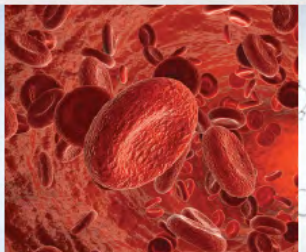
U.S. Food and Drug Administration

An Evaluation of the Prescription Drug User Fee Act (PDUFA) Workload Adjuster Fiscal Years 2009 - 2013

April 22, 2013



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Executive Summary

The Prescription Drug User Fee Act (PDUFA), most recently reauthorized under the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, enables the Food and Drug Administration (FDA) to collect user fees for Fiscal Year (FY) 2013-FY 2017. To support the fee-setting process, the FDA measures the workload associated with PDUFA-related activities in the human drug review process. User fees, used to support the resources necessary to expedite product reviews, are adjusted to account for changes in workload over time. The adjustment is determined by a quantitative tool called the Workload Adjuster.

Two independent evaluations of the Workload Adjuster are mandated by FDASIA. The first, undertaken from February to April 2013, evaluates whether the workload adjustment methodology reasonably represents actual changes in workload volume and complexity in the human drug review process from FY 2009-FY 2013. The second evaluation will be conducted in FY 2015.

The approach for this first evaluation focuses on the ability of the current Workload Adjuster methodology to effectively measure changes across two dimensions: workload volume and work complexity. The term 'workload volume' refers to the **number of work** units received by the FDA in the form of human drug review submissions and 'work complexity' refers to the **amount of work**, or level of effort, per submission. The evaluation team collected and analyzed data on the number and types of submissions received by the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) that are used as inputs into the Workload Adjuster and assessed the ability of this data to represent changes across these two workload dimensions. Overall, we evaluated four aspects of the Workload Adjuster: (1) the adequacy of the base submissions used to measure workload volume, (2) the adequacy of the change of review activities that are subsets of submission reviews and are used to measure work complexity, (3) the use of weighting factors, and (4) the application of 5-year rolling averages in workload calculations.

Our evaluation considered whether the Workload Adjuster reasonably represents major drivers of PDUFA-relevant workload throughout the human drug review process. Specifically, we consider whether review process changes that have taken place at the FDA as a result of legislation and process improvement initiatives are adequately captured by the Workload Adjuster. This includes the impact of changes based on Food and Drug Amendments Act of 2007 (FDAAA), which reauthorized PDUFA (PDUFA IV) and expanded FDA's authority and responsibility for pre- and postmarket drug safety.

Our evaluation of the Workload Adjuster methodology and results led to the following findings:

- Workload Volume: The current Workload Adjuster reasonably represents workload associated with the human drug review process, using the four submission types as input.
- Work Complexity: The amount of work per New Drug Application and Biological License Application (NDA/BLA) has increased substantially as a result of FDAAA related activities. The adjustments for the change in review activities (referred throughout the report as the "Complexity Factor") have produced negative adjustments to the Workload Adjuster calculations since its introduction to the model, which indicates that the work per submission

has been getting less complex and conflicts with our findings on NDA/BLA work complexity.

- There are additional weaknesses in the Complexity Factor. The five review activities used in the Complexity Factor calculation represent a small fraction of time spent by the FDA on the human drug review process. The Complexity Factor is calculated as a ratio, which is sensitive to change in the relative rates of growth between numerator and denominator. This calculation may lead to a counterintuitive overall negative adjustment where activities increase at a slower pace than the rate at which submissions are received.
- The weighting factors used within in the Workload Adjuster to proportionally distribute workload changes for different submission types remain relatively constant over time. Evaluation of the methodology used to derive these weights was not included in the scope of this evaluation.

The Workload Adjuster currently uses five-year rolling averages to measure changes in workload against the base years. We found that the introduction of three year rolling averages to the model would increase sensitivity to more recent trends, while the five year construct results in more stable and predictable model output from year-to-year.

Informed by these findings, we explored short term and long term alternatives to the current Workload Adjuster methodology. The alternatives included making no change to the Workload Adjuster, eliminating the Complexity Factor, and developing a new Complexity Factor. Our final recommendations are:

- In the short term, the FDA should consider removing the current Complexity Factor, which does not currently represent the total amount of work per submission.
- A more refined Workload Adjuster methodology would adequately capture changes in the complexity of work that the FDA performs. The revised methodology would account for the full range of activities associated with each submission type and the level of effort to complete these activities. Therefore, we recommend that the FDA further study alternative, more robust ways to quantify work per submission.

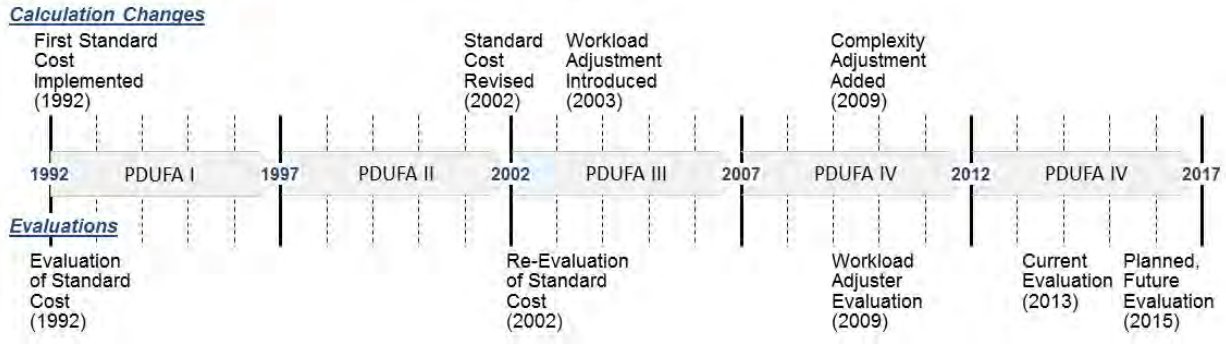
1 Background

Since its original passage in 1992, the Prescription Drug User Fee Act has authorized the FDA to collect fees from pharmaceutical and biotechnology companies to support the review of human drug applications.[1] Under PDUFA, user fees have supported increased resources in order to expedite product reviews.

The workload adjuster was introduced in 2002 as part of PDUFA III to allow the FDA to augment the total user fee revenue amount each fiscal year (after adjusting for inflation) to account for changes in workload volume in the human drug application review process. Workload volume is measured by the changes in the number of NDA/BLAs, new commercial investigational new drugs (IND), efficacy supplements and manufacturing supplements submitted to the human drug review program during the past 5 years.

Successive PDUFA reauthorizations (PDUFA II in 1997; PDUFA III in 2002, PDUFA IV in 2007, and PDUFA V in 2012) have mandated additional FDA statutory responsibilities and performance timelines. In response, the FDA worked with the Industry to redefine the measure of workload based on these legislative changes and the corresponding changes to the human drug review process. Figure 1, below, displays the historical timeline of PDUFA I through PDUFA V, key changes in the methodology for calculating the change in workload, and the independent evaluations related to the Workload Adjuster.

Figure 1: History of the Workload Adjuster



During PDUFA IV, the IND input changed from New IND submissions to All Active Commercial INDs[2]. This change was to account for activities that occur after the initial year following the IND submission, as products may spend many years in the IND phase.

[1] More information on the Prescription Drug User Fee Act can be found at the following website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

[2] Active Commercial INDs are defined as an IND that has received any Amendment/Correspondence from Industry within the specified PDUFA year.

