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Perception and Process at the Food and Drug Administration: Obligations and Trade-Offs in Rules and Guidances

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Perception and Process at the Food and Drug Administration: Obligations and Trade-Offs in Rules and Guidances

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I. INTRODUCTION

Rulemaking has become increasingly complex as government agencies must cope with the twin challenges of multiple constituencies and intense time pressures. A commonly-held perception inside and outside the Food and Drug Administration (FDA) is that rulemaking is both time-consuming and resource-intensive, and this perception is believed to impact decisionmaking processes. In particular, FDA is seen by many as having turned to guidance documents (or "guidances"), which represent a less formal means of communicating the agency's position on a wide range of issues.

This article examines rulemaking and guidance development at FDA, the perception of agency officials and FDA's various constituencies of these processes, the factors involved in choosing whether to pursue formal rulemaking or less formal controls, and the trade-offs represented by these choices. It also examines how rulemaking and guidance development takes place, providing appropriate examples to illustrate key points.

Section II of this article provides background on the use of rules and guidances at FDA. Section III presents findings from a series of semistructured interviews with FDA officials involved in the development of both rules and guidances. Section IV presents findings from a series of semistructured interviews with FDA stakeholders. Finally, Section V concludes with discussion of the findings and suggestions of issues for future study.

II. RULES AND GUIDANCES AT FDA

FDA is charged with

> protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation … ; for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.[1]

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[1] FDA, FDA's Mission Statement, *at* http://www.fda.gov/opacom/morechoices/mission.html (last visited May 5, 2005).

The development of rules and guidances are critical for FDA to fulfill this mission. Both rules and guidances represent ways in which the agency communicates with its constituencies: rules may interpret and/or implement a statute, whereas a guidance explains FDA's current thinking on a particular issue.

A. *Rules*

Rules developed by FDA and other federal agencies are legally enforceable. The rulemaking process is formalized in the Administrative Procedure Act (APA).[2] The APA, enacted in 1946, established the "notice and comment" rulemaking process, which requires that the government give notice of proposed rules, accept and respond to public comments in the final rule, and state the legal basis and purpose of its actions. Rules are published in the *Federal Register* and codified in the *Code of Federal Regulations* (C.F.R.). Most Centers[3] at FDA have standard operating procedures (SOPs), which are intended to guide agency staff on the process by which rules are developed. Rules may interpret statutes, establish new requirements that are legally enforceable, or amend or revoke an existing rule. For example, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Bioterrorism Act)[4] resulted in the issuance of two new rules by FDA in October 2003 addressing the safety of the nation's food supply.

As laid out in the APA, a notice of proposed rulemaking—including a statement of time, place, and nature of the public rulemaking proceedings; the reference to the legal authority under which the rule is proposed; and either the terms of substance of the proposed rule or a description of the subjects and issues involved—must be published in the *Federal Register*. After this notice is given, a period of public comment begins, during which interested parties can submit written data, views, or arguments on the proposed rule to the sponsoring agency. The agency is required to respond to these comments, and does so in the preamble to the final rule, which is published in the *Federal Register*. Informal rulemaking, in which the agency does not conduct formal hearings before issuing a rule, is commonly employed by FDA and other federal agencies. The APA does not require that public hearings be held in consideration of a rule.

In general, rules can result from legislation passed by Congress, court decisions, citizen petitions,[5] informal requests from affected parties, or emergency situations. For example, FDA recently issued rules to implement sections of the Bioterrorism Act,[6] including sections on prior notice and registration. FDA also issued in November 2003 an interim final rule establishing new restrictions and modifying existing restrictions on the import, capture, transport, sale, barter, exchange, distribution, and release of rodents in order to prevent the spread of monkeypox,[7] in response to an "emergency situation."

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[2] Pub. L. No. 79-404, 60 Stat. 237 (1946) (codified in relevant part at 5 U.S.C. § 553 (2004)).

[3] FDA is comprised of five Centers: Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), Center for Food Safety and Applied Nutrition (CFSAN), and Center for Veterinary Medicine (CVM). Combination products are evaluated through the Office of Combination Products (OCP), established in 2002 and located in the Office of the Commissioner (OC). The OC also issues rules.

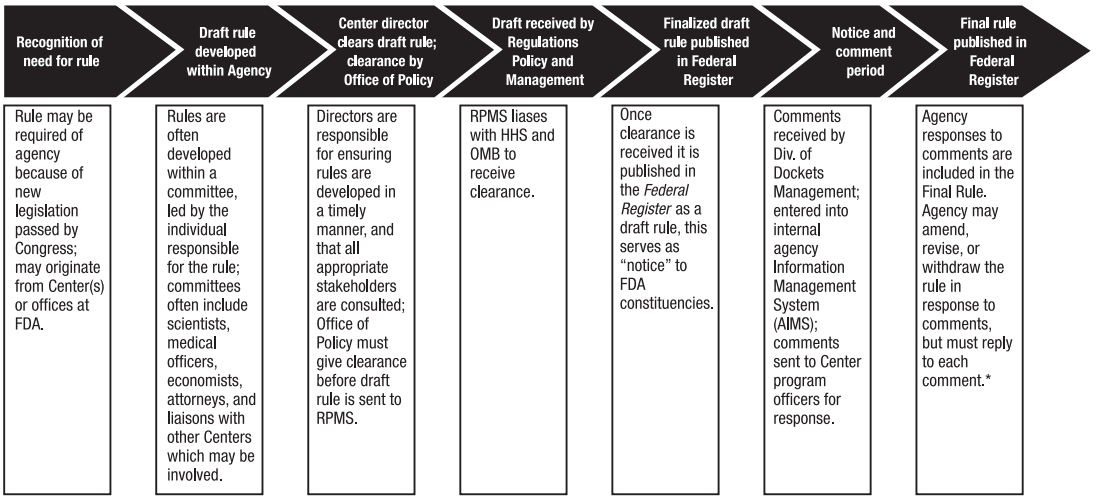
[4] Pub. L. No. 107-188 (2002) (codified in relevant part at 21 U.S.C. § 350d).

