Professional Flexible Labeling

Task Force Report II

Response to comments on the proposed model of a professional drug label

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Four sets of comments were received in response to the task force request for critique of their model professional veterinary drug label (see *JAVMA*, July 1, 1996, pp 83-91). Three of the 4 comments were obtained from practice specialty groups.

The following constitutes a synopsis of the comments received and the task force's corresponding response to these comments.

Summary of Comments

The professional flexible label (PFL) forwarded by the task force report was well received. The responses indicate that the model PFL would provide an excellent information resource, allowing attending veterinarians to respond to changing clinical needs. By providing information to assist in rational dose manipulation, practitioners would have the opportunity to adjust therapeutic interventions as needed while ensuring target animal and human food safety. However, negative aspects of the PFL were also acknowledged, and concern was expressed that greater availability of information could promote inappropriate drug use by some producers or practitioners.

The proposal for including multiple withdrawal times and expanded microbiologic information was consistently well received. Those practitioners involved in treatment of minor species expressed particular appreciation for the inclusion of microbiologic data pertinent to their practice situations.

Although the presence of pharmacokinetic information was deemed helpful, the ability of practitioners to interpret and apply this information was called into question. All commentaries indicated a need for an aggressive educational effort to facilitate use and interpretation of pharmacokinetic and microbiologic data. It was suggested that until such training is achieved, labels should include instructions on interpreting the PFL.

Two suggestions were provided with regard to the presentation of pharmacokinetic information. First, to increase its utility to the practitioner, blood concentration data should be presented on a linear rather than semilogarithmic scale. The latter may be highly useful for kinetic analysis, but is of limited value to the practitioner. Second, pharmacokinetic values should include range information similar to that used in microbiology. This range information would provide a better understanding of the amount of variability expected among individuals.

Commentaries pertaining to microbiologic data indicated the need to identify whether isolates were obtained from previously treated animals, untreated animals, or a combination of the two. The involvement of postantibiotic effects in the determination of appropriate dosing regimens should also be clarified.

A difference in opinion was expressed with regard to placement of information pertaining to microbiologic data for unapproved species. Practitioners specializing in treatment of minor species indicated the great importance of such information on product labels. Conversely, practitioners not specializing in treatment of minor species suggested that pathogen susceptibility information for disease conditions in unapproved species should be considered additional information, which should not be included in the supplemental section.

The model PFL did not provide any information pertaining to product contents (inert ingredients). Moreover, although the label indicated that the formulation was an aqueous solution, the label did not provide any chemistry information on the active ingredient (eg, pKa, environmental stability, partition coeffi-

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cients). This information is important for drug use in aquaculture. Without these facts, a label is of minimal value to aquatic animal specialists.

Commentaries acknowledged that the core elements of a flexible label include pharmacokinetic data (such as the area under the curve estimates), dosage ranges, withdrawal times, and pathogen susceptibility. Nevertheless, because clinical response (rather than data on pathogen susceptibility) provides the basis for adjustments in dosage, sponsors should include information to support dose selection decisions under various disease situations. By default, withdrawal time and cost constraints will encourage production medicine specialists to select the lowest possible dosage.

Readers expressed doubt about the ability of the FDA/Center for Veterinary Medicine (FDA/CVM) to implement the PFL concepts forwarded in the task force report. One point of concern was the potential conflict perceived between the proposed guidelines and the Animal Medicinal Drug Use Clarification Act. Additional difficulties pertained to the lack of ready access to auxiliary (electronic) databases by all practitioners.

Finally, it was emphasized that the FDA/CVM must not use the PFL format to impose new labeling burdens into the drug approval process. Rather, the PFL should provide a vehicle by which drug sponsors can incorporate additional or optional information into their product label. Ease of addition and updating such information is vital to the success of flexible labeling.

Task Force Response

The task force agrees that the fundamental goal of the flexible labeling initiative is to increase the availability and utility of animal drugs. Accordingly, it is imperative that the FDA/CVM refrain from imposing additional study requirements as a prerequisite for product approval. Within legal limits, the degree of flexibility associated with any product label should be left to the discretion of the drug sponsor. However, any information provided on the product label must be fully supported by scientific evidence.

The task force agrees that efficient and appropriate use of the concepts forwarded in the model PFL may require a period of adjustment. Accordingly, drug sponsors are encouraged to facilitate this learning process through the distribution of technical brochures and other appropriate educational materials. We concur with the recommendation that labels contain brief instructions to facilitate interpretation of the microbiologic and pharmacokinetic data. Such guidance would be highly beneficial to veterinary students as well as to licensed practitioners; however, we believe its inclusion on a PFL should be considered optional, not mandatory.