PDUFA IV also introduced an additional adjustment for changes in review activity. Referred to throughout this report as the Complexity Factor, this additional adjustment was designed to represent changes in the complexity of submission reviews (as measured by the quantity of work per submission for both IND and NDA/BLA submission types). This added dimension employs a ratio of specific, designated activities relative to their submission type that are weighted based on the percentage of FDA hours assigned to those activities. For NDAs/BLAs, the Complexity Factor is based on the number of labeling supplements, annual reports, and scheduled NDA/BLA Industry Meetings, relative to the number of NDA/BLA submissions. The INDs Complexity Factor is based on the number of Special Protocol Assessments (SPAs) and IND Industry Meetings scheduled, relative to the number of active Commercial INDs. A 2009 independent evaluation concluded that the PDUFA IV Workload Adjuster reasonably captured changes in workload for reviewing human drug applications under PDUFA IV.[3]

Most recently, FDASIA[4] reauthorized PDUFA through FY 2017 (PDUFA V). As directed by Congress in FDAAA, the FDA developed recommendations for PDUFA V through collaboration with Industry representatives, patient and consumer advocates, health care professionals, and other public stakeholders from July 2010 through May 2011. These recommendations included an FDA commitment to contract for two independent evaluations to review the adequacy of the Workload Adjuster. This report summarizes the findings from the evaluation of the Workload Adjuster for FY 2009 – FY 2013. A second report will be produced following the second evaluation in 2015.

[3] Deloitte & Touche, LLP, (2009, March 31). Evaluation of the adjustment for changes in review activities applied to the prescription drug user fee act (PDUFA) IV Workload Adjuster for FY 2009 -- final report. Retrieved from http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm164339.htm.

[4] The Federal Food, Drug, and Cosmetic Act, as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), Sec. 103., Authority to Assess and Use Drug Fees, Adjustments (C) The Secretary shall contract with an independent accounting or consulting firm to periodically review the adequacy of the adjustment and publish the results of those reviews. The first review shall be conducted and published by the end of fiscal year 2013 (to examine the performance of the adjustment since FY 2009).

2 Key Objectives and Scope of this Evaluation

The FDA engaged IBM to conduct the first evaluation of the Workload Adjuster, as required in PDUFA V. The first evaluation focuses on the performance of the Workload Adjuster version that set user fees from FY 2009 through FY 2013. After review of this report and receipt of public comments, the FDA may implement changes to the Workload Adjuster methodology. If the FDA adopts changes to the Workload Adjuster, the changes will become effective the first fiscal year after the year of adoption and remain effective through FY 2017. The objectives of this first PDUFA V Workload Adjuster evaluation are to:

- Evaluate the workload adjustment methodology to determine if it reasonably represents actual changes in workload volume and complexity in the human drug review process
- Make recommendations, if warranted, to discontinue, retain, or modify any elements of the Workload Adjuster based on the evaluation results

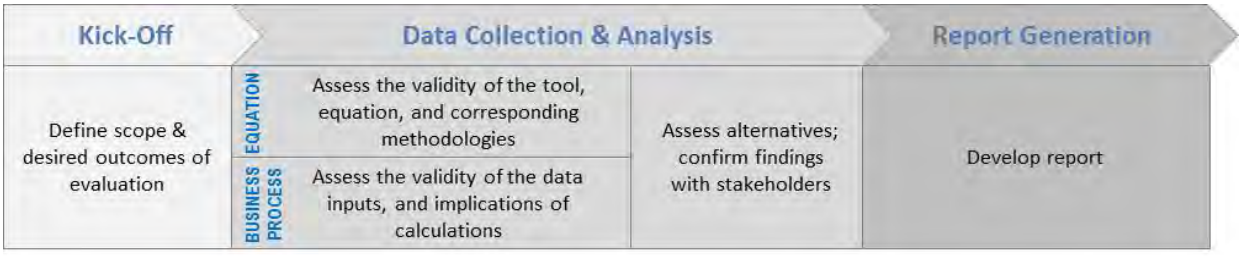
The short duration of this study limited the analysis to readily available information. There was insufficient time to assist the FDA in comprehensively quantifying changes in workload between FY 2009 and FY 2013 and for assessing whether additional measures could potentially be used as reliable components of the Workload Adjuster. The scope of the evaluation was bounded as follows:

- Examination of the FDA's methodology for measuring standard costs and the FDA's system for time reporting were not included in the scope of this evaluation, except as outputs from the time reporting systems were used as inputs to the Workload Adjuster.
- Recommendations to modify elements of the Workload Adjuster were reflective of sources of information at the FDA that were available to the evaluation team. Therefore, for instance, this evaluation does not make recommendations regarding measuring elements of time that are not currently tracked by the FDA.

3 Project Approach

To meet the objectives for this evaluation, the IBM team used a three step approach, as illustrated in Figure 2. The team compared data on FDA workload during FY 2009 – FY 2013 against the output of the Workload Adjuster and evaluated the Workload Adjuster methodology on its technical merits.

Figure 2: Evaluation Approach



We looked at workload as defined in two dimensions, volume and complexity:

- Volume is defined as the **number of work** units received by the FDA in the form of human drug review submissions;
- Complexity is the **amount of work, or level of effort**, required *per submission*. Complexity reflects the underlying characteristics of the incoming submissions as well as the nature of the current business environment and processes.

For this evaluation, we define total workload as the product of volume and complexity, or the **count** of work multiplied by the **amount** of work for each unit.

As noted in the previous evaluation[5], the Workload Adjuster and the Complexity Factor approach to workload measurement are unique to the FDA, and there is no precise metric or measurement to use as a basis for validating the accuracy of the methodology. Therefore, to assess the actual changes in total workload, we identified qualitative and quantitative data sources. CDER and CBER provided quantitative data sources for the period of this evaluation and two years preceding (i.e., 2007-2012, measured by fiscal or PDUFA[6] year, depending on the data). We used interviews with FDA executives, managers, review team staff, and others knowledgeable about PDUFA-related activities to collect qualitative data that provides insight into the primary factors that impact workload. We utilized these interactions, as well as FDA review process documentation, to identify examples of workload activities that represent important drivers of review workload over the full program of the human drug review process. We evaluated four aspects of the Workload Adjuster:

[5] Deloitte & Touche, LLP, (2009, March 31). Evaluation of the adjustment for changes in review activities applied to the prescription drug user fee act (PDUFA) IV Workload Adjuster for FY 2009 -- final report. Retrieved from http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm164339.htm.

[6] A PDUFA year was constructed by the FDA to measure submissions for the most recent time period. Since this calculation is done in July, the PDUFA year allows measurement through the preceding month: July 1 to June 30.

(1) the adequacy of the base inputs that are used to measure workload volume, (2) the adequacy of the review activities that are subsets of submission reviews and are used to measure work complexity, (3) the use of weighting factors, and (4) the application of five-year rolling averages in workload calculations.