[5] 21 C.F.R. § 10.30 (2004).

[6] Prior Notice of Imported Food Under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, 68 Fed. Reg. 5428-68 (Feb. 3, 2003); Registration of Food Facilities Under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, 68 Fed. Reg. 5377 (Feb. 3, 2003).

[7] Control of Communicable Diseases; Restrictions on African Rodents, Prairie Dogs, and Certain Other Animals, 68 Fed. Reg. 62,353-69 (Nov. 4, 2003).

EXHIBIT 1. RULEMAKING AT FDA



* It should be noted that the agency can make changes to the final rule, without triggering another notice and comment period, if the changes are considered a "logical outgrowth" of the proposed rule. Examples in case law include: *City of Stoughton*, 858 F.2d at 751; Anne Arundel County v. U.S. EPA, 963 F.2d 412, 418 (D.C.Cir. 1992); and Kooritsky v. Reich, 17 F.3d 1509, 1513 (D.C. Cir. 1994).

In addition to the APA, there are a number of laws that impact the development of rules, including the Federal Register Act,[8] the Small Business Regulatory Enforcement Fairness Act (SBREFA),[9] the Regulatory Flexibility Act (RFA),[10] the Paperwork Reduction Act (PRA),[11] the Unfunded Mandates Reform Act,[12] as well as a host of other laws particular to individual agencies. Beyond these statutes, a variety of Executive Orders, such as Executive Order 12,866, also apply. Signed by President Clinton in 1993, Executive Order 12,866 aimed "to enhance planning and coordination with respect to both new and existing regulations; to reaffirm the primacy of federal agencies in the decisionmaking process; to restore the integrity and legitimacy of regulatory review and oversight; and to make the process more accessible and open to the public."[13]

[8] The Federal Register Act delineates those documents that are required to be published in the *Federal Register*. 44 U.S.C.S. § 1505 (2004).

[9] The Small Business Regulatory Enforcement Fairness Act allows small businesses more influence in the development of regulations, provides compliance assistance with federal rules, and provides new mechanisms for addressing enforcement by agencies. *See* 5 U.S.C.S. § 801.

[10] The Regulatory Flexibility Act, passed in 1980 and amended in 1996 by SBREFA,

> requires agencies to take steps to collect input from small entities on regulations and to determine whether a rule is expected to have a significant economic impact on a substantial number of small entities. Moreover, federal agencies are required to identify alternative regulatory approaches for small businesses, small governmental jurisdictions and non-profit organizations.

5 U.S.C.S. § 601.

[11] The Paperwork Reduction Act, passed in 1980 and amended in 1995, aims "to have Federal agencies become more responsible and publicly accountable for reducing the burden of Federal paperwork on the public, and for other purposes." 44 U.S.C.S. § 3501.

[12] The Unfunded Mandates Reform Act "provides that each bill must be analyzed for its impact on local government and other entities before it can be voted on. In this way, its impact is known to the legislators before they impose it." 2 U.S.C. ch. 25. The Congressional Budget Office (CBO) is required, under that Act, to submit estimates of the direct costs of mandating compliance and the amount of authorization or budget authority if the estimates are at least $50 million per fiscal year in direct costs to state, local, or tribal governments, or at least $100 million per fiscal year in direct costs to the private sector.

[13] Executive Order 12,866, OMB WATCH (Feb. 10, 2002), *available at* http://www.ombwatch.org/article/articleview/180/1/67/ (last accessed Mar. 21, 2005).

B. *Guidances and Good Guidance Practice*s

Guidances represent the agency's current thinking on a particular subject. For example, FDA may wish to communicate its opinion on the validity of bioequivalence testing methods. Instead of responding individually to questions and inquiries from stakeholders, the agency will prepare a guidance to make its position known to all interested parties. Importantly, guidances are not legally binding; they do not create or confer any rights for or on any person, and do not bind FDA or the public. A person may use an alternative approach if such approach satisfies the requirements of the applicable statute and regulations.

While guidances do not bind the agency in any legal sense, FDA regulations state that FDA employees "may depart from guidance documents only with appropriate justification and supervisory concurrence."[14] Guidances can originate from any FDA Center or office, as well as in response to suggestions from the public.

The development and issuance of guidances at FDA was formalized in a final rule issued by the agency in September 2000.[15] The Food and Drug Administration Modernization Act of 1997 (FDAMA)[16] codified portions of the agency's good guidance practices (GGPs), adding statutory provisions for guidances to the Federal Food, Drug, and Cosmetic Act.[17] FDAMA directed the agency to issue regulations detailing its "policies and procedures for the development, issuance, and use of guidance documents."

