for the environment are discussed with respect to the methodological demonstration of the efficacy of the precautions.

Many products containing parasiticides for pasture animals carry a precaution that dictates that treated animals should not enter surface water at or after treatment. Apparently, the aquatic environment is at risk when treated animals have access to surface water, since residues of parasiticides are excreted with dung for days after treatment (Lumaret and Errouissi, 2002). According to the Notes for Guidance, the risk for surface water is based on an exposure model where 1% of the dosage (per ha) is excreted in a ditch (100 m^3) adjacent to the field. The resulting exposure concentration is compared to the toxicity of the crustacean *Daphnia magna*, taking an assessment factor of 100 into consideration. A risk quotient >1 indicates risk and calls for refinement of the assessment or risk mitigation measures. A few examples of products with this precaution are presented here.

The package leaflet of Eprinex Pour On (containing eprinomectin) carries the precaution 'treated animals

should not have direct access to surface water and ditches.' Without access to surface water, the treated animals will not expose the aquatic environment to excreted residues. The precaution on Eprinex Pour On eliminates demonstrably the risk to the environment since treated animals are not allowed to have access to surface water anymore. The precaution is technically sound. However, there is apparently no time period after which the risk of Eprinex Pour On would have become acceptable. It could be discussed whether this precaution is proportional since treated animals will have no longer access to fields with adjacent surface water.

The package leaflets of both Equimax oral gel for Horses (containing ivermectin and praziquantel) and of Noromectin 1.87% oral paste for Horses (containing ivermectin) carry the precaution: '*treated* animals should not have direct access to surface water and ditches *during treatment*.' Apparently, the treatment poses a risk to the aquatic environment, not the excretion of residues after treatment, which would be expected. Based on the Notes for Guidance the predicted concentration ivermectin in surface water would be 25 ng/l after the treatment of ponies (0.2 mg/kg bodyweight, 250 kg bodyweight, 5 animals per ha). Halley et al. (1989) reported an EC50 of 25 ng/l for ivermectin in *D. magna*. Applying the assessment factor of 100 results in a toxicological threshold of 0.25 ng/l. The risk quotient of 100 is above the threshold of 1. This precaution does not eliminate the risk of surface water contamination due to entry of residues excreted by the horses *after* treatment, which most likely was the intention.

The package leaflet of Triclaben 10% (containing triclabendazole) carries the precaution 'Cattle should not have access to surface waters within 7 days after treatment.' The package leaflet of Clik 5% Pour On (containing dicyclanil) carries the precaution 'The treated sheep should be kept away from water courses for at least 1 h after treatment.' Apparently, the risk to the aquatic environment is acceptable after 7 days, respectively, 1 h after treatment. These precautions provide clear instructions and the potential effect of these precautions can be demonstrated with the risk assessment methodology, since information on the excretion pattern of the active substance should be available (Montforts et al., 1999; Taylor, 1999).

Apart from the technical aspect, other legal aspects will determine the conformity with the EU Directive, as discussed above. Third parties will not be bound by the precautions stated above, inferring that treated animals will pose a risk to the environment after they have been sold to third parties within the stipulated time periods. The proportionality of the precautions should also be observed.

The product Sebacil Pour On (containing phoxim) is applied to pigs. The package leaflet contains the precaution: 'When spreading manure from treated animals on agricultural lands a safety distance of 10 m to adjacent surface waters must be kept to avoid exposure of the aquatic environment.' Apparently, the risk to surface water after manuring of land was not acceptable. In the methodology provided by the Notes for Guidance in Phase I, the concentration in surface water depends on the concentration in soil as a result of spreading of slurry. The model assumes a dilution factor of 3.3 on the porewater concentration and describes the partitioning function as follows:

$$PEC_{\text{porewater}} = \frac{PEC_{\text{soil}}}{Foc_{\text{soil}} \cdot K_{\text{oc}}},$$

where PEC_{soil} is the concentration in the soil in mg kg_{soil}^{-1}, Foc_{soil} is the fraction organic carbon in soil in kg kg^{-1}, K_{oc} is the partition coefficient organic carbon–water in l kg^{-1}, and $PEC_{\text{porewater}}$ is the predicted concentration in porewater in mg l^{-1}. The degree of surface water contamination in this exposure model is neither related to the actual transport processes (erosion, run-off, and drainage), i.e., the ratio between treated soil and receiving surface water, nor to the distance to the surface water. The water contamination depends on the equilibrium concentration between soil solids and soil porewater, and a dilution factor between soil porewater and surface water. The distance to the surface water is not modelled. The precaution must therefore have been based on an exposure assessment that handled this parameter of distance-to-edge, taken from a different source of exposure modelling. The German package leaflet, however, contains the precaution: 'Whenever slurry of animals treated with Sebacil Pour On is applied on agricultural fields, *because of the hazard of run-off*, a minimum distance of 10 m to surface waters should be observed.' The hazard of run-off is indicated here. The German EXPOSIT model is known to contain a function that calculates a reduction in run-off when a vegetative buffer strip is observed between the treated soil and the surface water. A 10 m vegetative buffer strip would reduce surface water contamination with 67% due to run-off (Winkler, 2001). Evidently, next to the process of run-off, drainage is a process to be considered (Kay et al., 2004), and the recommended no-spreading zone does not influence the contribution by drainage to the same extent. Moreover, in all operative drainage models, used in pesticide registration, the drainage model contains only a single soil column. The effect of a no-spreading zone, which would be a second soil column in the exposure model, is not demonstrable in drainage calculations with the currently available models in the frameworks of registration of veterinary medicines or plant protection products (VICH, 2000; FOCUS, 2001; WRc-NSF, 2001; Winkler, 2001).