We developed and analyzed potential alternatives or enhancements to the current Workload Adjuster. The alternatives were classified into two categories:

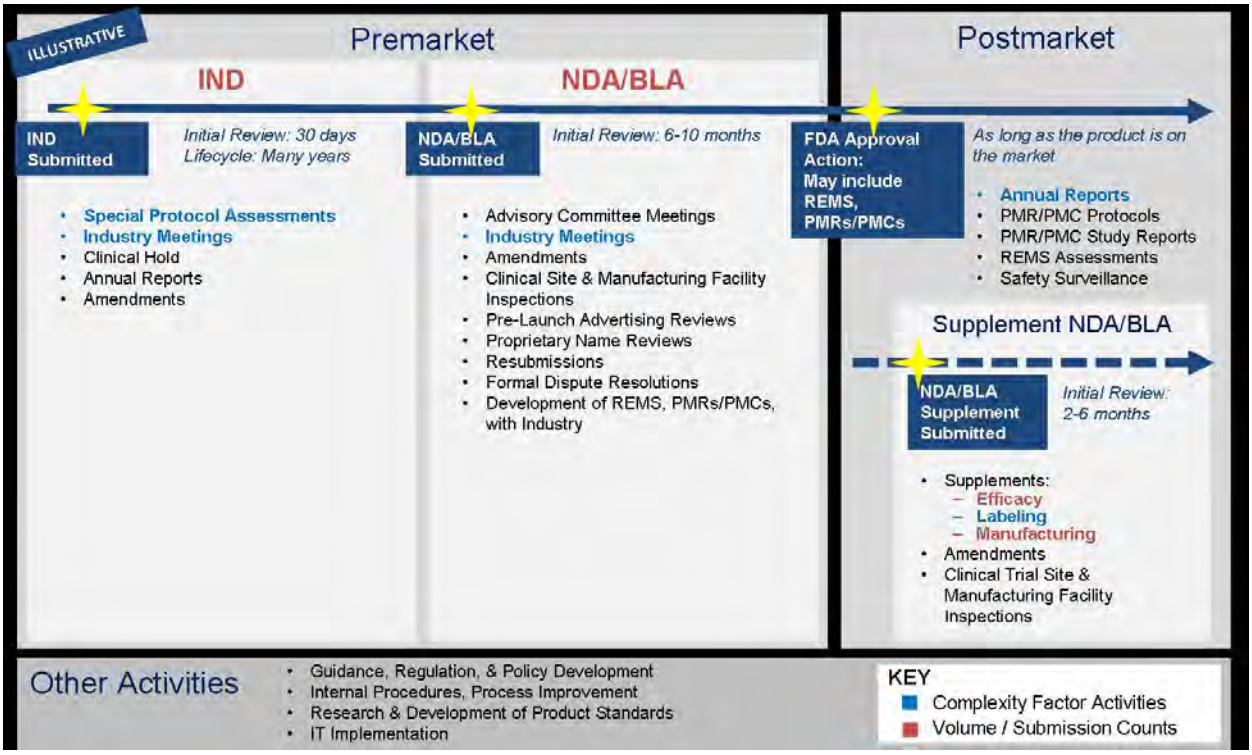
- Short-term options that may be implemented as part of the FY 2014 Workload Adjuster; and
- Longer term considerations that require additional evaluation.

This report presents the findings, conclusions, and recommendations of our analysis. In Section 4 we describe the workload within the human drug review program. Section 5 provides an evaluation of the Workload Adjuster by component. These sections are followed by recommendations in Section 6. Appendices provide background information.

4 Understanding Activities Associated with the Review of Human Drugs

The current and evolving human drug review workload in CDER and CBER must be understood in order to effectively evaluate the Workload Adjuster. To understand the activities involved in the review of human drugs, the team conducted interviews with FDA subject matter experts and identified quantitative information to support feedback, when available. The evaluation team used a product review program perspective as the context for understanding the activities associated with the review of human drugs. The Human Drug Review Program has two phases: premarket and postmarket, as illustrated in Figure 3, below.[7]

Figure 3: Human Drug Review Program – Sample Activities



The **premarket phase** consists of the Investigational New Drug phase, and the New Drug Application/Biologics License Application review phase.

During the IND-phase, the sponsor submits an IND application to the FDA prior to initiation of a clinical development program. CDER and/or CBER review staff assess the application to determine whether the IND should be placed on a clinical hold or whether it is safe to proceed with the planned clinical trials. If the FDA does not place the IND on clinical hold within 30 days of original submission, the sponsor may proceed with clinical trials. During this time, the IND is open and active, and the sponsor may submit amendments (e.g., protocol changes, new protocols) that require the FDA review and meeting requests that require FDA response.

[7] Figure 3 is an illustrative example of the Human Drug Life Cycle and does not include all human drug review activity.

The Workload Adjuster captures the number of active, commercial INDs, Industry Meetings, and SPAs. The number, frequency, and complexity of these submissions vary by IND, depending on factors such as therapeutic area, and sponsor resources. Some amendment submissions, such as complex protocols, require a significant amount of time to review, while others, such as sponsor change of address, may not require significant time. This variability within the submissions makes it difficult to determine the workload based solely on the number of applications submitted to the FDA. The current Workload Adjuster includes All Active Commercial INDs.

The NDA/BLA review phase begins after the sponsor completes the clinical development program and submits an NDA or BLA. Based on the data submitted with the application, the FDA review team evaluates the safety and efficacy of the human drug, following specific policies and procedures in order to perform high quality and consistent scientific reviews in accordance to Good Review Management Principles and Practices (GRMPs).[8] The review follows these Industry best practices in meeting the PDUFA performance goals agreed to by the FDA and Industry. Activities performed during this phase enable reviewers to determine whether or not to approve the human drug. As in the IND phase, during the NDA/BLA review phase, the applicant submits amendments and meeting requests. If the data submitted with the application provide enough evidence to support approval, the review division must determine if postmarket requirements (PMRs), postmarket commitments (PMCs), and/or risk evaluation mitigation strategies (REMS) are necessary as a condition of market approval. The Workload Adjuster includes new NDAs and BLAs as well as associated Industry Meetings.

The **postmarket phase** begins after the human drug receives marketing approval. During this phase, the applicant and the FDA continue to interact through the following: supplements (i.e., efficacy, manufacturing, labeling), postmarket activities associated with PMRs/PMCs and REMS, and annual status reports. When a sponsor submits a supplement, the FDA review team assesses the information provided to determine if the original application should be amended (e.g., change in indication, change in formulation, labeling change). Efficacy and manufacturing supplements have specific PDUFA goals, whereas labeling supplements have internal goals, established by the Centers. The FDA review teams strive to meet all goals, as resources allow. PMRs/PMCs and REMS have milestone associations, such as protocol submissions, study start and end dates, and final report submission dates. The FDA tracks the milestones and status of each PMR/PMC and REMS and reviews final reports to determine if they meet the agreed upon or required conditions. Annual reports contain valuable product information, including PMR/PMC status updates, and are reviewed as resources permit. The input for the Workload Adjuster includes the efficacy, manufacturing, and labeling supplements, as well as NDA/BLA annual reports.

FDA reviewers also contribute to **other activities**, such as the development of policies and procedures to support the regulatory review process. While the activities associated with policy

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[8] CDER Review Process – http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf

CBER Review Process - http://www.diahome.org/Tools/Content.aspx?type=eopdf&file=%2fproductfiles%2f8357%2fdiaj_12631.pdf

and procedure development may not directly apply to the review activities associated with a specific application, they do support the overall operating model by establishing standards and providing guidance to both Industry and FDA staff. These activities are not included in the current Workload Adjuster.

This summary of the human drug review program provides the foundation for understanding whether the current Workload Adjuster reasonably represents the review workload.