GGPs are defined as FDA's policies and procedures for developing, issuing, and using guidances. Guidances themselves are considered documents prepared for FDA staff, industry, and the public that describe the agency's interpretation of—or policy on—a regulatory issue such as the design, production, labeling, promotion, manufacturing, or testing of regulated products; the processing, content, and evaluation or approval of submissions; and inspection and enforcement policies.[18] Guidances do not include documents relating to internal FDA procedures, agency reports, general information documents provided to consumers or health professionals, speeches, journal articles and editorials, media interviews, press materials, warning letters, memoranda of understanding, or other communications directed to individual persons or firms. If communications directed to individuals or firms contain a new statement of policy or a change in policy, those communications would go through the GGP process.

Guidances are classified as Level 1 or Level 2 documents. Level 1 guidances are those that set forth initial interpretations of statutory or regulatory requirements, or that set forth changes in interpretation or policy that are of more than a minor nature, include complex scientific issues, or cover highly controversial issues. Level 2 guidances are those that set forth existing practices or minor changes in interpretation or policy.

Each year, FDA publishes its "Annual Guidance Agenda" in the *Federal Register*. This agenda is a list of possible topics for future guidance development or revisions during the coming year, and the agency seeks public comment on additional ideas for new guidances or revisions of existing ones.[19] The agenda is required under the GGP final rule described above.

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[14] *See* 21 C.F.R. § 10.115((d)(3).

[15] *See generally* 21 C.F.R. § 10.115.

[16] Pub. L. No. 105-115, § 405, 111 Stat. 2296 (1997).

[17] Pub. L. No. 75-717 52 Stat. 1040 (1938) (codified as amended, in relevant part, at 21 U.S.C. § 371(h)).

[18] 21 C.F.R. § 10.115.

[19] Annual Guidance Agenda Notice, 68 Fed. Reg. 16,523-41 (Apr. 4, 2003).

EXHIBIT 2. PROCEDURES FOR PREPARING A LEVEL 1 GUIDANCE

- FDA prepares a draft guidance document that embodies FDA's proposed position.
- FDA publishes a notice of availability in the *Federal Register* announcing that the draft is available; draft also is posted on the Internet and made available in hard copy.
- FDA provides a comment period during which individuals and organizations may submit comments on the draft. FDA may hold meetings or workshops and present the draft to an advisory committee for review. Meetings, workshops, and committee review are not common in the development of guidances.
- After the comment period closes, FDA reviews any comments and prepares the final version of the guidance document. FDA is not required to change the document based on public comments.
- FDA publishes a notice of availability in the *Federal Register* announcing that the final guidance document is available, the guidance is posted on Internet and made available in hard copy.
- The guidance is then implemented.

EXHIBIT 3. COMPARISON OF RULES AND GUIDANCES

	Rule	Guidance
Procedures for Development and Issue	• Proposed rules are published in *Federal Register*, followed by a comment period, revision, and publication of final rule in *Federal Register*. A final rule becomes part of *the Code of Federal Regulations* (C.F.R.).	• Procedures established under Good Guidance Practices specified in 21 C.F.R. § 10.115. A notice of availability of a draft guidance is published in the *Federal Register*, followed by a comment period, revision, and publication of a notice of availability of the guidance in the *Federal Register*. Public comments need not be considered nor addressed to the same degree as in rulemaking because a guidance is not legally binding. A guidance document does not become part of the C.F.R.
Enforceability	• All final rules are legally enforceable, although depending on the nature of the rule, some requirements are written as mandatory instructions whereas others are not.	• Does not establish legally enforceable rights or responsibilities; does not legally bind the public or FDA. • Intended to convey the agency's current thinking on a particular subject and explain how the agency believes the statutes and regulations apply to regulated activities.*
Binding on FDA Staff	• Yes.	• FDA employees may depart from guidances only with appropriate justification and supervisory concurrence.
Origin	• Guidances can originate within FDA, from the industry, or the general public	• Can result from legislation passed by Congress, Executive Orders, court decisions, petitions for rulemaking, informal requests from affected parties, and emergency situations.

* CBER, MANUAL OF STANDARD OPERATING PROCEDURES AND POLICIES, Regulatory—General Information; Procedures for the Preparation, Routing and Issuance of Guidance Documents, SOPP 8002, Version #3, at 2 (Jan. 15 2003).

C. *Standard Operating Procedures*

Like many organizations, FDA has SOPs that assist in many of the day-to-day operations of the organization, providing consistency and structure where possible. The levels of clearance required, the coordination of multiple Centers, and the technical aspects associated with writing rules and guidances often are described in SOPs. Several Centers have developed SOPs for the development and implementation of rules and guidances. While the terminology used in the SOPs (e.g., champion, lead, or chair) may vary and the details may differ, the core procedures are consistent across the Centers. Some FDA components, such as the Office of the Commissioner, have yet to adopt SOPs.

D. *Agency Discretion When Developing Rules or Guidances*

When faced with the choice between rulemaking and developing a guidance, the agency must evaluate each case individually. This choice is critical for several reasons: it will set the parameters of the agency's enforcement ability, it will govern FDA's impact on the industries it regulates, and it will have important implications for the translation of scientific advances into consumer health products. Thus, a careful examination of the factors that influence the decision whether to employ rules or guidances may prove useful.