Since the Notes for Guidance do not define the relative contribution of the process of run-off to the final water concentration, the influence on the final exposure

concentration could not be quantified. The methodology should be improved on these aspects to make these precautions demonstrably effective. Apart from the technical aspect, other legal aspects will determine the conformity with the EU Directive, as discussed above. Third parties will not be bound by the precautions stated above, inferring that the manure from treated animals will pose a risk to the environment after it has been sold to third parties.

Another example concerns the effect of the precaution on Nuflor Drinking Water Concentrate for Swine (containing florfenicol): 'Manure from treated pigs should be stored for 3 months prior to spreading and incorporating into land.' Apparently, the concentration of the residue in the manure was too high. The precaution addresses the manure storage in the exposure model, which is in potential important in limiting exposure of the environment (Pierini et al., 2004). The precaution may generate a necessary certain amount of dilution of the residue with clean manure during these 3 months. However, the Notes for Guidance refer for an example of the calculation of the soil exposure concentration to the paper by Spaepen et al. (1997). In this paper, the shortest dilution period is about 5 months for slaughtering pigs, making it less conceivable that the intended risk mitigating effect is dilution. It is more likely that the effect of degradation on the concentration of the residue was assessed in the dossier. The assessment of fate and distribution of veterinary medicines in manure during storage is complicated, due to the lack of technical guidance both for conducting degradation studies and for interpretation of the results and subsequent exposure modelling. The performance and evaluation of laboratory studies on the degradation in manure have been investigated (Bouwman and Reus, 1994), but have not yet resulted in internationally accepted test guidelines (Van Vlaardingen et al., 2001). Also there is currently no scenario that lays down representative worst case conditions for the modelling of degradation during manure storage (Montforts and Tarazona, 2003). Proportions of manure types and storage systems differ considerably between countries and will influence storage conditions and manure composition in different ways (Donham et al., 1988; Menzi, 2002). Conditions like oxygen levels, manure age, microbial activity and temperature will determine the fate of organic contaminants to a large extent, but are highly diverse within and between storage systems (Hoeksma et al., 1987; Novem, 1991; Arogo et al., 1999). Manure models that model manure loading, quality change, and fate of constituents do exist for nutrients, but are not operational for organic contaminants (Ni, 1999; Ni et al., 1999; Hilhorst and De Mol, 2002). Therefore, the waiting period would probably contribute to risk mitigation, assuming at least some degradation of the relevant residue, but the exact effect under relevant worst-case conditions cannot be quantified using available methodology. The methodology should be improved on these aspects to make these precautions demonstrably effective.

Again, apart from the technical aspect, other legal aspects will determine the conformity with the EU Directive, as discussed above. Third parties will not be bound by the precautions stated above, inferring that the manure from treated animals will pose a risk to the environment after it has been sold to third parties.

6. Discussion, conclusions, and recommendations

In this paper, we investigated what possibilities and obligations are created by the EU Directive 2001/82 EC, to bind authorities, applicants, and users, to instructions and prohibitions in the labelling to the product. The regulatory framework obligated applicants and authorities to assess the environmental risk of the use of the product. The CVMP Notes for Guidance provide for a methodology for establishing environmental risk following the use of the product under representative conditions. Risks arising from indirect exposure, by the spreading of contaminated materials such as dung and manure, are within the scope of the registration assessment. Doubts on the acceptability of environmental risks may constitute a reason for the applicant to change product characteristics or target species, and for the authority to deny marketing authorisation. The present article focuses on the alternative option to mitigate the risk to an acceptable level by special precautions in the information that accompanies the product.

The retrieved precautions address the fate of treated animals or the contaminated excreta, seeking to rule out or diminish the exposure of the environment. The grazing of treated animals in fields adjacent to surface water, the storage of manure, and the distribution of manure on land adjacent to surface water, are the components of the exposure methodology that are altered by the precautions, which subsequently ought to demonstrate the necessary reduction in risk. The intended addressee is therefore the keeper of the animals and the manure. Should the intended addressee not be addressed and bound by the precaution, or the risk reduction not be demonstrable, it has to be accepted that the risk will not be mitigated.