To provide further context for evaluating the effectiveness of measures of changes in workload, the evaluation team also gathered information regarding causes of workload change. Interviews with experts responsible for human drug reviews as well as those who are responsible for review performance management consistently revealed the following examples of drivers of workload that are not accounted for in the current Workload Adjuster:

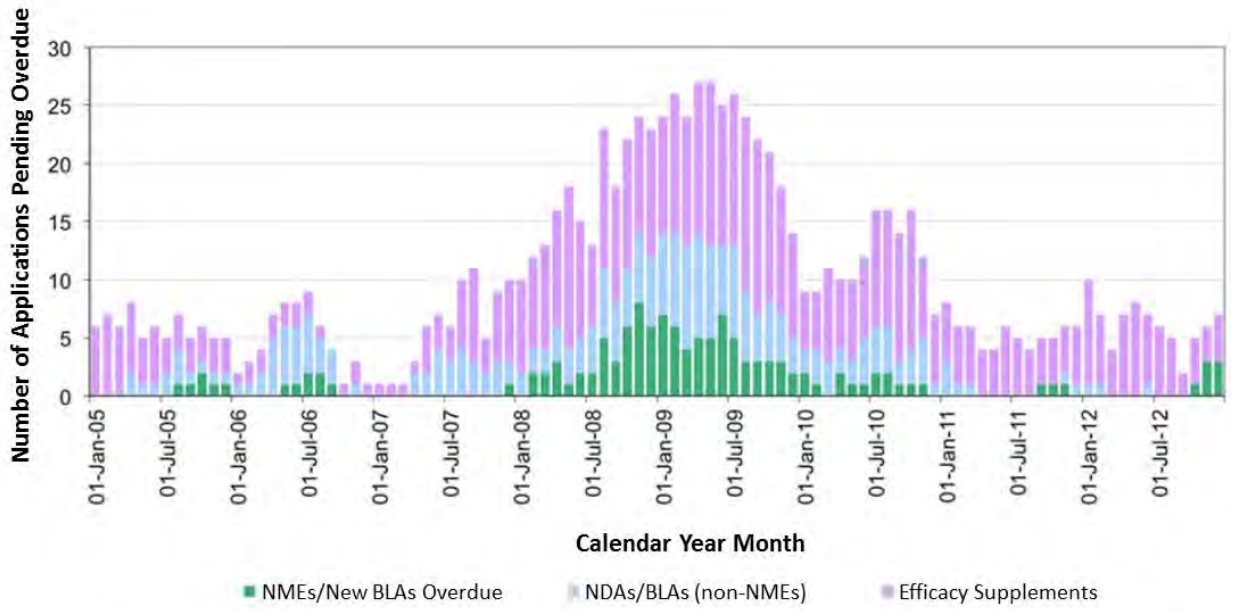
- The increasing scientific complexity of applications results in the requirement for additional reviews and thus a greater number of reviewers (e.g., multiple clinical reviewers are needed to support both pharmacogenomics and pharmacometrics analyses)
- An increasing number of companion diagnostic applications have been submitted
- New and increasing premarket and postmarket safety activities (e.g., PMRs/PMCs, REMS, FDAAA Safety Labeling Changes) result in additional submissions
- Formal dispute resolutions
- Increasing number of tracked safety issues that trigger the creation of an FDA-generated application to track and archive regulatory activities associated with a significant safety issue related to a marketed prescription or over-the-counter drug[9]

Signs of the changing (and increasing) workload are supported by evidence of overdue PDUFA Goals, annual report backlogs, labeling supplement backlogs, and higher rates of denied Industry Meetings. Each is further detailed below.

Following the passage of FDAAA, the number of missed CDER PDUFA submission review goals increased significantly for NDAs, BLAs and Efficacy Supplements (Figure 4, below). PDUFA goals have higher priority than any of the aforementioned activities, and the FDA review staff does everything possible to achieve these goals. Yet, even after reprioritization of activities, FDA experts indicated they were unable to meet these priority deadlines. As Figure 4 shows, the surge of overdue goals has decreased over time but has not disappeared.

[9] See further CDER Manual of Policies and Procedures. MAPP 4121.2 Tracking of Significant Safety issues in Marketed Drugs – Use of the DARRTS Tracked Safety Issues.

Figure 4: CDER Pending Applications with Overdue PDUFA Goals



Notes: CDER data as of 11/30/2012. Figures reflect the number of NDAs, BLAs, and efficacy supplements that are pending and overdue on their PDUFA goal date, evaluated on the first day of each month.
Source: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM331454.pdf

When workload increases and resources do not, management must prioritize activities according to the impact on the public safety and PDUFA performance goals. Activities that may be re-prioritized, as specified through interviews, FDA report reviews, and quantitative data, include:

- **Policy and Guidance Development, Process Improvement Activities –** When PDUFA reauthorization result in the need for establishment of new operating models, guidance, policy and process improvement, these activities compete with reviewing submissions. The impact may be significant, since FDA staff are directed away from activities (e.g., guidance development) that are necessary to support Industry and the submission of high-quality applications.
- **Meeting Requests** - Review divisions may deny Industry Meeting requests and provide written responses to questions, when appropriate, when prioritizing activities is required. Additional quantitative findings, which illustrate the increase in denied meeting requests, are presented in Appendix C, Figure 15.
- **Annual Report Reviews** - The review of NDA/BLA annual reports becomes a lower priority than activities directly associated with PDUFA performance goals.
- **Labeling Supplement Reviews** - Labeling supplement reviews are prioritized below activities that are associated with PDUFA goals. During interviews, the FDA experts indicated that labeling supplement backlogs indicate a stressed workforce and that this backlog has grown significantly over the years. Figure 16 in Appendix C shows this trend, a near tripling in the number of CDER NDA labeling supplements overdue between July 2006 and January 2013.

Additional indications that workload exceeds capacity are reinforced by an August 2010 report, in support of an independent resource estimation effort that identified discrepancies between CDER workload drivers (demands) and outputs (results), for FY 2009. Performance gaps were identified in biomarker qualification process completed (66.7%), IND annual reports reviewed (58.3%), sponsor formal meeting convened (38.9%), IND documents submitted by sponsors reviewed (34.1%), Class 2 resubmissions reviewed (efficacy supplements) (32%), safety/efficacy problems closed (29.1%), NDA/BLA label supplements reviewed (24.5%), and advertising complaints addressed (24.5%).[10]

[10]"FDA Medical Product Oversight: Baseline Assessment and Gap Analysis Report" (August 6, 2010).

5 Evaluation of the Workload Adjuster

The Workload Adjuster is designed to measure change in PDUFA-related workload as represented by the Human Drug Review Program. This evaluation of the Workload Adjuster assesses whether it reasonably represents changes in workload through the following approach for analyzing workload models:

- Break down the Workload Adjuster model into its components and describe the mechanics of how the model works
- Assess the Workload Adjuster as a reasonable representation of workload volume
- Assess the current use of the 5 year average against a 3 year average alternative
- Consider the method for weighting the volume and complexity factors of the model
- Assess the Workload Adjuster as a reasonable representation of workload complexity

5.1 The Structure of the Workload Adjuster

The Workload Adjuster is designed to measure change in PDUFA-related workload. It reports an overall factor, a point estimate representing the percent change in total workload from the current, rolling 5-year period of observation to an overall base 5-year period.

