What's Next After 50 Years of Psychiatric Drug Development: An FDA Perspective

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This article discusses changes in psychiatric drug development from a US Food and Drug Administration (FDA) standpoint. It first looks back at changes that have been influenced by regulatory process and then looks forward at FDA initiatives that are likely to affect psychiatric drug development in the future.

FDA protects the public health by ensuring the safety and efficacy of drug products introduced into the US market. FDA works with drug sponsors during development, and, when applications are submitted, reviews the safety and efficacy data and the proposed labeling. Drug advertising and promotion and postmarketing surveillance also fall within FDA's responsibility.

Among the many changes in psychiatric drug development over the past 50 years, several have been particularly influenced by FDA. Populations studied have expanded diagnostically and demographically, and approved psychiatric indications have become more focused on the clinical entities actually studied, including in some cases specific symptom domains of recognized syndromes. Trial designs have become increasingly complex and informative, and approaches to data analysis have evolved to better model the reality of clinical trials.

This article addresses 2 general areas of innovation at FDA that will affect psychiatric drug development in years to come. Several programs falling under the general heading of the Critical Path Initiative, ie, biomarkers, adaptive design, end-of-phase 2A meetings, and data standards, are described. In addition, a number of important safety initiatives, including Safety First, the Sentinel Initiative, the Safe Use Initiative, and meta-analysis for safety, are discussed.

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Drug development for psychiatric products has changed substantially over the past 50 years. This article will discuss this evolution from the standpoint of US Food and Drug Administration (FDA)'s role in this process and will then describe FDA initiatives that will have important effects on psychiatric drug development in the future.

FDA'S ROLE IN DRUG DEVELOPMENT

FDA's primary role is to protect public health by ensuring the safety and efficacy of drug and biologic products and also medical devices that are introduced into the US market.[1] This communication will be limited to FDA's role in drug development. FDA's authority to regulate drug development derives from the Federal Food, Drug, and Cosmetic Act (FD&C Act).[2] Regarding efficacy, the FD&C Act states that approval of a drug requires "substantial evidence" from "adequate and well-controlled investigations."[3] *Substantial evidence*, although not well-defined in the statute, is generally interpreted to mean sufficient evidence, but not necessarily overwhelming evidence. *Adequate and well-controlled investigations* are defined in FDA's regulations[4] that identify an array of study designs that can meet this standard, ranging from historical control to double-blind, placebo-controlled trials. For psychopharmacologic drug products, however, it is generally accepted that the most easily interpretable design is the placebo-controlled trial.[5] The FD&C Act describes the requirement for safety as follows: (1) must "include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling" and (2) "the results of tests show that such drug is safe under such conditions."[3] The safety requirement is interpreted to mean that a drug development program must have included all safety testing that would generally be considered necessary to adequately assess the safety of the new drug product, and that the results of these tests must establish that the new drug is reasonably safe, given the seriousness of the condition being treated and the circumstances of use. Both of these requirements are, of course, matters of judgment. What can be considered sufficient safety testing is an evolving standard that becomes better defined as we continue to learn about the adverse effects that drugs can have, eg, there is a recent requirement that prospective suicidality assessments must be included in psychopharmacologic drug studies. FDA also has a major role in deciding how the package insert (labeling) is written and in regulating drug advertising and promotion, which are largely based on the specific language included in the package insert.

FDA has oversight over the IND (investigational new drug) process under which new drug products are studied and developed in human subjects.[6] Once a drug sponsor has developed a product to the point where it is ready to be introduced into humans, ie, there is sufficient information about

its chemistry, manufacturing, and controls (CMC) and sufficient nonclinical safety data to justify safe human use, it must apply for an IND. From that point forward, FDA oversees all human trials with that product; every protocol must be submitted before it is initiated and serious unexpected adverse events that occur must be reported promptly. FDA then determines at each point in development that continued testing in humans is justified. Once a drug sponsor has completed its development and submits a new drug application (NDA),[7] FDA has the responsibility for carefully reviewing all aspects of this complex package of CMC, nonclinical, pharmacokinetic, and clinical data to determine whether or not the new product can be approved and marketed. FDA continues to have oversight over drug products after they reach the marketplace. This oversight includes assessment and monitoring of additional trials a sponsor decides to conduct, evaluation of new safety signals that emerge from postmarketing use of a drug, evaluation of new claims arising from continued development, and monitoring of drug advertising and promotion.

