Available online at www.sciencedirect.com
SCIENCE DIRECT®
Regulatory Toxicology and Pharmacology 42 (2005) 324–327
Regulatory Toxicology and Pharmacology
www.elsevier.com/locate/yrtph

Demystifying 21 CFR Part 556—Tolerances for residues of new animal drugs in food

Steven D. Brynes

Center for Veterinary Medicine, United States Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, USA

Received 12 April 2005

Abstract

21 Code of Federal Regulations Part 556 (Tolerances for Residues of New Animal Drugs in Foods) is one of the Center for Veterinary Medicine's most significant set of regulations. However, in many respects, it is outdated. Subpart A (General Provisions) defines tolerance designations that are obsolete, while Subpart B (Specific Tolerances for Residues of New Animal Drugs) is inconsistent in terminology and often confusing. The purpose of this paper is to define the older terms and update the reader as to current concepts that apply to tolerance-setting for new animal drugs. A list of useful definitions appears at the end of the article.
Published by Elsevier Inc.

Keywords: Code of Federal Regulations; 21 CFR 556; Animal drug residues; Tolerances; Safe concentrations

1. Introduction

The Federal Food, Drug, and Cosmetic Act (FFDCA) provides the authority for the Secretary of Health and Human Services to establish and promulgate regulations on tolerances for residues of drugs in food-producing animals. The Secretary has redelegated this authority to the Food and Drug Administration (FDA). Accordingly, FDA has published general considerations on new animal drug tolerances (Subpart A) and the specific tolerances for residues of new animal drugs (Subpart B) in 21 CFR Part 556.

Although Part 556 (Tolerances for Residues of New Animal Drugs in Food) is one of the Center for Veterinary Medicine's most significant set of regulations, it contains obsolete definitions, outdated terminology, and a patchwork format that has evolved over time. The net result is a regulation that does not reflect current practice and which may be difficultly or inconsistently interpreted. The purpose of this paper is to define the older terms and update the reader as to current concepts that apply to tolerance-setting for new animal drugs.

2. Discussion

21 CFR Part 556 assumed its present format with the October 2, 1970, Federal Register publication (35 FR 15372). Known then as 21 CFR Part 135 g, the regulation introduced the language of 556.1 that has stood for 35 years. Nevertheless, 556.1(a) often leaves the reader perplexed, rather than edified. For example, Subpart A-General Provisions refers to "finite residues," "finite tolerance," and "negligible residues," terms that have fallen from use and which do not reflect the tolerance-setting procedures that FDA has applied for more than 20 years.

In addition, as presently written, 21 CFR 556 Subpart B (Specific Tolerances for Residues of New Animal Drugs) represents a patchwork of different styles for listing tolerances that has evolved over approximately 40 years. As a result there is a lack of uniformity in the listings. Thus, the acceptable daily intake (ADI) and safe concentrations are given for some, but not all drugs; some

E-mail address: sbrynes@cvm.fda.gov.

0273-2300/$ - see front matter. Published by Elsevier Inc.
doi:10.1016/j.yrtph.2005.05.009

tolerances are qualified as being for negligible residues; and some listings specify "no residue," "zero" tolerance, or tolerance "not required" with, arguably, no adequate definition or distinction given for these important terms.

FDA's human food safety evaluation of residues of new animal drugs has progressed steadily over the past 50 years. Prior to the mid-1970s, FDA assigned tolerances based primarily on a small number of toxicity studies, typically 90-day feeding studies in laboratory animals. From the results of these studies, FDA determined the "no-observed-effect level" (no-effect level or NOEL). FDA then adjusted the NOEL (1) for the differences between test animals and humans by application of a safety factor (the NOEL divided by the safety factor gives the ADI) and (2) for consumption (a total dietary exposure of 1500 g of food per day of which muscle was considered to be 500 g) vs. body weight (historically FDA used an average human weight of 50 or 60 kg; currently, FDA uses 60 kg in its calculation). Because these studies did not assess lifetime effects (which could only be observed in long-term feeding studies), FDA applied a 2000-fold safety factor to the calculated value and generally set the tolerance for "negligible" residues of these drugs at 0.1 ppm in muscle and 10 ppb in milk, even if the computed tolerance exceeded the calculated values.

