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Review

Current FDA regulatory guidance on the conduct of drug discrimination studies for NDA review: Does the scientific literature support recent recommendations?

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ABSTRACT

Background: The Controlled Substances Staff of the Center for Drug Evaluation and Research at the US Food and Drug Administration and the Pharmaceutical Research Manufacturers Association (PhRMA) conducted a series of open forum dialog sessions between 2006 and 2016. A Cross Company Abuse Liability Council (CCALC) was formed during the process of this unique collaborative effort between Industry and Federal Regulators whose goals were to establish the development of standards for the preclinical screening of new molecular entities for schedule control actions required as part of every New Drug Application process. The draft guidance document was published and disseminated in 2010, which allowed for alternative approaches to each study protocol requirement needed for NDA review, if the approach satisfied the requirements of the applicable statutes and regulations (i.e., the controlled substance act). In a series of recent pre-study protocol reviews requested by confidential Pharmaceutical Sponsors of MPI Research, the CSS staff appeared to change its policy and set forth to require all drug discrimination study data to be generated under "extinction" test sessions. MPI Research is a Contract Research Organization acting on behalf of pharmaceutical companies and bound under separate confidentiality agreements.
Purpose: The purpose of this review is to highlight the data appearing in peer-reviewed scientific journals that do not support the regulatory administrative constraints on one specific testing methodology (extinction) to the exclusion of another (reinforced test sessions). Conclusion: This mind shift represents a restrictive administrative policy by the FDA that is not supported by the published data.

1. Introduction

As part of every New Drug Application (NDA) process the US Food and Drug Administration (FDA) must review all relevant and supplied preclinical study data for identification of any relevant indicator that is predictive of schedule control actions under the U.S. Controlled Substances Act (Title 21, Chapter 13, USCA), also known as the Controlled Substances Act. Under U.N. Treaty obligations and US federal statutes, the FDA and Drug Enforcement Administration (DEA) independently review all available safety, toxicity, developmental, pharmacokinetic, and carcinogenicity data for any relevant scientific finding of fact that supports any one or all of the 8 factors that must be considered by both agencies as part of labelling and schedule control actions.

Under the CSA (§811.c.) there are 8 factors that the DEA considers with respect to each drug or substance proposed by the Secretary of Health and Human Services (FDA) as part of the NDA approval and marketing process:

1) The drugs actual or relative potential for abuse;
2) The scientific evidence of the pharmacological effect of the new drug, if known;
3) The state of current scientific knowledge regarding the drug or other like substances;
4) The history and current patterns of abuse (of any drug with similar structure or function);
5) The scope, duration, and significance of abuse related to the new drug or similar drugs already on the market;
6) Any risk of the new entity to public health;
7) The psychic or physical dependence liability of the new drug; and
8) If the new drug is an immediate precursor or prodrug of a drug already controlled in the CSA.

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Over the last decade, the Controlled Substances Staff (CSS) of the Center for Drug Evaluation and Research (CDER) of the FDA has worked diligently with the Pharmaceutical Research and Manufacturing Association (PhRMA) to establish a dialog on the development of standards for the preclinical screening of new molecular entitites (NMEs) for schedule control actions required as part of every New Drug Application (NDA) process. This has been a unique collaboration between government and industry to develop strategies that align nonclinical drug safety, toxicology, and pharmacokinetic evaluations related to the preclinical screening of NMEs for their potential to be diverted, misused and abused once approved for human consumption. Risk assessment plans for abuse potential are reduced through knowledge and best scientific practices. It was the intent of both industry and government regulators to develop a plan that was clear, concise, and in accordance with national and international drug control policies. The current thinking within the US Federal Public Health Policy (National Research Council, 1983) and the European Monitoring Centre for Drugs and Drug Addiction (2009) in regards to risk assessment, in general, is that the agencies must consider actual, not just ideal (medically indicated) use; the analysis must go beyond the clinical study, the risk assessment must consider how people actually use drug substances outside the scope of medical practice which includes consideration of cognitive and behavioral factors affecting human judgment and decision-making (FDA, 2013).

The PhRMA members created a Cross Company Abuse Liability Consortium in 2006. The purpose of the group was to improve public health by advancing the science of assessing abuse potential across the product life cycle and to promulgate "industry best practices" by working with regulators, academic researchers, and public policy advocates. In 2016 the Consortium was formally consolidated as a tax-exempt organization under the new title of Cross Company Abuse Liability Council (CCALC).