There is often confusion about certain activities that FDA does not regulate, in particular, off-label use. Once approved, a drug product generally may be used by prescribers for any use they deem justified, even if the use is not FDA approved. In rare circumstances, however, FDA may restrict the use of a drug to prescribers who have had training in the drug's use or who carry out particular safety assessments. The drug clozapine is marketed under a restricted distribution system requiring that all patients and prescribers must be registered and that a white blood cell count must be obtained at a specified frequency to identify neutropenia as soon as feasible. In labeling, FDA also identifies safety information that can affect use, eg, warnings about certain off-label uses. The antipsychotic drugs have a box warning alerting prescribers to a risk of excess mortality associated with the use of these drugs in patients with dementia, even though they are not approved for use in this population.[8] Some drugs are recommended for use only in patients who have failed alternative treatments.

EVOLUTION IN REGULATORY ASPECTS OF PSYCHIATRIC DRUG DEVELOPMENT OVER THE PAST 50 YEARS

There have been many changes in psychiatric drug development programs over the past 50 years, including the illnesses studied, the nature of the claims sought, the diversity of patients included in clinical studies, and the complexity of trial designs and data analysis. Many of these changes were a result of the evolution of this research field, but in some instances these changes resulted from FDA initiatives and regulatory actions. This section will briefly review these changes and bring the reader to where we are at present from a regulatory perspective in psychopharmacologic research.

Increasing Specificity of Targeted Indications

Drug product labels from 20+ years ago reveal that psychiatric drug indications at that time were often quite broad and general, eg, drugs were approved for the treatment of anxiety or depression, or in the case of schizophrenia, for the "management of the manifestations of psychosis." This was true despite the fact that the development programs in these instances were quite narrow, focusing, for example, on patients with generalized anxiety disorder, major depressive disorder, and schizophrenia. Since that time, labeling claims have gradually shifted to more narrow indications focusing on the clinical entities actually studied in these programs. This change in focus came about at least in part because of FDA's efforts to prevent drug sponsors from promoting their drugs for indications not studied in their development programs. Development programs have now been conducted and drugs have now been approved for essentially all of the anxiety disorders, including generalized anxiety disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, and posttraumatic stress disorder. In addition to multiple approvals for major depressive disorder (MDD), including recent approvals for 2 atypical antipsychotics as adjunctive therapy in patients with MDD not adequately responding to other antidepressants, drugs are now approved for bipolar depression, seasonal affective disorder, and treatment-resistant depression. A selective serotonin reuptake inhibitor (SSRI) is approved for treating bulimia and PMDD, a number of atypical antipsychotics are now approved for treating bipolar mania, and a number of new drugs and new formulations of older drugs are approved for treating attention-deficit/hyperactivity disorder (ADHD).

In addition to a broader array of approved indications, FDA has endorsed, and drug sponsors have pursued, other clinical entities for which drug approvals have not yet been accomplished. The entity "psychosis of Alzheimer's disease" has been accepted by FDA as a legitimate drug target,[9] as have psychotic depression, cognitive deficits in schizophrenia,[10] and negative symptoms in schizophrenia.[11] The latter 2 clinical entities represent a departure from the usual focus in psychopharmacologic drug development programs on *DSM*-recognized diseases and syndromes to a focus on specific symptom domains or symptom clusters that are part of a broader syndrome. FDA has traditionally resisted focusing on specific symptoms of a recognized entity as legitimate drug targets, out of concern for "pseudospecificity,"[12] ie, a concern that the claim is artificially narrow and is constructed purely for reasons of establishing a market niche. An example of a pseudospecific claim would be for hallucinations in schizophrenia for a drug that in fact is effective in treating an array of positive symptoms. On the other hand, as noted, FDA has accepted a more narrow focus for certain targets, eg, cognitive deficits in schizophrenia and negative symptoms in schizophrenia, since these are well-recognized aspects of this condition that are not well addressed by currently approved drugs that treat mostly the positive symptoms. FDA has, in fact, already approved drugs for certain more narrow targets, eg, certain intramuscular formulations of atypical antipsychotics for agitation in schizophrenia and bipolar disorder, clozapine for suicidality in schizophrenia, and 2 atypical

antipsychotic drugs for treating irritability associated with autistic disorder.

