Companies Unite to Advance Regulatory Landscape of Abuse Potential Assessment

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The US Food and Drug Administration (FDA) is collaborating with private and public stakeholders in an effort to address critical public health needs and to bridge scientific gaps.[1] One of these collaborations focuses on abuse potential and involves three key groups: the Controlled Substance Staff (CSS) of FDA, the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Cross Company Abuse Liability Consortium (CCALC).

CCALC is a "grass roots" organization made up of representatives from many pharmaceutical companies. Critical accomplishments of this partnership include the PhRMA/FDA 2008 Dialogue Session on Abuse Potential Assessment,[2] the issuance of FDA's Draft Guidance on the Assessment of Abuse Potential[3] in 2010 and the FDA/CCALC 2010 Dialogue Session on the Draft Guidance.

This article describes the regulatory history of abuse potential assessment, the formation of CCALC and details of key milestones.

Historical Background

Laws designed to control abuse of substances have existed in the US for more than 100 years, dating back to sections in the 1906 *Pure Food and Drug Act*,[4] which (a) deemed confectionaries to be adulterated if they contained narcotics, and (b) required drug labeling to declare if the product contained abuse-able ingredients.[5] Various laws followed affecting substances with abuse potential, culminating in the *Comprehensive Drug Abuse Prevention and Control Act* of 1970 (e.g., *Controlled Substances Act* or *CSA*),[6] which set the current legislative framework for scheduling and control of drugs with the potential for abuse in the US.

The *CSA* was implemented to comply with international treaties on substances of abuse, most prominently the World Health Organization (WHO) 1961 Single Convention on Narcotic Drugs,[7] which was the basis for international drug control. Following passage of the *CSA*, international agreement was reached regarding expanding the scope of drug control, and the 1971 Convention on Psychotropic Drugs was implemented.[8]

In July 1990, FDA, through the Drug Abuse Advisory Committee's Subcommittee on Guidelines for Abuse Liability Assessment, issued the first *Draft Guideline for Abuse Liability Assessment*.[9] Several draft documents were subsequently issued and, in 2003, the CSS was created within FDA to oversee the evaluation of abuse liability, drug dependence and risk management, and make recommendations on drug scheduling of new compounds.

In 2006, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) released a guideline for the nonclinical investigation of dependence potential.[10] This guideline specified a two-tiered approach for all drugs and their metabolites that enter the Central Nervous System (CNS) for which no class-specific standards are available and for which dependence potential has yet to be determined.

First, the substance's pharmacological profile (receptor binding and *in vitro* activity) should be evaluated and animal behavioral studies should be conducted to assess the substance's reinforcing properties and liability for physical dependence. Notably, the guideline contained two provisions counter to the common practice at the time: 1) a clear preference for using rodents instead of nonhuman primates in behavioral pharmacology assays; and 2) a recommendation that the assays be conducted under Good Laboratory Practice (GLP) conditions to the greatest extent possible, in compliance with ICH S7A.[11]

Subsequent to the adoption of the EMA guideline in 2006, Health Canada published its guidance in 2007,[12] the ICH M3 Step 4 was published in 2009,[13] and FDA published its draft guidance in 2010.[14] While the EMA guideline addresses the nonclinical evaluation and the Canadian guidance addresses the clinical evaluation, FDA draft guidance addresses clinical, nonclinical, chemistry and manufacturing and postmarketing aspects of abuse potential assessment.

The guidelines are in agreement regarding general concepts. All recognize that no single procedure can provide a complete evaluation of the abuse potential of a compound, testing should be flexible, and regulatory assessment and decision making should be based on the full array of data available. Although both nonclinical and clinical assessment procedures are considered, human data are still expected to carry the greatest weight in the regulatory review and decision-making process regarding a drug's abuse potential.

While the US Code of Federal Regulations (21 CFR 314.50(d)(5)(vii))[15] dictates that a description and analysis of information related to abuse of any compound that has potential for abuse, regardless of the indication be included in a New Drug Application (NDA), available guidelines suggest a similar comprehensive assessment of abuse potential is expected to be included in marketing applications in other major regions. Considering the increasing focus of regulatory agencies on safety aspects of drug development in general—reflected in the requirement of detailed risk management plans, postmarketing commitments and larger safety databases, and the growing worldwide problem of prescription drug abuse—it is likely the assessment of drugs with abuse potential will continue to increase in importance in the future.

Formation of CCALC

In early 2006, out of a desire to advance the science and regulatory environment of abuse

potential assessment, colleagues from several pharmaceutical companies decided to organize a meeting to discuss their experience and challenges. Interest was high, and a total of 38 representatives from 18 companies attended the initial meeting in June of that year.

The discussions revealed companies were experiencing similar issues with the assessment of abuse liability both with regard to diverging opinions on scientific methodology (study design and interpretation of data) and in their interactions with regulatory agencies. It was agreed there was benefit to working together to share information (non-proprietary, non-competitive) and to influence the external environment.

Four workgroups were formed: regulatory, nonclinical, clinical and risk management. Each identified topics of interest and developed action plans. The workgroups functioned independently and provided updates on their activities at quarterly meetings with the group at large. This group became known as the Cross Company Abuse Liability Consortium and has been operating ever since with a distribution list of approximately 80 individuals from more than 20 companies. The cohesion of the group is maintained by the members' common interest in abuse potential assessment.

Collaboration Milestone

The first major initiative of CCALC was to organize a dialogue session with CSS and other FDA stakeholders to clarify specific scientific abuse liability assessment issues. In conjunction with CSS, it was agreed to discuss hypothetical drug development case studies that included scientific results where there were likely differing opinions in interpretation such as whether there was a "signal" of abuse or a range of options for further development where guidance was needed.