The agency may have no choice but to issue a rule, as in the case with a statute directing the agency to issue a rule on a particular issue, or in the case where an existing rule must be amended or revoked. In these cases, only rulemaking can be considered, as the APA defines a rule as:

> [T]he whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency . . . .[20]

In cases where the agency desires legal enforceability, this can be achieved only through rulemaking, as guidances are not legally binding. Conversely, if flexibility in application without the requirement of legal enforceability is sought, a guidance may be more appropriate. Finally, in circumstances where the science or technology may be evolving rapidly, such that more speed and flexibility are needed, guidances are likely to be considered the best solution. If a rule is urgently needed, additional resources can be committed, and the rule promulgated expeditiously, within the constraints of clearance procedures required by the Centers for Medicare & Medicaid Services (CMS) (formerly known as the Health Care Financing Administration) and the Office of Management and Budget (OMB).

III. WITHIN THE AGENCY

A. *Perceptions of Rules and Guidances*

The development and implementation of rules and guidances involve individuals across FDA's Centers and offices. To gain insight into these processes, semistructured

[20] 5 U.S.C.S. § 551(4).

interviews were conducted with key individuals at the agency, focused on understanding the agency's views on rules and guidances.

Individuals were identified by the authors in conjunction with officials in FDA's Office of Policy. They included staff involved in various aspects of the development of rules and guidances, including the management of the development of these documents within two centers—the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER)—and compliance with the PRA. Staff involved in the interface between the agency and OMB and the Department of Health and Human Services (DHHS), and staff within FDA's Office of the General Counsel (OGC) were interviewed.[21] Eight current FDA officials were interviewed at length, focusing on the questions outlined in Exhibit 4 below.

EXHIBIT 4. SEMISTRUCTURED INTERVIEW QUESTIONS FOR FDA OFFICIALS

- What is your view on the relative merits of developing rules versus guidance documents—both in the context of your Center (e.g., CBER, CDER, etc.) and across FDA?
- What is your role in the development of rules and guidance documents? I would like to understand how you and your Office interact with individuals and Centers within FDA, other government agencies, industry and the general public.
- Please describe the process by which rules and guidances are developed within your Center (e.g., CBER, CDER).
- Please describe the kind of data collected by you and your Center—for example, do you collect data on all rules and guidances issued each year, the timeline for creation and issuance of each?
- Additional questions relating to a specific Office's role were included when appropriate. For example, when asking about a particular final rule, an official from OGC was asked specifically about OGC's role in rulemaking.

B. *Relative Merits of Rules and Guidances*

FDA develops and implements many rules and guidances each year. The consensus among those interviewed is that rules and guidances are intended to serve very different purposes, and that the relative merits of employing one or the other depends on the agency's ultimate goal in a given matter. Guidances, for example, are employed to convey the current thinking of the agency in a less formal manner than in a rule. In many cases, guidances are used to communicate very detailed—often scientific—information to FDA's constituencies. Those interviewed agreed that due to the rapid pace of scientific advancement, guidances—with their less rigorous review and clearance process (as compared to notice-and-comment rulemaking stipulated by the APA) and their nonbinding nature—provide the best means of providing information to assist industry in understanding and complying with regulatory requirements. According to those interviewed, GGPs have made the process and reach of guidances clearer, both internally and externally.

The importance of guidances in an era of complex science was a common theme in the interviews. One FDA staffer interviewed said that guidances provide "very, very detailed protocols, incredibly detailed," and were perceived as helpful to industry. "Guidances provide for quicker communication, more flexible, allowing us to communicate in a way that I think is helpful and timely. Industry likes them … they like the black and

[21] The interviewees did not include representatives from CFSAN, CDRH, or CVM; due to the variation across FDA Centers, this study was limited by their exclusion.

white, not the grey." Another FDA official interviewed commented that the pace of scientific evolution makes guidances "the most pragmatic way" to disseminate information.

While both rules and guidances tend to originate in the same manner—a fairly organic process in which individuals or working groups within Centers and offices raise a topic, usually with the assistance of legal counsel to advise on whether a rule or guidance is appropriate—rules are subject to more stringent regulatory requirements and are subjected to higher levels of clearance and greater scrutiny than guidances because rules are legally binding.

From the perspective of many of those involved in developing rules and guidances, rules are viewed as requiring more time and effort: "To do a rule, it's a huge ordeal … there are economic analyses of the impact, notice and comment, involvement of OMB, etc." Another commented on the limitations of rulemaking: "In an ideal world, we would always do rulemaking, but it is not as responsive and there is a lot of process involved, not only internal to the agency, but outside FDA."

The length of time required to develop rules and guidances was an issue emphasized by many. At the same time, respondents cited instances when these processes were expedited as examples of the agency's ability to act in a timely fashion. A 1992 report by the General Accounting Office (GAO) studied the timeliness of rulemaking at FDA.[22] One of the recommendations of the GAO report was the establishment of an automated tracking system within the agency to "analyze FDA's entire regulation workload and prepare reports to responsible agency officials."[23] Such a system, the Federal Register Document Tracking System (FRDTS), is now in place, although its success has been limited. According to some of those interviewed, while the Centers are supposed to enter a rule into the system as soon as a decision is made to pursue rulemaking, this in fact rarely happens. Instead, this information is entered into the system when the proposed rule is published in the *Federal Register*. Importantly, the FRDTS does not capture the work on the proposed rule leading up to its publication.