Broadening of Diversity of Populations Studied

There has also been a broadening of the populations included in drug development programs, including both demographic diversity and comorbidity. Inclusion of broad populations in development programs is important because it increases the ability to generalize the findings to the population that will eventually be treated with a new compound after approval and marketing. FDA has encouraged inclusion of broader populations through guidance documents and special initiatives. An International Conference on Harmonisation (ICH) guidance on the elderly[13] encourages including the elderly in development programs for drugs likely to be used in elderly patients, and an FDA guidance on gender[14] encourages including both genders in drug development. FDA has also launched several initiatives intended to increase the study of drugs in pediatric patients to provide clinicians with better information on use of drugs in this population for which much prescribing is currently off-label. The Food and Drug Administration Modernization Act (FDAMA 1997)[15] gave FDA authority to grant additional market exclusivity to companies that conduct studies in pediatric patients, and this authority was continued in the Best Pharmaceuticals for Children Act (BPCA) of 2001. The Pediatric Research Equity Act of 2003 (PREA) gave FDA authority to actually require pediatric studies in certain situations. In addition, the Food and Drug Administration Amendments Act of 2007 (FDAAA) reauthorized FDA's authority for both granting exclusivity and requiring pediatric studies in certain instances.[16] These programs have led to approvals of psychiatric drugs for the treatment of MDD, obsessive-compulsive disorder, schizophrenia, and bipolar disorder in pediatric patients. Current regulations (21 CFR 314.50) require analysis of safety and effectiveness findings by age, gender, and race.[17]

The study of drug treatment in certain psychiatric conditions with comorbid conditions that historically have been viewed as potentially problematic has led to approvals of labeling that assures clinicians of the safety of certain compounds in patients with these comorbid conditions, eg, sertraline in patients with comorbid acute coronary syndrome and atomoxetine in patients with comorbid Tourette's disorder. Although progress has been made in increasing the diversity of the populations studied in psychiatric drug development programs, more effort is needed to expand the range of patients included in trials.

Evolution of Clinical Trial Designs

Trial designs have also changed considerably over the past 20 to 30 years. Earlier development programs for psychiatric drugs generally involved relatively short-term studies (3–6 weeks) comparing a flexible-dose of new drug, often titrated to response, and placebo. Recent trials more often include fixed-dose designs and active controls for assay sensitivity. FDA has encouraged fixed-dose designs because these can provide clinicians with useful dose response information.[18] Examples of where these programs have been useful include risperidone and desvenlafaxine for which, in both instances, the dose response curve for effectiveness showed no added benefit for higher doses, but clearly more adverse effects for those doses were observed. There have been suggestions that this design leads to a higher failure rate than flexible-dose studies, perhaps because the multiple active drug arms raise expectations of benefit and thereby enhance placebo response.[19] Other analyses have not observed this difference.[20] An active control arm is used to show that a trial has "assay sensitivity," ie, the ability to distinguish effective from ineffective treatments. The active control arm is, in a sense, an insurance policy for a drug sponsor, as the interpretation of a "failed" 3-way study including an active control that also fails to beat placebo is different from a 2-way trial where new drug fails to beat placebo, a "negative" trial in FDA's view. Increasingly, companies are conducting "add-on" studies in which a second drug is added to an initial drug to which patients have had a partial but suboptimal response. Such studies have been done in MDD, generalized anxiety disorder, bipolar mania, and schizophrenia.

A study design of interest, but rarely used, is a study in nonresponders in which failures on a treatment are randomized to the failed treatment and the new drug. Such a study in nonresponders to typical antipsychotic drugs led to the approval of clozapine.[21]

Some programs have included fixed combination designs. These are studies comparing a combination of drugs with the 2 separate drugs in the combination. Symbyax (fluoxetine/olanzapine) was studied in this way and is approved for both bipolar depression and treatment-resistant depression.

At FDA's urging, it has now become standard for companies to conduct maintenance studies, not typically as part of an initial program, but postmarketing (phase 4), using a "randomized withdrawal" design, in which responders from an open-label run-in period on a drug are randomly assigned to continuation of that drug or to placebo, with time to relapse as the endpoint of interest.