Several constraints have been identified that make risk mitigation measures technically or legally ineffective, hence unsuitable for labelling and packaging (see Table 1 for an overview).

First, through the Directive precautions are not legally binding to veterinarians and farmers (the consumers). In that sense, no precaution can be considered an effective risk reduction measure. National legislation concerning the veterinary practice must turn these recommendations into legal injunctions, to make the pre-

Table 1
Overview of selected precautions included in the package leaflet of veterinary medicines with a view to mitigate environmental risk

Product	Precaution	Problem	Solution
Eprinex pour on	Treated animals should not have direct access to surface water and ditches	Addressee, proportion	Include transfer of liability to other parties, define waiting period
Equimax oral gel for horses; noromectin 1.87% oral paste for horses	Treated animals should not have direct access to surface water and ditches during treatment	Addressee, efficacy	Include transfer of liability to other parties, define waiting period
Triclaben 10%	Cattle should not have access to surface waters within 7 days after treatment	Addressee	Include transfer of liability to other parties
Clik 5% pour on	The treated sheep should be kept away from water courses for at least 1 h after treatment	Addressee	Include transfer of liability to other parties
Sebacil pour on	At application of slurry of treated animals on agricultural fields a minimum distance of 10 m to bordering surface waters is to be observed	Addressee, efficacy	Include transfer of liability to other parties; improve exposure assessment methodology
Nuflor drinking water concentrate for swine	Manure from treated pigs should be stored for 3 months prior to spreading and incorporating into land	Addressee, efficacy	Include transfer of liability to other parties; improve exposure assessment methodology

cautions work. The way precautions are worded, in relation to the national legislation determines the national legal status, and thus their efficacy as risk reduction measure. It is imperative that the legality of the precautions and the possible subjects and addressees of the precautions are defined in national regulation, and that this is harmonised between Member States. One way would be to incorporate in the Directive that consumers are bound to the precautions. Member States will have to transpose this into national legislation. By means of a Regulation this prescription would have direct effect on the consumers in all Member States.

Second, precautions can be used to control the fate of the treated animal and the manure containing excreted residues, provided the legal person addressed is the keeper of the treated animals. If the product is to be administered by the veterinarian, environmental precautions regarding the treated animals or manure are thus not binding. The legislation at hand also does not transfer precautions regarding the treated animals and the manure to third parties. The solution to these shortcomings is to include this transfer of responsibilities to second and third parties, either in the precautions themselves or in the legislation, and to prohibit both trade and use of the animals and manure in the precautions during the time that the precaution is operative.

Third, precautions are only acceptable under the Directive if their potential effect can be demonstrated using the risk assessment methodology. Thus, the precautions forbidding release of treated animals or manure containing residues into the environment are technically effective, since the effect can be demonstrated in the methodology. The impact of temporary storage of manure containing residues cannot be quantified because of a lack of standardised model conditions. Likewise, the precise effect of the precautions prohibiting the spreading of manure within a certain distance to the surface water can as yet not be quantified with available exposure assessment methodology. The flexibility of the risk assessment methodology to deal with temporal and spatial differentiation in the exposure and effect assessment should be improved accordingly.

Fourth, whether the precautions on confinement of the animals or the manure (for a time period or infinitely) leaves the farmer with reasonable alternatives is an issue of proportionality. Precautions that are impossible to incorporate in Good Agricultural Practice should be avoided.

Discharges of slurry and chemical substances are in the EU also regulated by community legislation such as the Nitrate Directive and the Directives on water pollution 76/464/EEC, on groundwater protection 80/86/EEC, and in the near future the Water Framework Directive (2000/60/EC). This type of legislation operates from the starting point that all actions that may lead to pollution are forbidden unless a permit is granted by the national competent authority. This legislation addresses different authorities than the Directive 2001/82/EC does. The permit ought to regulate the emission (e.g., by prescribing application or purification techniques) as well as the maximum permissible concentration of the substance in the environment. The Marketing Authorisation is not a permit in this sense, but could provide for a firm scientific basis for the decision making by competent authorities. Ineffective precautions coerce the competent authorities to regulate the emission of residues. Also for products where the risk/benefit balance was favourable despite an environmental risk, the use or subsequent emission of res-

idues necessitates regulatory consent. For example, for the use of Slice (containing emamectin) in the UK it will be necessary to obtain consents from the local environmental authorities (Anon., 2003). No-spreading zones for manure are already Good Agricultural Practice in some Member States, for example in the UK (DEFRA, 2002). Alternative solutions to the use of precautions in the product information may thus be found in establishing precautions in permits, or in codes of Good Agricultural Practices, issued in these frameworks (Van Rijswick, 2003). Inevitably, the scientific and juridical underpinning of the precautions in these frameworks should be as meticulous as in the framework of registration, and will also require a flexible risk assessment methodology to quantify the impact of temporal and spatial differentiation of residue emissions.

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