One agency official speculated that this occurs because, if a rule were entered into the system at the time it was decided to begin the rulemaking process, then it would be very clear how long the rulemaking process actually takes (i.e., there is a bias toward inaccurate reporting because of concerns that delays will be scrutinized). Thus, the tracking system may show artificially-rapid rulemaking because of what could be termed a "censoring bias" due to incentives not to enter information into the FRDTS. Another possibility—unexplored in this study—may be that FDA staff is wary of using the tracking system because it may bring premature attention from stakeholders early in the rulemaking process, before the agency has had time to develop a careful proposal.

At the same time, however, there is a sense that the development of guidances has come to resemble rulemaking in terms of the extent of clearance and time required to develop and implement them. This view was expressed clearly by one individual: "Ideally, they [guidances] should be faster and more flexible, but in practice, they may take as long as rules to develop." If a new guidance has any paperwork burdens (e.g., additional forms to be filed with FDA), the PRA demands the same oversight for the guidance as that which applies to a rule, including oversight by OMB. While a guidance cannot impose a burden or require a form because technically it is voluntary, it can trigger a paperwork burden to the extent that information must be reported to FDA.

[22] U.S. GENERAL ACCOUNTING OFFICE (GAO), FDA REGULATIONS: SUSTAINED MANAGEMENT ATTENTION NEEDED TO IMPROVE TIMELY ISSUANCE (Report of the GAO Human Resources Div. to the Subcomm. on Health and the Environment, House Comm. on Energy and Commerce) (Pub. No. 92-35) (Feb. 1992).

[23] *Id.* at 8.

Some of those interviewed registered disagreement over the proliferation of guidances emerging from the Centers, arguing that in many instances these documents should be developed as rules instead. Further, one individual argued that even when rulemaking is appropriate, the rulemaking process often was not followed correctly. Two specific examples of this are discussed *infra* Section IV.

C. *Trends in the Use of Rules and Guidances*

The perception among some of those interviewed is that guidances seem to be used more frequently than rules. A detailed analysis of published records from FDA over the calendar years 2001 through the first eleven months of 2003 show that, in fact, guidances outnumber rules by a substantial margin. The results are depicted in Exhibit 5.

This analysis was performed on published records lists supplied by FDA, and contained all documents published by FDA in the *Federal Register*, divided into the following categories: Advance Notice of Proposed Rulemaking, Notice of Proposed Rulemaking, Direct Final Rule, Final Rule, Interim Final Rule, and Notice. This last category included draft and final guidances, as well as routine announcements of public meetings, withdrawals of approval, etc. The analysis employed several exclusion criteria to identify only those rules and guidances that reflected policymaking at FDA.

All Notice of Proposed Rulemaking, Direct Final Rule, Final Rule, and Interim Final Rule categories were combined into the "rules" category. Excluded then were documents related to administrative and routine matters: notices of public hearings, administrative revisions to rules (e.g., technical amendments, confirmations of effective date), dosage forms for sponsors, change of sponsor or sponsor's address, revision of administrative actions and procedures, meetings and correspondence, public calendars, delays and partial delays of effective date, partial stays of effective date, withdrawals of product approval, delegations of authority and organization, reorganization, and republication.[24] Documents related to the initial classification of a medical device were retained, as well as documents related to reclassification of a product to a less-stringent control. All notices were reviewed to ensure that only draft and final Level 1 guidances were included in the analysis. Documents labeled "Level 2 Guidance" were excluded because, as discussed previously, these guidances set forth existing practices or minor changes in interpretation or policy. If a guidance was not designated as "draft" or "final," it was considered final. This analysis did not distinguish between documents (guidances or rules) that were initiated by FDA and those that were required of the agency due to statutory directive.

Exhibit 5 demonstrates that, across FDA the number of guidances exceeds rules by a substantial margin over the three calendar years observed (i.e., 2001, 2002, and 2003). Indeed, over twice as many guidances as rules were issued during that time period.

[24] In some cases, the delay of effective date or withdrawal of a product may represent a policy change, but for purposes of this study, such documents were not included in the analysis.

EXHIBIT 5. NUMBER OF GUIDANCES AND RULES, BY CENTER, CY 2001-2003.[25]

CENTER AND YEAR	RULES	DRAFT GUIDANCES	FINAL GUIDANCES	TOTAL GUIDANCES	RULES: GUIDANCE RATIO
CDER 2001	3	18	14	32	1:10.7
CDER 2002	13	14	12	26	1:2
CDER 2003	11	26	16	42	1:3.8
CBER 2001	6	11	9	20	1:3.3
CBER 2002	0	7	7	14	0:14
CBER 2003	1	3	10	13	1:13
CDRH 2001	12	10	9	19	1:1.6
CDRH 2002	24	12	13	25	1:1.0
CDRH 2003	12	8	19	27	1:2.5
CFSAN 2001	8	2	8	10	1:1.3
CFSAN 2002	7	4	9	13	1:1.9
CFSAN 2003	11	2	7	9	1:0.8
CVM 2001	2	4	9	13	1:6.5
CVM 2002	4	6	8	14	1:3.5
CVM 2003	2	3	7	10	1:5
OC 2001	4	0	0	0	4:0
OC 2002	4	5	2	7	1:1.8
OC 2003	5	2	2	4	1:0.8
Total 2001(FDA)	35	45	49	94	1:2.7
Total 2002 (FDA)	52	48	51	99	1:1.9
Total 2003 (FDA)	42	44	61	105	1:2.5

[25] CY 2003 through November 14, 2003.