Finally, there have now been a few large simple trials for psychiatric drugs, primarily to answer questions about comparative risk, eg, the Zodiac trial for ziprasidone versus olanzapine to observe for cardiovascular risk[22] and the Sertindole Cohort Prospective (SCoP) Study for sertindole versus risperidone to examine cardiovascular risk.[23]

Increasing Innovation in Data Analysis Approaches

Approaches to data analysis have also evolved. For many years, analysis using the last observation carried forward (LOCF) was the standard approach to dealing with missing data in evaluating drug trials at FDA. In more recent years, the advantages of other models, in particular the mixed model repeated measures (MMRM) approach, have been recognized,[24] and these MMRM approaches are currently preferred for analyzing psychopharmacologic trial data in

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the division of psychiatry products at FDA. It is important in using any model, including the MMRM model, to assess for whether or not the assumptions of the model are satisfied. In the case of the MMRM approach, it is assumed that dropouts are missing at random (MAR). It is critical, therefore, to obtain as complete information as possible on why patients leave these trials early.

WHAT TO EXPECT FROM FDA OF THE FUTURE WITH REGARD TO PSYCHIATRIC DRUG DEVELOPMENT

FDA has launched a number of initiatives in recent years that will undoubtedly affect the landscape of drug development in years to come, including psychiatric drug development programs. This article will focus on changes that generally fall into 2 areas: (1) critical path initiatives and (2) safety initiatives.

Critical Path Initiative

The Critical Path Initiative (CPI) is FDA's strategy for modernizing the approaches by which FDA-regulated products are developed, manufactured, evaluated, and used.[25] This effort was launched in March 2004 to address an observed decline in the number of product applications being submitted to FDA, despite an abundance of important breakthroughs in biomedical science and an ever increasing number of resources being devoted to developing such products. For drug products, the target of this initiative is the "critical path," ie, the pathway from discovery of a new compound of interest to ultimate launch of that product. The goal was to diagnose the roadblocks in this path and find solutions. The initial announcement requested an identification of specific activities along this path that could help to modernize product development sciences. There was a robust response to this request, and, in March 2006, FDA released a report[26] that included a list of 76 opportunities for development projects that could lead to advances in product development. These opportunities included projects in the areas of biomarkers, trial design, analysis, bioinformatics, among others. Numerous projects are now underway. This section will summarize several areas of interest that should impact positively on drug development within the area of psychopharmacology in years to come.

Biomarkers. Despite substantial progress in psychopharmacology over the last 50 years, there is abundant evidence for a current problem in psychiatric drug development. There have been no real "breakthrough" drugs since the SSRIs/SNRIs and the atypical antipsychotics. Most psychiatric new drug approvals in recent years have not been "novel" compounds, but rather, active enantiomers of already approved racemic mixtures, active metabolites of parent drugs that have activity very similar to the parent, or other "me-too" drugs (ie, members of the same class with minor differences). Such modestly different drugs can sometimes have important advantages, but major gains are rare. The newer drugs have generally not been found to be any more effective than older drugs, eg, as suggested by the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study for antipsychotics,[27] and the Agency for Healthcare Research and Quality (AHRQ) analysis for antidepressants.[28] Only 37% of patients with MDD experienced a remission with the initial drug used for treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.[29] Polypharmacy also continues to be very common in psychopharmacology,[30] suggesting that the need for more effective agents is apparent. Also of concern is the high failure rates for registration trials in psychopharmacology, eg, about a 50% failure rate in depression trials[5] and a rising failure rate in schizophrenia trials.[31] A fundamental problem is the fact that there is only a limited understanding of psychiatric disorders at a biologic level, so that psychiatric disorders are defined on the basis of symptoms rather than biologically. It is difficult to design drugs for diseases that we do not understand at a biologic level.

It is a widely held view that biomarkers might help in psychiatric drug development. FDA defines *biomarkers* as "measurable characteristics that reflect physiological, pharmacological, or disease processes in animals or humans."[26(pR-9)] Although biomarkers have many potential applications in drug development, the focus in this article will be on finding biomarkers that can predict efficacy or risk associated with psychiatric drug treatment, although markers that signal a low likelihood of spontaneous improvement (response in a placebo group) could also be very useful. The main goal of biomarker application in predicting efficacy and risk is to subgroup the population into responders/nonresponders and into those at risk/not at risk for some adverse event of interest. Our limited understanding of the biology of psychiatric disorders greatly limits our search for target markers. Examples of possible biomarkers include imaging measures, serum assays, genetic assays (genomic markers), physiologic measures, histopathological findings, psychological tests, and demographic variables (age, gender, race).

There are 2 principal ways a biomarker (B) could subdivide the population, ie, on the basis of differences in exposure (by far the best developed group of biomarkers) or differences in pharmacodynamic response. In either case, the differences could divide patients on the basis of either efficacy or risk. For example, if marker positive patients (B+) differ from marker negative patients (B–) by having higher exposures to a drug, that difference could translate into a difference in efficacy, eg, better efficacy in B+ patients, or a difference in risk, eg, a greater risk in B+ patients. Similarly, a pharmacodynamic difference between B+ and B– patients, unrelated to exposure, could be reflected by differences in efficacy or risk.