A series of open-forum dialog sessions (2008, 2010, 2013, 2015) have been conducted between members of the CSS staff at FDA and members of the CCALC that was instrumental in developing the FDA's draft guidance document titled, "Guidance for Industry: Assessment of Abuse Potential of Drugs" (FDA, 2010) and for the discussion of critical details of data collection to support the guidance expectancies. The guidance document was intended to guide sponsors in developing preclinical screening programs for all new drug products that affect the central nervous system. Publication of the draft guidance document by the FDA clearly acknowledged that regulatory guidance documents, in general, do not operate to bind the FDA or the pharmaceutical industry (public). The FDA guidance document listed the major behavioral assays that should be used for assessment of the new drugs' potential for abuse:

1) Self-administration

1a) Conditioned place preference; that is not as rigorous a behavioral test as self-administration in determining the rewarding properties of a drug, but can be used based on the insolubility of the new drug for IV administration.

2) Drug Discrimination
3) Locomotor Activity Monitoring
4) Dependence Liability Screening

The guidance clearly allowed for alternative approaches to study designs for NDA review, if the approach satisfied the requirements of the applicable statutes and regulations (i.e., the controlled substance act). This change has no impact on those companies outside the U.S. or who design the study protocol in accordance with the EU's abuse liability guidelines (EMeA, 2006). The EU guidelines allow differential behavioral paradigms to be used without restrictions on the schedule of reinforcement (FR10 vs VI5, etc), training drug (controlled vs non-controlled), testing conditions (reinforced vs extinction), and allows for differential routes-of-administration that best categorizes the pharmacokinetics of human drug abuse patterns for that specific training drug. For example, FDA requires all drugs in the DD protocol to use the same route-of-administration for both testing and training. While cocaine is not abused using the oral route of administration, the current FDA policy is to require oral cocaine training conditions in the rat, if the test compound is intended for oral use.

The purpose of this paper is to address a recent critical study design issue that has arisen since those initial dialog sessions with respect to one of the 3 core behavioral assays required for NDA submissions – the study design of drug discrimination testing of NMEs. (The reader is directed to study design and general reviews of the assay by Glennon and Young, 2011; Stolerman, 1993; or Colpaert and Slangen, 1982). The discussion of the best approach for testing of new compounds is not a new one, it has been debated in public forums, scientific meetings, and "in print" for over 40 years. What is relatively new is that the Controlled Substances Staff at the FDA has taken a position to accept only one side of the debate with, what appears to be, a lack of historical control data to do so.

1.1. The dependent variables in drug discrimination study designs

In 1971 Charles Catania, among others, concluded that drugs are stimuli. The term "stimulus" was previously defined by Thompson and Schuster (1968) simply as "an aspect of an organism's environment that can be shown to covary with some aspect of the organism's behavior" (p. 85). As such, drugs can serve to function as antecedent variables (unconditioned or conditioned stimuli, discriminative stimuli) which serve to elicit or evoke behavioral responses or as consequence variables (reinforcement or punishment), which serve to increase or decrease the likelihood of a specific behavioral response. In drug discrimination training, internal or subjective changes induced by drug administration come to predict occasions when a class of responses (e.g., lever press) is reinforced and other interoceptive stimuli predict occasions when those responses are not reinforced, or when they are reinforced contingent on a different operant (Rilling, 1977). In the standard drug discrimination design, drug and vehicle training sessions are alternated daily for 5–7 days per week. Over successive training sessions, a set of objectively verifiable behavioral criteria establish that stimulus control of the two stimuli has been achieved. A drug that has acquired control over a subject's behavior is tantamount to saying that the drug has been established as a signal or cue for reinforcement, or as a signal that a certain class of responses will be reinforced (Mackintosh, 1977).

Much like with other operant conditioning procedures, animals can be trained to make highly specific responses based on these discriminations (Kallman and Rosecrans, 1978). This is evidenced by a vast literature demonstrating differential responding according to pharmacological class (e.g., sedative or stimulant), mechanism of action (e.g., dopaminergic or serotonergic), dose selected for training, as well as structural chemistry (optical and positional isomers, salts of isomers, etc.; Glennon and Young, 2011). Although animals are able to discriminate between the presence and absence of both peripherally- and centrally-active drugs (Colpaert et al., 1975), the assay is typically used for characterizing compounds suspected to penetrate the blood-brain barrier (BBB).

One way to demonstrate that a particular drug has established discriminative stimulus control is to show that changes in some features of the stimulus result in a correlated change in response allocation between two stimuli (drug vs. saline). As described by Järbe and Swedberg (1982) the typical drug discrimination study design used to support scheduling decisions by FDA, DEA, and NIDA