The one-day session on 20 February 2008, sponsored by PhRMA, was attended by approximately 15 FDA staff and 50 representatives from 25 sponsor organizations and companies.[17] CCALC members presented four hypothetical case studies, followed by specific questions on both nonclinical and clinical aspects of the assessment of abuse liability, and CSS representatives presented their respective responses. The four cases with corresponding primary question(s) are summarized below.

- Novel mechanism for a sexual dysfunction indication: *What package is needed to substantiate that this product does not have abuse potential?*
- Chemical class with historic evidence of abuse potential: *Is there an opportunity to demonstrate that a novel member of this class does not have abuse liability? Alternatively, if scheduling consistent with the rest of the class is acceptable to the sponsor, what is the minimum necessary abuse liability testing?*
- Novel mechanism for CNS indication predominantly treated by scheduled products: *What package is necessary to differentiate the new product from the predecessors? Is there a higher burden of evidence in some indications?*
- Chemical class that is CNS-penetrant without historic association with abuse: *How much data are sufficient to confirm that an agent in this class does not have abuse potential?*

Some of the key viewpoints provided by CSS included:

- Abuse liability assessments should not be conducted until Phase 2 studies are completed.
- Multiples up to three times the human clinical effective dose (Ceff) are acceptable in general for all clinical and nonclinical studies.
- Rats are acceptable for nonclinical self-administration and drug discrimination studies, and in some circumstances may be preferred.
- Full characterization of abuse potential requires assessment of physical dependence.
- In some circumstances, if there are no abuse liability signals in nonclinical studies and no clinical adverse events (AEs) suggestive of abuse liability, specific clinical pharmacology study might not be necessary.
- In general, human data are weighted more heavily than nonclinical data. In some circumstances, if a signal is seen in human studies, nonclinical behavioral studies may not be necessary.

- Abuse liability studies are still needed even if the sponsor is willing to accept scheduling because an accurate assessment is needed for labeling.
- AEs from all clinical studies at all phases of development should be reviewed for events suggestive of abuse liability, and all relevant AEs should be reported, not just the most frequent.
- The potential for withdrawal effects in humans needs to be addressed.
- Scheduling is set at the level of a drug substance, not a specific formulation.
- A list of clinical AEs considered related to abuse liability was provided.
- CSS is willing to provide input at key FDA meetings or upon request.

Although time for in-depth discussion was limited, insightful and useful information was exchanged. Both CCALC and CSS slide decks were made publicly available and can be found on the FDA CSS website.[18] Participants agreed a subsequent meeting would be beneficial to discuss, among other items, postmarketing assessment and procedural topics.

Publication of FDA Draft Guidance

FDA continued its work on a draft guidance following the 2008 Dialogue Session. The draft guidance was issued in January 2010[19] and numerous discussion points from the 2008 meeting were incorporated or considered in its development. CCALC engaged in a detailed review during the comment period and identified multiple areas where the guidance could be improved.

It was felt the addition of a few new concepts plus clarifying language would make development pathways clearer for sponsors, thus reducing uncertainty and decreasing the need for frequent consultation with FDA. Eliminating uncertainty in the guidance was a key goal for CCALC, with the expectation that clarity would minimize the risk of sponsors' spending considerable time and resource on abuse potential plans that did not ultimately align with FDA's expectations.

Key comments proposed by CCALC were incorporated into many of the individual companies' and PhRMA's submissions to the docket. These are summarized below.

- Clarify the scope of the guidance to include all potential medicines in development that have abuse potential, not just CNS-active agents, and include a description of the development pathway expected for large molecules.
- Add decision trees to guide the research pathway, recognizing that the development pathway for a new molecular entity should differ from development of a drug in an established and DEA-controlled drug class (e.g., opioids).
- Include additional procedural details regarding the CSS review process, timelines and communication with the sponsor.
- Improve the process of working with DEA and sponsors to ensure delays in scheduling post-FDA approval are minimized, with the overall goal of identifying a process where a DEA *Federal Register* notice would be published immediately after NDA approval.
- Clearly separate suggestions of exploratory research that are voluntary options for sponsors and not a routine expectation for all molecules.
- Expand the postmarketing section.

During the commenting period and in an attempt to better understand stakeholder comments on the draft guidance, CSS approached CCALC to explore the possibility of another dialogue session focused on the guidance. This second session occurred on 2–3 November 2010.

Dialogue Session Regarding the FDA Guidance

The goal of the November session was to foster understanding of the respective positions of

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CCALC and FDA on abuse liability assessment. The session topics included:

- definitions
- regulatory issues
- nonclinical issues
- clinical issues
- statistical issues
- postmarketing experience issues

Sessions were structured with a presentation of relevant issues and proposal for improvement by CCALC, followed by FDA's comment on the respective proposal. Both CCALC and FDA invested significant resources in preparing for this meeting, which resulted in a very helpful exchange of information.

FDA indicated a willingness to accept additional written comments and the minutes of the session were submitted to the docket. Communications and publications by CCALC are planned to further disseminate details of the discussions from this dialogue session.

Summary

The Cross Company Abuse Liability Consortium is an excellent example of a successful and productive collaboration between industry and FDA. The primary goal of the collaboration is to achieve progress in the vastly complex field of assessing the abuse potential of drug products and ultimately protecting public health. These efforts result in greater understanding of the expectations and challenges faced by each stakeholder group, which in turn leads to improvements in the science and regulation of abuse potential.

Although the FDA/CCALC collaboration has advanced the assessment of abuse potential, there is much more to be done. With the solid collaborative relationship in place, there is a unique opportunity to continue the dialogue and pursue additional progress in this field.

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