There are already many examples of genomic biomarkers that predict exposure, ie, pharmacokinetic differences based on different activities in metabolizing enzymes. Information about individual differences in levels of several polymorphic enzymes, with resulting differences in drug

exposures, is reflected in labeling for a number of drugs. These enzymes include CYP2C9, CYP2B6, CYP2C19, and CYP2D6. Atomoxetine, a selective norepinephrine reuptake inhibitor approved for the treatment of ADHD, is cleared predominantly by CYP2D6, and 2D6 poor metabolizers (PMs) have 10-fold higher plasma levels of atomoxetine than 2D6 extensive metabolizers (EMs).[32] Since the clinical relevance of this difference in exposure is not clear, the labeling for atomoxetine mentions the availability of genetic tests to determine 2D6 metabolizer status, but does not require such testing. Another example of a drug affected by 2D6 metabolizer status is codeine, an analgesic. Codeine is metabolized to the active species, morphine, by CYP2D6, and the drug has little or no effect in 2D6 PMs, who produce little active analgesic. On the other hand, 2D6 ultrametabolizers (UMs) produce toxic levels of morphine, and there have been reports of deaths in infants breastfeeding from mothers who are 2D6 UMs who have been given codeine.[33] It is also known that 2D6 PMs have approximately 8-fold increases in plasma levels of desipramine after exposure to desipramine, compared to 2D6 EMs.[34] Thus, genomic biomarkers have already had a substantial impact on the prescribing of medications, including psychiatric drugs.

There are fewer examples of biomarkers that predict differences in pharmacodynamic responses, and most are in the oncology area where the diseases are often understood at a molecular level. There are several oncology drugs for which biomarkers predict better efficacy for marker positive patients. The HER2 gene expresses a cell surface receptor that is needed for growth of breast cancer cells, and this gene is overexpressed in about 20% of breast cancers.[35] Trastuzumab (Herceptin) is an antibody that blocks this cell surface receptor. There is a kit available for identifying this subgroup of breast cancer patients, and clinical trials and other data suggest that it is primarily this subgroup that benefits from Herceptin treatment.[36] Labeling recommends Herceptin only for this HER2 positive subgroup of breast cancer patients.[37] For psychiatric drugs, there are some early findings suggesting that biomarkers may help in predicting responsiveness to drugs. One such example is for SSRIs and serotonin genes. Several studies suggest that an allele of the polymorphic serotonin transporter gene (5-HTTLPR) is associated with an SSRI response in Caucasians.[38] Data from the STAR*D trial suggest that a polymorphism in the *HTR2A* receptor gene is associated with a positive response to citalopram, an SSRI.[39] Although these findings are not as robust as the findings for several oncology drugs, they nevertheless give some encouragement that searching for biomarkers for psychiatric drug response may be fruitful.

On the safety side, there is an example of a biomarker that is a fairly strong predictor of the occurrence of serious skin reactions (Stevens Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]) in patients receiving the drug carbamazepine. The incidence of SJS/TEN is approximately 1–6/10,000 in Caucasians treated with carbamazepine compared to a much higher incidence of 30/10,000 in some Asian countries.[40] There is a strong association between the HLA-B* 1502 variant and the occurrence of SJS/TEN with carbamazepine in Asian populations.[41] The positive predictive value of this marker for SJS/TEN is 0.1 (ie, about 10% of patients who are positive for this marker develop SJS/TENS when treated with carbamazepine), and the negative predictive value is 1.0 (ie, there are no cases of SJS/TENS in patients who are negative for this marker). The labeling for carbamazepine recommends testing for this variant in Asian patients, and recommends an alternative drug if the test is positive for the allele, unless there is some compelling reason not to choose an alternate drug.