Because the susceptibility of some microbes can, and do, change over time, the periodic update of susceptibility data should be strongly encouraged. Accordingly, the microbiology section should be designed to permit sponsors to update without necessitating that FDA/CVM reevaluate the data supporting other portions of the label. The model PFL provided 1 possible configuration by which such flexibility could be achieved. Other formats may be equally suitable.

The more difficult question to address is whether labels should describe the treatment history of animals from which these isolates were obtained. Certainly, there are many examples in which prior drug exposure has been correlated with decline in pathogen susceptibility. However, the collection of historic drug use data will be difficult to standardize. First, it would be necessary to identify what is meant by "prior drug use." Would this imply drug administration to an individual, or would it equally apply to use within a herd or production unit? Should "use" be categorized according to duration of exposure? Should period of exposure be considered relative to time of isolate collection? The task force maintains that such a requirement would be an unnecessary burden; therefore, inclusion of such information should be considered optional, not mandatory. However, sponsors should be permitted to include this information on a product label if it is interpretable.

With regard to microbiologic information on isolates from unapproved animal species, an alternate suggestion would be to limit supplemental information to organisms that are not specific to an unapproved target animal. Organisms unique to an unapproved animal species would be relegated to the additional information portion of the label. A further restriction could be that these unique organisms not be isolated from food-producing animals for which there are insufficient human food safety data. However, the task force recognizes that practitioners treating minor species would be negatively impacted by this alternative suggestion. Many of the minor animal species will never have substantial drug approvals simply because of economic reasons. Therefore, the solution of linking minimal pharmacokinetic data from the unapproved species to the listing of any microbial information specific to that species should remain a viable option. Accordingly, the only restriction placed on the inclusion of such information would be that these data are consistent with other portions of the product label. For instance, if the drug is known to be toxic in a particular animal species, organisms unique to that animal species should not be placed on the product label.

The task force agrees that to maximize its utility to veterinary practitioners, pharmacokinetic (blood concentration vs time) profiles should be represented on a linear rather than semilogarithmic scale. However, it should be noted that under some circumstances, the logarithmic scale may be more informative. For example, time above minimum inhibitory concentration may be better resolved with the use of semilogarithmic rather than linear plots.

We are reticent to recommend that drug sponsors provide variability estimates for the pharmacokinetic parameters. Although the point estimates provide an approximate value from which the practitioner can

adjust a dosage, the inclusion of variability estimates implies a knowledge of the target animal population. This rarely is the case. Because of cost limitations associated with veterinary drug development, the sample sizes for pharmacokinetic investigations tend to be small. Moreover, the study population usually represents a limited segment of the potential target animal population (eg, studies conducted in a single breed). Resulting variability information may be highly inaccurate and misleading. Therefore, the task force concludes that unless a large body of data has been gathered on drug pharmacokinetics, point estimates (mean, median, or mode) are the preferred method of data presentation.

With respect to information on inert ingredients, the task force acknowledges the importance of this information to some practice specialties. However, because product formulation is proprietary, its release must be left to the discretion of the drug sponsor. Nevertheless, the task force does agree that expanding the amount of data conveyed on the chemistry of the active ingredient would be valuable, not only with respect to drug use in aquatic species, but also for understanding potential limitations/interactions associated with drug use within all animals.

The task force acknowledges that the FDA/CVM is subject to certain legal restrictions concerning the contents of a product label. Accordingly, the FDA/CVM cannot allow the drug label to contain any information not consistent with current laws and statutes. For example, current statutes prohibit labels from containing information that cannot be included in promotional and advertising materials. Consequently, some aspects of the model PFL (such as the inclusion of a section containing "additional information") may not be feasible in the current regulatory environment. With these limitations in mind, the task force recommends that future FDA/CVM PFL guidance documents provide a brief summary of where it diverts from the task force recommendations and explain the basis for these diversions. If reasons pertain to legal restrictions, the CVM should cite the specific laws that prevented full expression of the task force PFL proposal. This will provide the information necessary to initiate revision of existing laws or to identify alternative mechanisms for meeting practitioner needs.

It is the task force's hope that the PFL process will retain its current momentum, remaining fluid and providing opportunities for meeting the changing needs associated with veterinary medicine. Optimally, the FDA/CVM will identify any legal barriers that block the implementation of the PFL concepts and will work with drug sponsors and veterinary practitioners to develop creative alternatives for overcoming these legal hurdles. Accordingly, the task force requests that the FDA/CVM continue to provide guidance on identifying those regulations that could and should be rewritten if we are to develop labels that meet the diverse needs associated with the practice of veterinary medicine.

The flexible labeling workshops and subsequent task force report provided a forum for exchange of ideas with regard to flexible labeling and identified practice needs across the veterinary medical profession. Having done this, the task force now provides this report for the FDA/CVM to use in developing policies pertaining to the PFL. It is the recommendation of the task force that the FDA/CVM use as many of the items contained in the report and subsequent comments as is legally possible.