FDA followed similar procedures in assigning what FDA called "finite tolerances," which are tolerances that were set at the calculated level (i.e., not capped at 0.1 ppm in muscle and 10 ppb in milk) except those tolerances needed to be supported, at a minimum, by lifetime feeding studies in two rodent species, a 6-month or longer study in a nonrodent mammalian species, and a multiple-generation reproduction study. In view of the more extensive data base, FDA normally applied a 100-fold safety factor in calculating the ADI and tolerances.

It is important to note that the earliest tolerances generally referred to the parent drug. Consequently, residue chemistry studies, including residue depletion studies which served as the basis for assigning preslaughter withdrawal periods for tissues and withholding times for milk, and the analytical methods used to collect the data, focused on parent drug.

From the mid-1970s through the present, FDA's human food safety evaluation of animal drug residues evolved with improvements in science. FDA no longer relied solely on the results of two 90-day studies to assign tolerances. As a first step in the toxicological evaluation of a new animal drug, FDA implemented a threshold assessment to determine whether residues of the drug posed a carcinogenic risk. A relatively new group of studies, mutagenicity assays, plays a key role in the assessment. And recently, as an extension of its human food safety concerns for antimicrobials, FDA began considering microbiological effects, both in the target animals and humans, when assigning tolerances for antimicrobials used in food-producing animals.

In addition, FDA began to assess the total residue, rather than just the parent drug, and to establish tolerances that would reflect the total residue. Consequently, FDA requested drug sponsors to conduct total residue depletion and metabolism studies to characterize the drug's depletion from edible tissues and its metabolic profile in the tissues. Such studies relied upon experimentation with radiolabeled drug. At the same time, FDA implemented the target tissue and marker residue concepts. The target tissue is the edible tissue selected to monitor for the total residue in all edible tissues of the target animal. The target tissue is usually, but not necessarily, the last tissue in which the total residue depletes to its safe concentration. The safe concentration is the maximum amount of total drug-related residue that is allowed in a specific edible tissue of an animal treated with the new animal drug. The marker residue is the residue selected for assay whose concentration is in a known relationship to the concentration of the total residue in the target tissue. This relationship is used to calculate the tolerance. When the marker residue exceeds the tolerance, the total residue also exceeds the safe concentration. The marker residue can be the parent drug, a metabolite, or a combination of residues for which a common assay can be developed. The relationship between the safe concentration and the tolerance, determined in studies using radiolabeled drug, is graphically shown in Fig. 1.

About 25 years ago, FDA began to list tolerances using the total residue, target tissue and marker residue concepts. However, FDA has not been consistent in setting out or describing the assigned tolerances. In particular, the inclusion of safe concentrations in certain listings has led to some confusion. Some readers have, on occasion, misinterpreted safe concentrations for tolerances. Because a tolerance can be a small fraction of the safe concentration, such a misunderstanding could have serious consequences for those wishing to develop an analytical method for a specific drug. In view of this

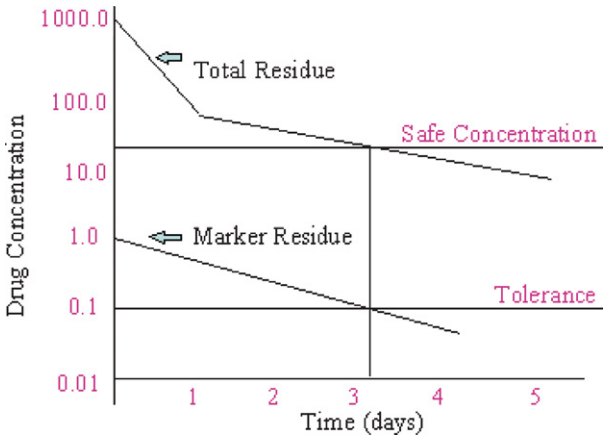

Fig. 1. Setting a tolerance.