D. *Perceptions of Trends in Use of Guidances and Rules*

Several individuals involved in both rulemaking and guidance development and implementation voiced concern about the increased layers of review for guidances. Some of these layers are no doubt the result of the implementation of the GGPs discussed previously. Individuals worried that the additional scrutiny of guidances may detract from their utility as they become less flexible and responsive. "There is an inherent tension between the need for flexibility and the legal considerations in terms of getting input from various parties. To the extent that guidances start looking like rules and there is the perception that guidances are setting regulatory standards, then there is a concern that they get more process and more clearance," was a comment echoed by several of the individuals who were interviewed.

The increase in time and effort required for developing guidances is perceived as the result of many factors. For some, this is a by-product of the formalization of the guidancemaking process in the GGPs: "GGPs have almost elevated guidancemaking to rulemaking level," remarked one individual. Other interviewees credited regulatory requirements, such as the PRA, for bringing guidances to the level of examination usually reserved for rules, which legally bind the agency and those regulated.

Transparency of process is an important issue for both rules and guidances. The *Unified Regulatory Agenda*, the annual publication that lists the rules and guidances federal agencies aim to pursue in the coming year, was suggested by one individual as an example of the lack of transparency. The *Unified Regulatory Agenda* may publish the titles of various regulatory documents under consideration, but this individual felt that, not only were the titles often inconsistent with the actual rule or guidance that eventually was developed, but the *Agenda* did little to explain the content and intent of each document. The *Agenda*, in fact, may be more of an indication of the political environment of FDA. One agency official commented on the varying perspectives of different administrations on the *Agenda*'s content. For example, under a recent administration, FDA was encouraged to be overinclusive in listing its regulatory plans for the coming year; another administration had urged the agency to be underinclusive. Thus, it appears that assessing agency performance based on its success at achieving the aims set out in the *Unified Regulatory Agenda* may be misplaced.

E. *The Agency's Perceptions of Its Stakeholders' Perceptions*

A common theme throughout the interviews of FDA officials was that rules and guidances are appreciated by industry because they eliminate "grey zones" and "clarify and elaborate on regulations." The agency officials argued that this is important for regulated constituencies to understand FDA's expectations.

IV. LOOKING IN FROM THE OUTSIDE

A. *Industry Perceptions of the Rule and Guidance Development Processes*

Equally important to understanding the impact of rules and guidances are the perceptions of those regulated by FDA regarding the relative merits of both forms of agency reach, and the process of rulemaking and guidance development.

To better understand the perceptions of FDA's regulated constituencies, semistructured interviews were conducted over a period of several months with indi-

viduals representing FDA constituencies. Many of those interviewed had been FDA employees at one point, and in their current positions they represented clients' regulatory interests, often by interacting directly with FDA. Individuals were identified by the authors in collaboration with FDA officials, and they were asked a set of questions as outlined in Exhibit 6 (see below). Twelve individuals representing the interests of the biotechnology, pharmaceutical, and food industries were interviewed.

EXHIBIT 6. SEMISTRUCTURED INTERVIEW QUESTIONS FOR INDUSTRY REPRESENTATIVES

- FDA issues numerous rules and guidance documents each year. What is your view on the relative merits of developing rules versus guidance documents?
- What are the considerations in deciding whether a rule or guidance is appropriate?
- Are there instances you recall in which a rule was issued, when you believed a guidance document was warranted, and vice versa? Can you provide examples?
- What is your perception of the manner by which rules and guidance documents are developed at FDA—i.e., from the outside looking in, how does the process appear to function—is it transparent, etc.?
- To what extent are FDA constituencies included in the rule and guidance development process?
- How do you and your organization interact with FDA in the context of rule or guidance development? Is there a difference between the two mechanisms?

1. *Choosing Between Rules and Guidances*

In general, all of those interviewed agreed that the major difference underlying the use of a rule or guidance is that rules are used when mandated by statute or when the agency desires legal enforceability. Rules, some remarked, should be restricted to those areas where there were repeated and accepted standards of addressing an issue (e.g., the reporting of adverse events during clinical investigations). In cases where there is no accepted standard or the science is too cutting-edge to result in consensus, guidances can provide constituencies with a sense of the agency's position on a particular issue.

When a rule is not required by statute or other mandate, the choice to pursue a rule or a guidance is influenced by the agency Center where the document originates. According to one interviewee with extensive experience in the field, "different Centers behave differently." This individual commented that the "culture" of whether to pursue rules or guidances takes form around the mission of a particular Center. A Center that is heavily invested in premarket review (e.g., CDER) may tend to develop regulations that are more procedural, with extensive use of guidances, because the enforcement mechanism is largely premarket. On the other hand, in the area of food regulation, where enforcement is focused on the postmarket setting, regulations are required for enforceability. According to this individual, the choice of rules and guidances is part cultural and is partly defined by the nature of the work.

2. *Rulemaking Procedures*

One individual discussed the Clinical Laboratory Improvements Amendments (CLIA) waiver regulations, which were proposed as a rule in 1995.[26] Many comments to the notice of proposed rulemaking were submitted, but the rule was never finalized. The

[26] CLIA Program; Categorization and Certification Requirements for a New Subcategory of Moderate Complexity Testing, 60 Fed. Reg. 47,982 (proposed Sept. 15, 1995).

individual interviewed suggested that the various agencies involved (e.g., the Centers for Disease Control and Prevention (CDC), CMS, and FDA) disagreed over which agency was responsible for making waiver determinations. "Technology and lab practices have evolved since then," commented this individual, "and if the 1995 criteria were to be retained, only a few products would be waived and virtually no new products would achieve waiver. Industry argued that safety and efficacy had already been examined in the 510(k) or PMA/BLA review by FDA. Included in that review is adequate quality control provisions, in-depth examinations of performance characteristics, and instructions for use."