Although there are not, as yet, biomarkers that reliably predict responsiveness to psychiatric drugs, there is much interest in exploring for such markers. Consequently, it is important to plan for development programs involving biomarkers, and to try to address the practical issues and questions that emerge in such endeavors. Pharmaceutical sponsors are of course very interested in knowing what is required to get potentially useful biomarker information into a drug label. One critical issue is the need for hypothesis testing to establish a biomarker as a predictor of responsiveness. Before deciding on what hypotheses to test in definitive trials to support labeling, it is important to conduct enough pilot work to establish the best path forward. If, for example, it appears, based on pilot data, that a drug may work only in a subset of the population, it may be difficult to show that it is effective in a broad population, eg, patients with a *DSM-IV* diagnosis of schizophrenia. In that case, it may be preferable to study the drug initially in a subgroup of that larger population defined by some biomarker, eg, a genomic marker G, rather than the usual approach of testing in the broad population first. If this trial in the G+ subgroup were successful, it would then be important to examine the response in the G– population. If the drug is shown to work only in the G+ patients, and not to work at all in G– patients, this finding would support labeling targeting G+ patients. If, on the other hand, a sponsor wishes to obtain both a broad claim for a drug in the overall population, but, in addition, a specific claim in G+ patients, eg, a claim that this subgroup is particularly responsive, a different strategy would be needed. The sponsor would need to test the drug first in the overall population, and if successful, then in G+ patients. It is important to emphasize that it will always to necessary to examine the response in G– patients, even if not a formal test. If a drug works equally well in both G+ and G– patients, there would, of course, be no reason to include this genomic information in the label.

There are also other issues that need to be addressed in considering the use of biomarker information in drug development programs. Adaptive designs may be appropriate to increase the power for looking at a particular subgroup. The completeness of the biomarker information is also an important issue. Ideally, one would have biomarker information on the entire sample of patients, and randomization would be stratified on this basis. It is also important for sponsors to

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understand that, if a drug is going to be labeled as needing testing of a biomarker, it will generally be necessary to assure the availability of a Center for Devices and Radiological Health (CDRH)–approved diagnostic kit. Thus, it would be necessary to have a parallel program underway in CDRH for the development and marketing of this kit.

Adaptive designs. *Adaptive design* is a term generally intended to refer to changes in the design or analysis of a clinical trial guided by examination of the accumulated data at an interim point with the goal of making the trial more efficient. Greater efficiency might mean fewer patients, shorter duration, greater likelihood of demonstrating an effect if one exists, or a more informative trial in other ways, eg, better information on dose response. FDA recently released a draft guidance on "adaptive design clinical trials for drugs and biologics" that is intended to assist sponsors in planning and conducting adaptive design clinical studies.[42] A study with an adaptive design includes a prospective plan for a modification of some aspect of the design or hypothesis testing based on an interim look at the data. The types of possible modifications are wide-ranging, and include changes in randomization procedure, treatment regimens, sample size, schedule of patient evaluations, primary endpoint, secondary endpoints, concomitant medications, and analytic methods. It is critical that whatever modifications are made are assessed for their effect on Type I error rate and that any needed adjustments are made. FDA will be focused on ensuring that Type I error is controlled. FDA encourages the consideration of adaptations to improve the efficiency of drug development. The division of psychiatry products also encourages such adaptive planning, and we expect to see the increasing use of such designs in psychiatric drug development programs in the future.

End-of-Phase 2A meetings. FDA is now offering End-of-Phase 2A meetings (EOP2A) to sponsors to provide early guidance on trial design for later phases of development.[43] The focus is on using clinical trial simulation and quantitative modeling based on prior knowledge (eg, on the drug, the disease, placebo response) to help in dose selection and other design features for future trials. The appropriate time for these meetings would be in early phase 2 after completion of an initial proof of concept study in patients. The basis for these discussions could be information of varying types, including biomarkers, surrogate endpoints, prior clinical trials data, or preclinical data. The information could come from a sponsor's resources or from FDA's own archived data. Sponsors need to take the initiative in requesting an EOP2A meeting, and would then interact with FDA staff in planning the meeting. Although there have not been any EOP2A meetings for psychiatric drug development programs to date, it is hoped that these meetings will begin to have an important role in psychiatric drug development programs of the future, as data resources and psychiatric disease understanding improve. With recent advances in genetics and neuroscience, there is reason to be hopeful that mental disorders can be reconceptualized in a way that is more conducive to drug discovery and development in this area.[44]