The two major components of the Workload Adjuster are 'workload volume, ' which refers to the **number of work** units received by the FDA in the form of human drug review submissions and 'work complexity,' which refers to the changes in the **amount of work**, or level of effort, per submission. The count of work is measured through changes in submissions for the four main inputs (by submission / application types), represented as a five-year average, compared to the base of the prior PDUFA period, or as otherwise specified in the legislation. The Complexity Factor, which measures *change in the review activities*, accounts for the work activities associated with a submission. The percentage change in both work counts and work amount are weighted by a measure of overall effort expended on each type of submission, derived from the Standard Cost model, which is defined in Section 5.4.

The FY 2013 Workload Adjuster calculations are shown in Table 2 below. A description of each of the columns follows the table.

Table 1: FY 2013 Workload Adjuster Calculations

Application type	Column 1	Column 2a	Column 2b	Column 2c	Column 3	Column 4	Column 5
	5-Year Average base years 2003–2007	5-Year Average 2008–2012	Adjustment for changes in review activity	Column 2a increased by column 2b	Percent change (column 1 to column 2c)	Weighting factor	Weighted percent change
NDAs/BLAs	123.8	134.4	0.08%	134.5	8.6%	39.6%	3.42%
Active commercial INDs	5,528.2	6724.2	−3.13%	6513.7	17.8%	40.3%	7.18%
Efficacy supplements	163.4	153.8	NA	153.8	−5.9%	9.5%	−0.56%
Manufacturing Supplements	2589.2	2575.4	NA	2575.4	−0.5%	10.6%	−0.06%
FY 2013 Workload Adjuster							9.99%

Column 1 shows the five-year rolling averages for base years 2003-2007 for each application submission type.

Column 2a shows the five-year rolling averages for FY 2008-2012 for each submission type.

Column 2b shows the percent change in the Complexity Factor for NDAs/BLAs and Active Commercial INDs submission types. The Complexity Factor is generated for each of the review activities (Labeling Supplements, Industry Meetings, and Annual Reports for NDAs/BLAs and SPAs and Industry Meetings for Active Commercial INDs). This factor is a product of percent change in level of effort and average time weighting. The Complexity Factor is calculated as follows:

- **Level of Effort** – A ratio is calculated as the current five-year average counts for each activity, over its corresponding submission type (ex. the five year average of labeling supplements / the five year average of NDA/BLAs). The same ratio is calculated for the base five-year period. The percentage change between these two indicates the current year relative to the base year for each activity.
- **Average Time Weighting Factor** – Multiply the percent of time spent on each review activity by the percent of total time spent on the corresponding submission type for each year. The average time weighting factor for the current year is calculated by computing the average for each activity for the most recent five-year period.
- **Final Activity Factor** – Multiply the level of effort percentage derived in step 1 by the average time weighting factor percentage from step 2 to arrive at the final activity factor for each review activity.
- **Complexity Factor** – Add the activity factors for each review activity to calculate the Complexity Factor for both NDAs/BLAs and Active Commercial INDs submission types.

Column 2c shows the adjusted five year rolling averages after Column 2a is adjusted for the Complexity Factor shown in Column 2b. The adjusted five-year rolling averages apply to NDA/BLA and Active Commercial IND submission types. The Complexity Factor is not associated with Efficacy and Manufacturing Supplements.

Column 3 shows the percent change in workload from Column 1 to Column 2c.

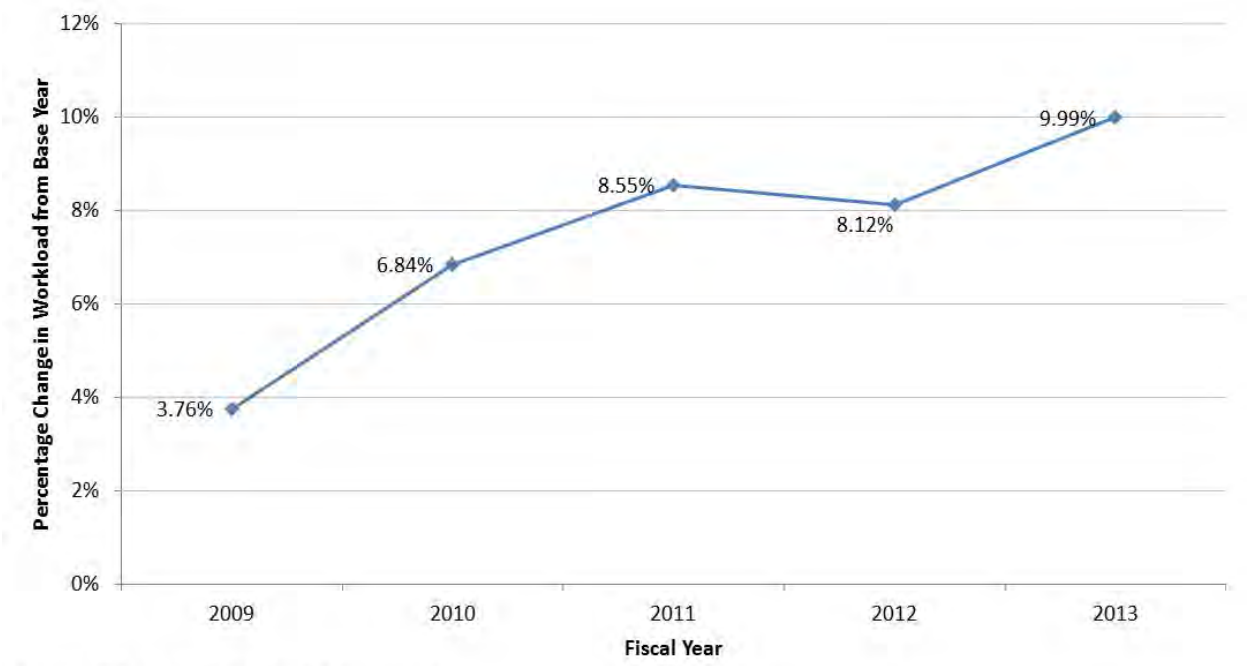
Column 4 shows the weighting factors that are applied to the submission types. Weighting factors in Column 4 are generated from the standard cost model and are the average weights over the most recent five-year period.

Column 5 shows the workload adjustment for each submission type. The weighted percentages are calculated by multiplying Column 3 by Column 4. The sum of these weighted percentages represents the total adjustment in workload for FY 2013 (9.99%).

5.1.1 The Results and Sensitivity of the Workload Adjuster

The result of the Workload Adjuster calculations is a single point estimate that represents the percentage change in total workload since the base period. Figure 5 displays the outputs of the Workload Adjuster since FY 2009.