Had the waiver criteria been part of a guidance, argued this FDA stakeholder, there would be more interchange of ideas among industry groups, laboratories, standards organizations, and government agencies, and that interchange of ideas would be less formal and less constrained than in a rulemaking process.

> It would also be nonbinding: if you can show an alternate criteria to FDA's satisfaction it would be acceptable. As technology and methods advance, the guidances are easier to change than regulation. There would be more opportunity for good products to be waived. In addition, the industry has argued that based on CMS's original requirements the costs would increase and the availability (access) of medical care may decrease. By agreeing to a more flexible guidance as opposed to a rigid rule, this may be avoided.

Another individual interviewed cited FDA's January 2004 announcement[27] of a "future intent of interim final rule" related to the use of bovine products in cosmetics and dietary supplements as an example of when a rule was appropriate, but the process flawed. While the interim final rule has yet to be published, the announcement led to "massive confusion in various FDA-regulated industries and a stream of trade association meetings through which FDA apparently learned a lot about the practical impact its announced actions—if implemented—would have," said this stakeholder.

The interim final rule remains unpublished, "[a]nd it [the agency] shouldn't publish a document of this degree of practical and complex impact without a real notice of proposed rulemaking but only a press release," said the same individual. "Indeed, if the agency at this point were to go straight to final without a proposal, how in the world could it justify its action as a public health emergency authorizing invocation of 'good cause' to skip notice and comment? It couldn't."

B. *Industry's Perception of the Enforcement Differences Between Rules and Guidances*

While the enforcement implications differ for rules and guidances, in practice most of those interviewed said that industry treats guidances no differently than rules. This reality was highlighted by the majority of those interviewed, although the explanations differed slightly.

In the majority of cases, guidances are treated the same way as rules (that is, industry follows them as if they were legally binding) because industry desires consistency. One comment from an industry representative was particularly revealing:

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[27] Press Release, DHHS, FDA, Expanded "Mad Cow" Safeguards Announced to Strengthen Existing Firewalls Against BSE Transmission (Jan. 26, 2004), *available at* http://www.fda.gov/bbs/topics/news/2004/hhs_012604.html (last visited Mar. 18, 2005).

> At the end of the day, they [industry] don't care, as long as they can rely on it … . Lack of consistency drives them crazy. Most business people don't know the difference between a reg and a guidance, so by and large the business field does not care. All they want is clarity.

Industry desires consistency in terms of what the agency expects from both them and their competitors. According to those interviewed, a level playing field is of paramount concern.

Another individual commented that many guidances "take on the weight of a rule" mostly because industry is loathe to diverge from the agency's current thinking embodied in the guidance. "The fact that most everyone follows the guidance," remarked this individual, "doesn't make it a bad thing."

Some of those interviewed were less reassuring in their explanations of why industry may not differentiate between guidances and rules. In some cases, guidances have been issued when rulemaking should have been undertaken instead. In other cases, some individuals at FDA, contrary to the statutory GGP provision,[28] have conveyed the message that guidances are binding.

The advent of the GGPs, which formalized guidancemaking, was noted as important in this regard; according to those interviewed, the GGPs have made guidances resemble rules in their formality and language. On the other hand, the consistency resulting from the GGPs was appreciated by almost all of those interviewed.

1. *Transparency of the Process*

There were contrasting opinions on the transparency of the process of making rules and guidances. Some of those interviewed found FDA to be very "responsive" and believed they had relatively unimpeded access; one individual interviewed commented that he could just pick up the phone and call a contact to "get a behind-the-scenes read on the issue." Further, the agency was described as "less antagonistic to industry" now than in the past.

In contrast, others believed the process to be rather opaque. Once draft guidances or proposed rules are published in the *Federal Register* (a notice of availability (NOA) in the case of guidances; the entire draft in the case of rules), they often are viewed by industry as mostly final. One interviewee's comment was that, even though FDA accepts comments from the public (and is required to respond to each in the case of rules), it is very unusual for FDA to actually change its position or incorporate any of the feedback into the guidance or final rule. In essence, some individuals felt that the drafts are actually final in that input and consultation with stakeholders does not really happen.

While there are public meetings for this purpose, those who believed the administrative process to be opaque related that these meetings do not appear to result in the incorporation of the views of stakeholders; instead, they argued, the meetings merely present opportunities for monologues or prepared statements on particular topics. At the same time, the lack of transparency was viewed as almost inherent to the process. From FDA's perspective, commented one individual, there actually is a disincentive to involve stakeholders early in the drafting process. Doing this is time-consuming and opens the agency up to criticism and demands from stakeholder groups to be actively involved.