Data standards. One of the challenges of FDA's regulatory role is reviewing massive amounts of data generated during the development of drug products. This task has been facilitated in recent years by the transition from a paper to an electronic environment. This transition has been helped by agreement on specifications for an electronic common technical document (e-CTD).[45] There remain, however, obstacles to the efficient review of data, in particular, the very different formats used by different pharmaceutical sponsors for storing and sending data to FDA. These differences not only complicate the review of individual applications but also make it much more difficult to conduct meta-analyses across applications to look for safety signals that may not be detectable in individual programs. Differences in data standards include differences in file names, variable names, coding terminology, and data structures. In order to address this problem, FDA has begun to adopt standards established by the Clinical Data Interchange Standards Consortium (CDISC),[46] a nonprofit group whose goal is the development of such standards. One such standard that FDA has adopted is the Study Data Tabulation Model (SDTM) for clinical trial data. SDTM is a major advance, however, it is a 2-dimensional (flat file) structure that does not lend itself to addressing the complex relationships among data elements that characterize clinical reality. So an additional goal is to add another element to the overall model, ie, one developed by Health Level Seven International (HL7), a standards development organization for health care information exchange.[47] HL7 standards have been adopted internationally for health care information exchange and electronic health records (EHRs), and offer the advantage of 3-dimensional or even multidimensional representation of data. The resulting model will hopefully have the combined advantages of both individual elements.

Safety Initiatives and New FDA Authorities Regarding Safety Matters

One of FDA's responsibilities is to monitor the safety of its regulated products after marketing. For years, the mainstay of FDA safety monitoring has been the voluntary spontaneous reporting system, currently known as AERS (Adverse Event Reporting System). FDA does have a data mining capability with AERS to do proportionality analyses in order to sharpen its signal detection capability. Such data-mining explorations determine whether certain drugs have a greater proportion of their overall AERS reports representing a particular type of adverse event compared to other drugs, which would suggest that these drugs have a greater potential for this adverse event than comparator drugs. The methods for this data-mining approach are illustrated in an analysis of diabetes-related adverse events associated with the use of different antipsychotic agents in the AERS database; the analysis found important differences among the various drugs in the signal for such events.[48] FDA also has limited cooperative agreements with different outside groups to conduct observational studies to follow up on certain safety

questions of interest, and has also relied on sponsors and the medical literature to learn about new risks emerging after a drug product has been marketed. Although these systems have been successful in identifying a number of new risks for drugs, they have not always been as efficient and timely as one would like. Consequently, FDA has launched a number of initiatives to enhance its ability to detect new safety signals and better understand drug risks. Recent legislation has also given FDA new authority to ask sponsors to conduct safety studies in certain circumstances.

New safety authorities under FDAAA 2007. FDAAA 2007 provided FDA with a number of new authorities, and several relate specifically to safety.[49] First, FDA can, in certain circumstances, require the conduct of studies and trials focused on specific safety issues. Second, FDA can now require sponsors to make certain safety-related labeling changes. Finally, FDA can require sponsors to develop and comply with risk evaluation and mitigation strategies (REMS), which are programs targeting a particular safety issue for a particular drug to ensure that it is detected and managed appropriately. The simplest REMS would be a medication guide, a patient-oriented document to provide patients and their families useful information about how to safely use a drug product. More complicated REMS might involve restricted distribution systems, focused monitoring and assessments, and even patient registries that would permit systematic tracking and assessment of all patients who receive a particular medication. Clozapine, for example, is available only under a program that restricts use to patients for whom health care providers are willing to register the patient and ensure that required blood testing is conducted; this is essentially a registry.

Safety First. FDA has always been concerned about and focused on the safety of drug and other FDA-regulated products. Safety First should be viewed as a renewal of FDA's commitment to this responsibility.[50] For drug products, this is an overall framework for integrating and implementing the policies, procedures, practices, and technology needed to meet this responsibility throughout a drug's lifecycle. Safety First will incorporate the implementation of FDA's new authorities under FDAAA 2007 and follow-up on various Institute of Medicine (IOM) reports and other activities related to ensuring the safety of drug products. Part of the implementation of this effort has been the creation of safety teams within each review division that include, at a minimum, a deputy for safety and a safety project manager. Safety issues will be formally tracked in the same way that drug applications are currently tracked to ensure they are fully addressed.

Sentinel Initiative. This initiative was launched by FDA in May 2008, in response to a mandate under FDAAA 2007, and is intended to complement existing systems FDA uses to track reports of adverse events linked to its regulated products. The Sentinel Initiative would enable FDA to actively query diverse automated health care data holders—like electronic health record systems, administrative and insurance claims databases, and registries—to evaluate possible medical product safety issues quickly and securely.[51] This system, unlike AERS, would be an active surveillance system that would allow for not only signal detection, but also signal strengthening and validation. It would also involve the use of linked automated health care data from multiple sources, unlike FDA's current contracts that are limited to single databases. It would be a resource for conducting observational studies using existing databases.