Figure 5: Workload Adjustment Since FY 2009



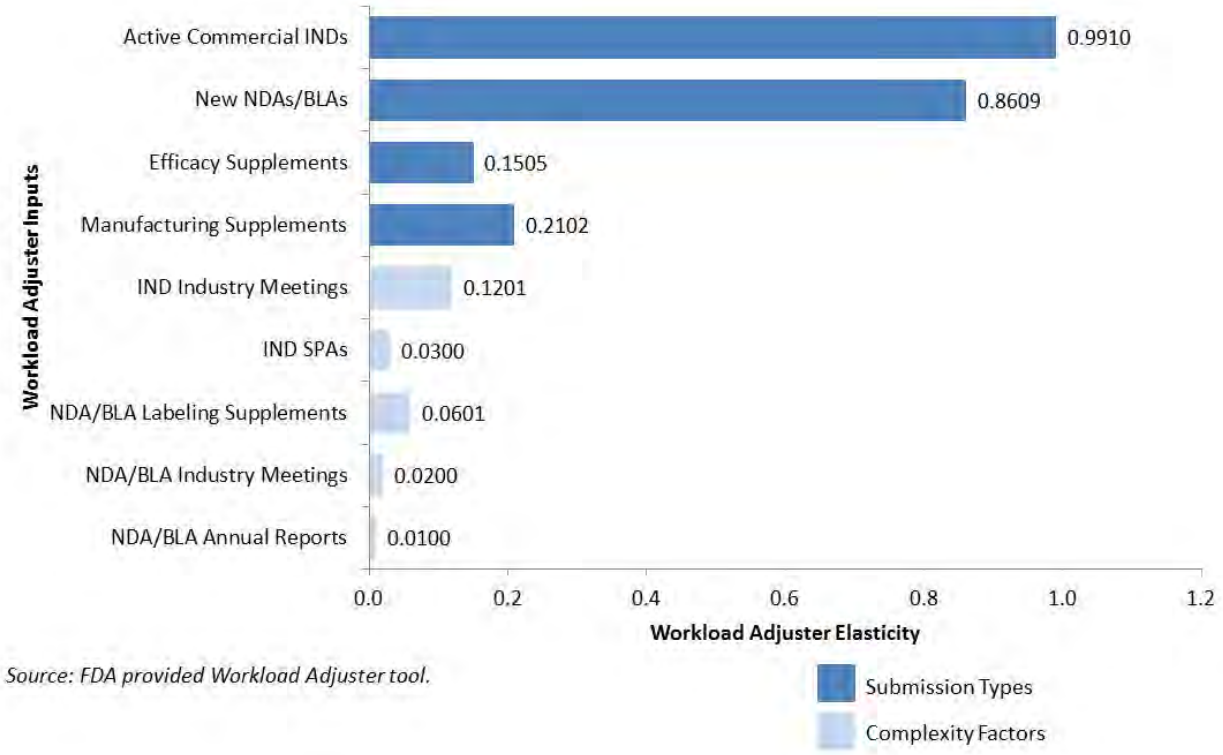
Source: FDA provided Workload Adjuster tool.

In order to precisely validate the overall workload adjustment, a comparison of a 9.99% workload adjustment for FY 2013 would have been assessed against an alternative estimate (i.e., another model or total hours) that used a different method to arrive at the same result. While the evaluation team does validate the method and results of the components in our study, such precision could not be evaluated for the overall result (9.99% in FY 2013) during this study, through available data.

Sensitivity analysis was conducted on the Workload Adjuster to determine which features had the most impact. In order to compare the relative leverage of each feature, we used an elasticity approach, altering each input 1 percent and recording the change in the resulting output of the workload adjustment factor.[11] Results of the sensitivity analysis performed for the four main inputs and the five complexity factor inputs in the Workload Adjuster are provided in Figure 6, below. These estimates represent the percentage change in the Workload Adjustment factor due to a 1% change in submission volume. As an example, the elasticity in 2013 for NDA/BLA submissions is 0.8609. A 1% increase in the NDA/BLA submission count equates to a 0.8609% increase in the Workload Adjustment. Therefore, if the 2013 Workload Adjuster is 9.99%, an additional 1% increase in NDA/BLA submission counts (holding all other variables constant) would produce a Workload Adjuster of 10.08% (9.99% * (1+0.008609)).

[11] This did not represent a full scenario since we were unable to change all interrelated features, notably Standard Cost, which would be affected by submission variation.

Figure 6: Sensitivity of Inputs and Complexity Factors on Workload Adjustment Factor



Source: FDA provided Workload Adjuster tool.

- The Workload Adjuster is most responsive to changes in the number of INDs and NDAs/BLAs due to their heavy weighting in calculating the factor (approximately 40% each), followed by Manufacturing Supplements and Efficacy Supplements. The analysis of the impact of submission types on the Workload Adjuster allows us to assess their relative contribution to the overall Workload Adjuster calculation and confirms that the Workload Adjuster responds to changes in each submission type as expected.
- Relative to submission changes, the complexity factors pose a relatively modest adjustment to the overall workload adjustment. As an example, the elasticity in 2013 for the IND Meetings complexity factor input is 0.1201. A 1% increase in the IND Meetings complexity factor input equates to a 0.1201% increase in the Workload Adjustment. Therefore, if the 2013 Workload Adjuster is 9.99%, the updated 2013 Workload Adjuster would be 10.00% (9.99% * (1+0.001201)). Among the Complexity Factors, the Workload Adjuster is most sensitive to IND Meetings and NDA/BLA Supplements, followed by IND SPA, NDA/BLA Meetings, and NDA/BLA Annual Reports.

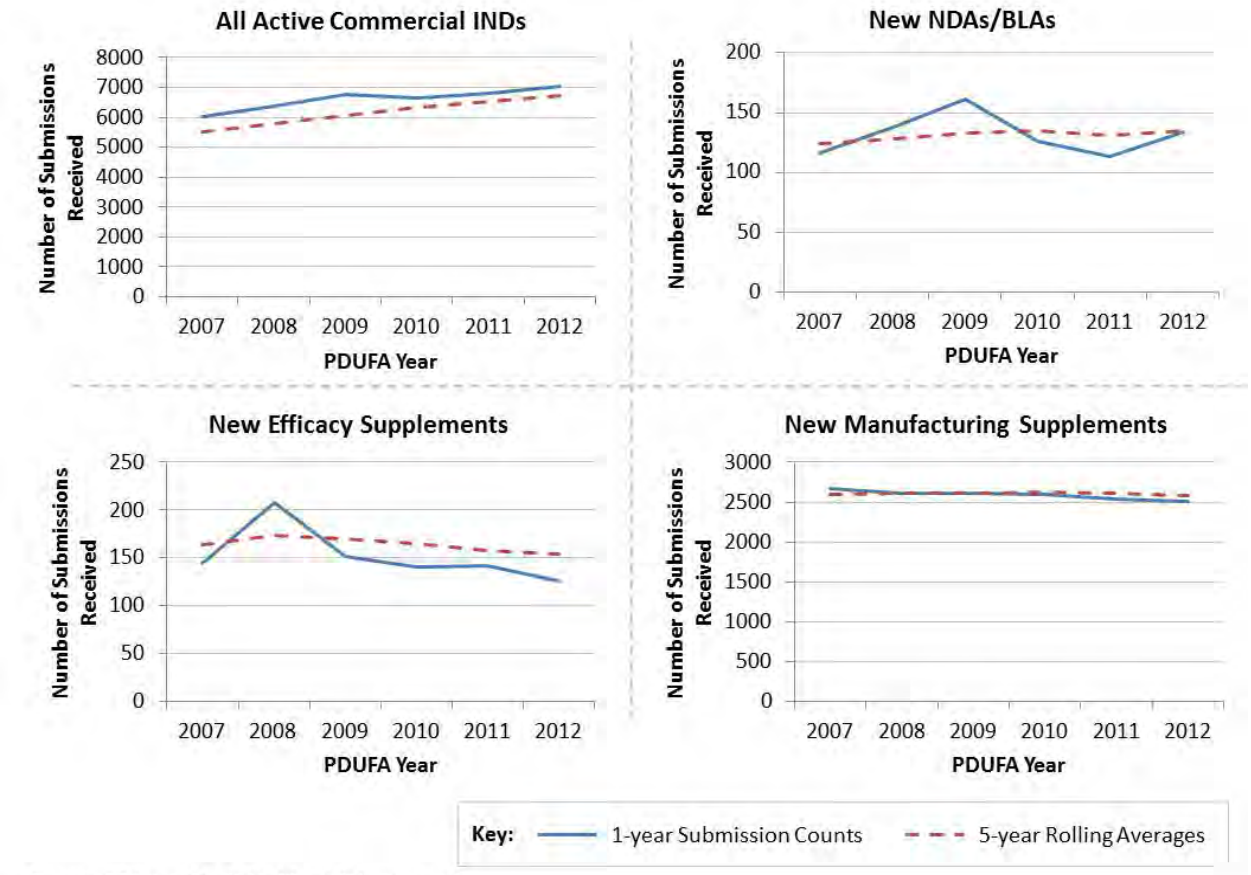
With this understanding of the mechanics of the Workload Adjuster, the evaluation team assessed the performance of each of its components.