One individual suggested that in areas where the expertise needed to develop a particular guidance or rule resides outside of the agency (as may be the case in very

[28] *See* 21 U.S.C. §§ 371(h)(1)(A), (h)(2).

novel or innovative science), the inclusion of all stakeholders prior to the development of draft guidances or rules is essential. The recent development process for the guidance on pharmacogenomics data submission was cited as a good example of creating more transparency.[29]

2. *Timeliness in the Development of Rules and Guidances*

A recurrent theme was the length of time required for FDA to take a position (either with a rule or guidance) on a particular issue. As mentioned above, industry appears to want to know "what the rules are," so it can play by them; uncertainty was viewed as uniformly undesirable, especially in the form of long waiting periods. As one individual who previously worked within the agency commented, "On the outside, I really appreciate the impact on companies from delayed rulemaking and the inconsistent application of guidances." This same individual noted that when the agency focuses on timeliness, it is able to work quickly. This sentiment was echoed by many of those interviewed, and specific examples of the thirty-month stay rule of June 2003[30] and rules required by the Bioterrorism Act of 2002[31] were cited as rules in which the intense focus of the agency resulted in timely action.

Part of the problem of timeliness was explained by those interviewed as a function of changing priorities of the agency, many times as a result of changes in leadership. In some cases, rules and guidances were issued in a very timely fashion, but this is usually the exception and this occurs usually when an issue becomes a priority for the Commissioner or other agency leaders (often at the DHHS level), so that a disproportionate amount of agency resources is committed to that particular issue.

Another aspect of the concern over timeliness was voiced concerning the existence and persistence of draft guidances, often for years after an NOA is published in the *Federal Register*. These documents, although in draft form and not issued as final documents, come to represent final guidances. There is a similar concern over the persistence of proposed rules. A 1992 GAO report found that the rulemaking process was plagued by delays. In fact, the report found that, of the 301 regulations published as proposed rules, seventy-two percent were in pending status for more than five years.[32] The report found that, despite a variety of factors cited by the agency as reasons for delay in issuing regulations (many of which were reiterated in interviews by the authors for this article), these challenges could have been—and on occasion had been—overcome. Although the empirically-rigorous GAO report is more than ten years old, and arguably dated, some of the issues identified in that report were echoed in interviews conducted for this project.

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[29] CDER, FDA, DRAFT GUIDANCE FOR INDUSTRY: PHARMACOGENOMIC DATA SUBMISSION (Nov. 2003), *available at* http://www.fda.gov/cder/guidance/5900dft.pdf (last accessed Mar. 18, 2005).

[30] The final rule allows for one 30-month automatic stay in the delay of generic and section 505(b)(2) drug approvals when patent infringement litigation is filed. The Hatch-Waxman Act allows for the automatic stay in order to protect intellectual property, but the final rule limited it to one stay in order to prevent abuse of what had become, according to the Federal Trade Commission and others, a loophole for brand-name firms to block entry of generics to the marketplace. In addition, the final rule tightened requirements and increased information for drug patent submission and listings to FDA's *Orange Book*. This was intended to prevent brand-name firms from submitting additional patents for listing in order to block generic entry. This rule was drafted and finalized over a period of several months. *See* 21 C.F.R. § 314.

[31] The rules implementing the Bioterrorism Act show how rules can be drafted quickly when sufficient resources are applied and short deadlines are mandated.

[32] GAO, FDA REGULATIONS: SUSTAINED MANAGEMENT ATTENTION NEEDED TO IMPROVE TIMELY ISSUANCE, *supra* note 22.

V. DISCUSSION AND CONCLUSIONS

The development of rules and guidances at FDA is a critical component of the agency's mission, and has far-reaching implications for both the regulated industries and the healthcare market as a whole. The opinions set forth in this article are those of a couple dozen individuals, and subject to the limitations of a small-sample interview survey. The combined regulatory experience of those interviewed and the salient issues raised, however, make it a valuable contribution to our understanding of the perceptions of both agency officials and their constituencies.

The research presented here suggests that agency officials are aware of the tension between rule and guidance development, and that there is an overall perception—confirmed by data analysis—that guidances are being used more frequently than notice-and-comment rulemaking.

Our research does not address whether the major perceived advantage of guidances (i.e., the speed with which they can be developed and implemented) is a fact, or whether this perceived advantage has been compromised by additional layers of oversight in recent years. Some agency officials and stakeholders suggest that increasing formality in the creation of guidances and more extensive oversight may hinder the speed and flexibility of their development. To the extent that rulemaking and guidance development are approximating each other in terms of time and resources required, some of the advantages of guidances may be diluted.

Future study of cases where there is a choice of employing a rule or a guidance (i.e., where the agency must decide whether or not legal enforceability is essential) is warranted. It is in these instances that a greater understanding of the decisionmaking process might provide insight into the relative merits of rules and guidances, and perhaps provide some intuition to explain recent trends in the use of both. In addition, a clear understanding of the time to develop rules and guidances is warranted. As discussed above, FRDTS may not be the appropriate source of data for such an analysis because of the reporting bias existent in the agency's Centers. One approach would be to repeat the 1992 GAO study today, and to incude both rules and guidances. Further, knowledge of the allocation of resources (i.e., personnel) to rulemaking and guidance development may shed some light on concerns raised by those interviewed.

There are several other potential areas for future research identified in the course of this study. If guidances are indeed being used more frequently than rules, research to understand the strengths and weaknesses of guidance development should be considered. This study did not evaluate whether the number of guidances issued by FDA as compared to rules has increased or decreased from 2001-2003 as compared to an earlier time period (e.g., before GGPs were in place). Furthermore, an analysis of how FDA's experience compares to those of other federal agencies would allow for best practices to be shared across agencies often facing similar regulatory challenges.