Safe Use Initiative. It is often said that FDA "does not regulate the practice of medicine" and this is certainly true. Nevertheless, FDA is concerned about unnecessary injuries and deaths that result from medication errors, many of which are preventable. The S*afe Use Initiative* is intended to foster public and private collaborations within the health care community in order to reduce preventable harm by identifying these risks and implementing interventions with partners in the community.[52] These partners include federal agencies, health care professionals and professional societies, pharmacies, hospitals, and other health care entities, patients, caregivers, consumers, and their representative organizations. Pilot programs are underway, and this initiative can be expected to expand FDA's collaborations with the community in years to come.

Meta-analyses for safety assessment. One approach FDA has used in recent years to detect signals for relatively uncommon serious adverse events is to conduct meta-analyses of placebo-controlled registration trials for which it has complete access to the trial data through NDAs and supplements. There are a number of examples of such analyses, including several in the area of psychiatric drugs. Because of concerns about possible treatment-emergent suicidality (suicidal ideation or behavior) in association with the use of antidepressants, 2 meta-analyses were conducted of placebo-controlled antidepressant trials. One of these involved pediatric trials[53] and the second involved trials in adults.[54] These meta-analyses confirmed a signal for treatment-emergent suicidality, in particular at the younger end of the age spectrum, and current antidepressant labeling has a box warning alerting clinicians to this risk. Meta-analyses of placebo-controlled registration trials were also conducted for the atypical antipsychotics. One of these examined mortality in elderly patients with dementia being treated for psychosis and other behavioral symptoms, and found an excess risk of mortality compared to placebo in these patients being treated with atypical antipsychotic drugs.[55] Other meta-analyses of placebo-controlled registration trials in this same population for certain drugs in the atypical class found an excess risk of cerebrovascular adverse events (strokes and transient ischemic attacks) for drug compared to placebo.[56] These adverse event findings are reflected in the labels for antipsychotic drugs. It can be anticipated that additional meta-analyses to explore adverse event signals will be conducted for psychiatric drug trials, and such analyses will be facilitated by the increasing standardization of clinical trials data that are submitted to FDA.

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CONCLUDING COMMENTS

FDA has helped to shape psychiatric drug development programs over the past 50 years and will continue to do so as the field progresses. Changes over the past 50 years that have had regulatory impact include expansion of the illnesses studied and the claims sought, increasing diversity in the populations studied, and innovation in both study design and data analysis. Several initiatives by FDA will have broad impact in drug development, including an impact on psychiatric drug development and practice. The Critical Path Initiative (CPI) includes a number of programs intended to increase the efficiency of drug development. One area of great interest under CPI is that of biomarkers, and there is hope that biomarkers might also streamline psychiatric drug development, both by identifying responsive subgroups and by identifying patients at particular risk for drug side effects. Other CPI initiatives include adaptive design, End-of-Phase 2A meetings, and data standards. Adaptive designs could help in a number of ways, by providing greater efficiency and increased chances of successful programs. End-of-Phase 2A meetings should help to make better use of available data and emerging understanding of psychiatric disease to better design later phase 2 and phase 3 clinical trials. Establishing data standards for NDA submissions could increase the efficiency of FDA reviews and facilitate meta-analyses that could help in assessing possible drug class risks. FDA has also launched a number of safety initiatives intended to ensure the safety of marketed products. FDA has new safety-related authorities under FDAAA 2007, and has moved to elevate safety considerations in FDA's organizational structure. The Sentinel Initiative promises to increase FDA's ability to detect safety signals by making more efficient use of large postmarketing databases, and the Safe Use Initiative seeks to reduce medication errors for marketed products by forming partnerships within the health care community. FDA's increasing use of meta-analyses for safety should help to assess safety concerns for drug classes. All of these initiatives can be expected to have important effects on psychiatric drug development and practice as well.

Drug names: atomoxetine (Strattera), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), codeine (Butalbital and others), desipramine (Norpramin and others), desvenlafaxine (Pristiq), fluoxetine (Prozac and others), imipramine (Tofranil and others), morphine (Apokyn, Kadian, and others), olanzapine (Zyprexa and others), olanzapine and fluoxetine (Symbyax), risperidone (Risperdal and others), sertraline (Zoloft and others), trastuzumab (Herceptin), ziprasidone (Geodon).

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