5.2 Evaluation of Volume (Counts of Submissions)

Workload volume for this evaluation is measured by submission counts. As noted in Section 1, the current base workload is represented by Active Commercial INDs, NDAs and BLAs, Efficacy Supplements, and Manufacturing Supplements.

The inputs to the workload volume component of the Workload Adjuster were examined to understand how each of the submission types changed over the period of this evaluation. Recent submission trends for each of the four main inputs are shown below in Figure 7. Efficacy and manufacturing supplements appear to have a small downward trend. Active Commercial INDs have an average percent change between -1.4% and 5.7% year to year between PDUFA years 2009 and 2012. In contrast, NDA/BLA volume is highly variable ranging, with a percentage change between -21.7% and 18.6%, in part because the base is new applications (rather than including all active applications like IND). This analysis provides insight into how the trends and variability of the individual components of volume should influence the overall trend and variability of the Workload Adjuster.

Figure 7: Submission Counts for Main Workload Adjuster Inputs by PDUFA Year



Source: FDA provided Workload Adjuster tool.

The evaluation team explored the technical representation of workload volume and determined that these calculations adequately measure change in the four submission types specified under the statutorily defined activities that constitute the human drug review program.. Section 5.5.2

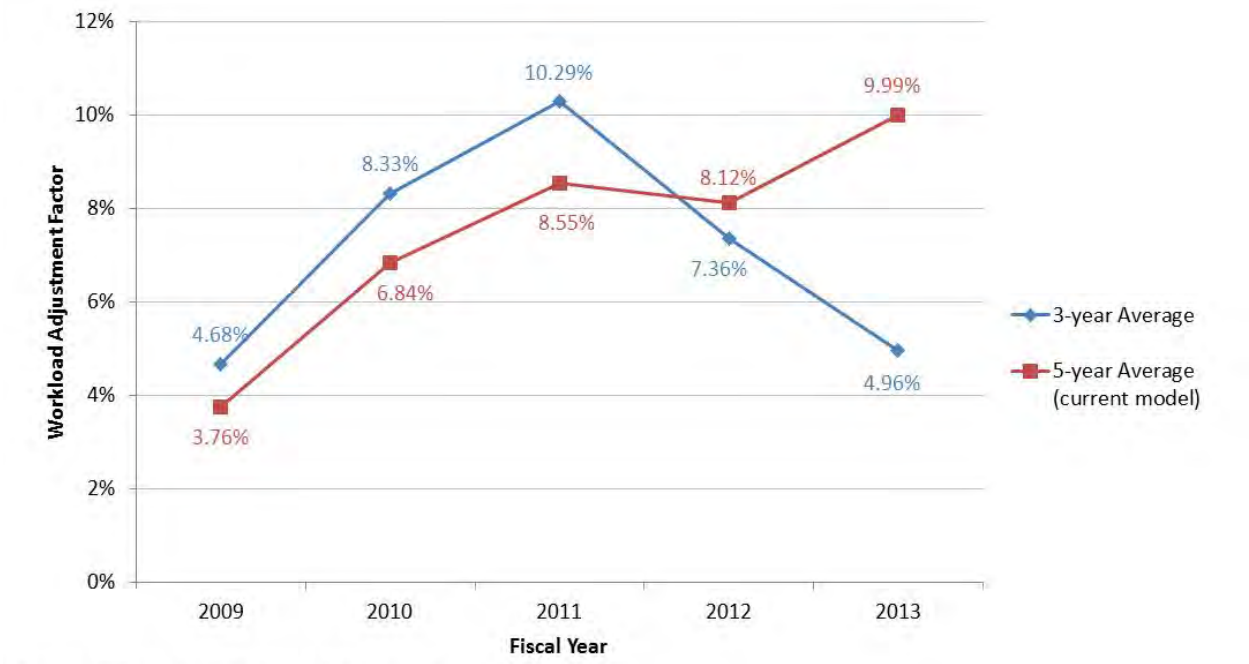
addresses how review activities have changed since the Complexity Factor was created. Many of the new activities occur during the postmarket phase. The current measure of volume captures New NDAs/BLAs, not those that are ongoing. We were not able to quantify the impact of using all Active NDAs/BLAs versus only the New NDAs/BLAs. We also recognize that not all Active NDAs/BLAs require constant action in the same way that Active INDs and New NDAs/BLAs do. Therefore, we do not find this to be a weakness of the Workload Adjuster. We recommend that this area be studied to determine how best to incorporate activities such as REMs and PMRs.

5.3 Evaluation of Five Year Rolling Averages

The Workload Adjuster measures change in five year rolling averages from a base five year average. For the time period of this review, the base is PDUFA Year 2003-2007. The adjuster output should be interpreted as the amount workload has increased since the base period of PDUFA Year 2003-2007. This methodology typically results in an output that increases in magnitude every year away from the base. During the first year after the base period (in this case PDUFA Year 2004-2008) the base five year average and the rolling five year average overlap four years of inputs. Naturally, the difference between these periods will tend to be small due to the overlapping years. In the subsequent years, the number of shared years decreases, and the difference between the base and rolling averages increases. This generally results in a larger output. During five year negotiations, a new base dollar amount is set, and this amount is adjusted by the difference in workload from the base years to the current year.

Analysis was performed to determine whether the five year rolling average was a reasonable approach to measuring changes in work volume. Figure 8 below shows the Workload Adjustment Factor had all steps been done based on a three year rolling average compared to the five year rolling average. Since the average covers a smaller range of dates, the variability in the results is greater with a three year rolling average.

Figure 8: Workload Adjuster 3-Year vs. 5-Year Rolling Average



Source: FDA provided Workload Adjuster tool.

The decision as to which range to use for the average is a tradeoff between sensitivity and stability. The greater the date range, the less volatile the effect one year has on the Workload Adjuster output, which means that a five year rolling average (vs. three year) generates a smaller percent adjustment for an extreme year. The FDA expressed that stability is an important consideration for both the FDA and Industry to ensure that the availability of resources to conduct review is stable and predictable from year to year.

5.4 Evaluation of Weighting Factors

The weighting factor represents the relative resource investment by the FDA for each of the submissions. The weighting factor derives from the Standard Cost model, which represents the full costs of the process for the review of human drug submissions allocated among major types of submissions that require FDA review, as defined by the FD&C Act. Standard costs include all costs associated with submission review, including rent, overhead, and centrally funded costs. The evaluation team did not evaluate the methodology for Standard Costs yet noted that its impact was relatively stable throughout the period of evaluation at roughly 40% each for INDs and NDA/BLAs, and 10% each for Efficacy and Manufacturing Supplements.

5.5 Evaluation of the Representation of Amount of Work per Submission

Workload complexity is defined as the amount of work associated with each submission. PDUFA IV acknowledged that the amount of work was changing and thus added the Complexity Factor for INDs and NDA/BLAs to represent this change by measuring a subset of inputs and process activities (for example, Industry Meetings, Labeling Supplements). The current

methodology was developed in 2006, recognizing that "complexity factor components were based on observable changes in new application review and base workload inventory."[12] A previous study confirmed that the Complexity Factor was performing as expected in FY 2009, two years after its implementation.[13]

This evaluation examined the Complexity Factor's accuracy and validity within the Workload Adjuster as a measure that reflects the change in workload complexity. Our evaluation team analyzed how the Complexity Factor has performed from FY 2009-FY 2013 by comparing the Workload Adjuster with and without the Complexity Factor. We assessed whether the inputs to the current Complexity Factor still reasonably represent workload complexity, in practical terms, and whether the methodology is sound for the future.

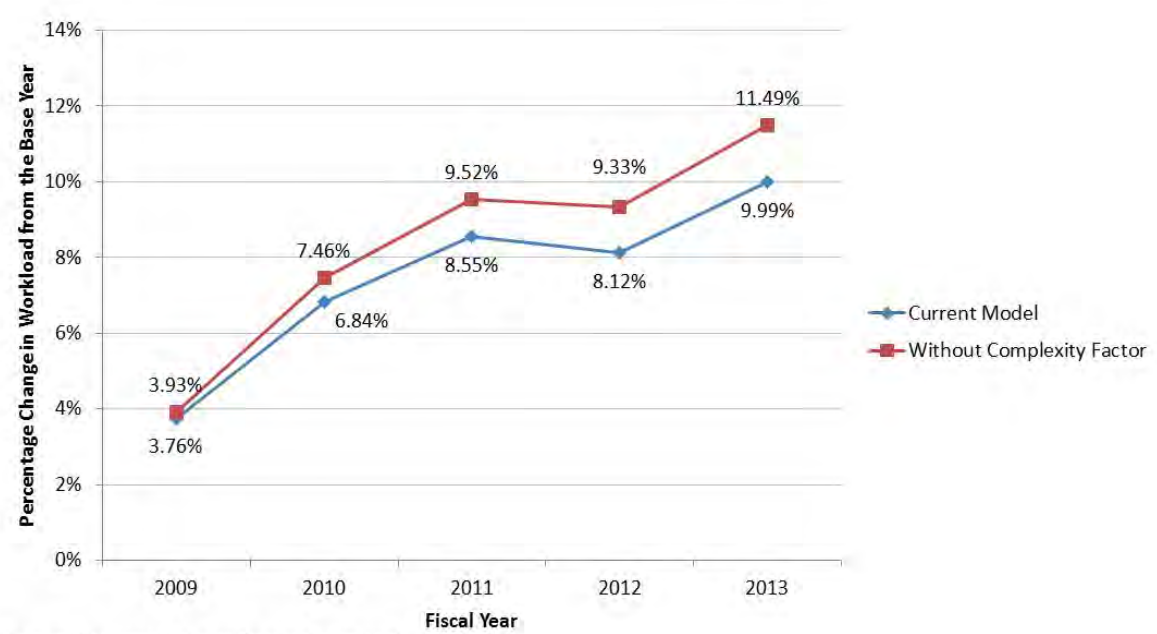
5.5.1 Description and Behavior of the Complexity Factor

The Complexity Factor for FY 2009 – FY 2013 has shown that the work per IND and NDA/BLA is decreasing. In FY 2013, this was a decrease of 1.5 percentage points, bringing down the Workload Adjuster factor from 11.49% to 9.99%. Figure 9 shows the Workload Adjuster with and without the Complexity Factor.

[12] These statements are supported by internal presentations from 2006 provided by FDA.

[13] Deloitte & Touche, LLP, (2009, March 31). Evaluation of the adjustment for changes in review activities applied to the prescription drug user fee act (PDUFA) IV Workload Adjuster for FY 2009 -- final report. Retrieved from http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm164339.htm.

Figure 9: Impact of Complexity Factor on Workload Adjustment Factor[14]



Source: FDA provided Workload Adjuster tool.

An inherent challenge in the design of the Complexity Factor is the selection of specific activities. Five inputs (or activities) are used to proxy the current change of complexity associated with all active commercial INDs and new NDAs/BLAs, as detailed in Table 2, below. In order for the methodology to be valid, the proxies must be representative and reflect overall work per submission with reasonable fidelity over time. These complexity factor activities, originally identified in 2006, seemed to strongly reflect changes in workload. For example, evidence pertaining to INDs suggested a 30% increase in IND Industry Meetings and 90% increase in SPAs, between FY 2002 and the time of the 2006 evaluation.[15]

[14] In order to interpret the years, consider that the factor of 3.93 calculated in 2008, applies to fees in FY 2009, October 1, 2008.

[15] This rationale for selection was seen in internal FDA presentations cited at the end of this report: "Proposed Workload Adjuster Methodology Revisions" dated June 16, 2006 and "Workload Adjuster Discussion" dated July 21, 2006, as well as the FDA-internal narrative describing changes proposed for the Workload Adjuster, "Proposed PDUFA IV Workload Adjuster Modification" dated November 1, 2006. The evaluation team did not evaluate these statements in actual data.

Table 2: Current Complexity Factor Results and Activities

Submission Type / Conclusion	Review Activity as Indicator	Description of Activity
IND: The amount of work associated with an IND in the FY 2013 period is approximately 3.13% less than it was during the base period.	Special Protocol Assessments	The FDA reviews SPAs submitted by sponsors to assess whether they are adequate to meet scientific and regulatory requirements identified by the sponsors. Work involves sponsor communications, both oral and written, during review process plus any in-house meetings to discuss these communications.
	Industry Meetings	Formal meetings may be held between the FDA and sponsors or applicants regarding the development and review of products in human drug applications. Work includes review of Industry submitted meeting request and corresponding questions and materials, scheduling the Industry meeting, internal meeting, and reaching to and/or assigning reviewers. In addition to the meeting, the FDA has correspondence and preparation activities.
NDA / BLAs: The amount of work associated with a NDA/BLA application in the FY 2013 period is approximately 0.08% more than it was during the base period	Industry Meetings	Same as IND meetings.
	Annual Report Reviews	A report submitted annually by the applicant within 60 days of the anniversary date of FDA approval of the application. The FDA reviews annual reports, including the ‘ Annual Status Report of Postmarket Study Commitments’ section, as well as completing an Annual Status Report Review: Postmarket Requirements and Commitments Summary form, as applicable.
	Labeling Supplements	After product approval, the sponsor may submit a labeling supplement to change the pertinent information about the appropriate use of the approved human drug. The FDA reviews product labeling information, after approval of the original NDA/BLA for market.
Efficacy Supplements There is no change in the amount of work for these submissions	N/A	
Manufacturing Supplements There is no change in the amount of work for these submissions	N/A	

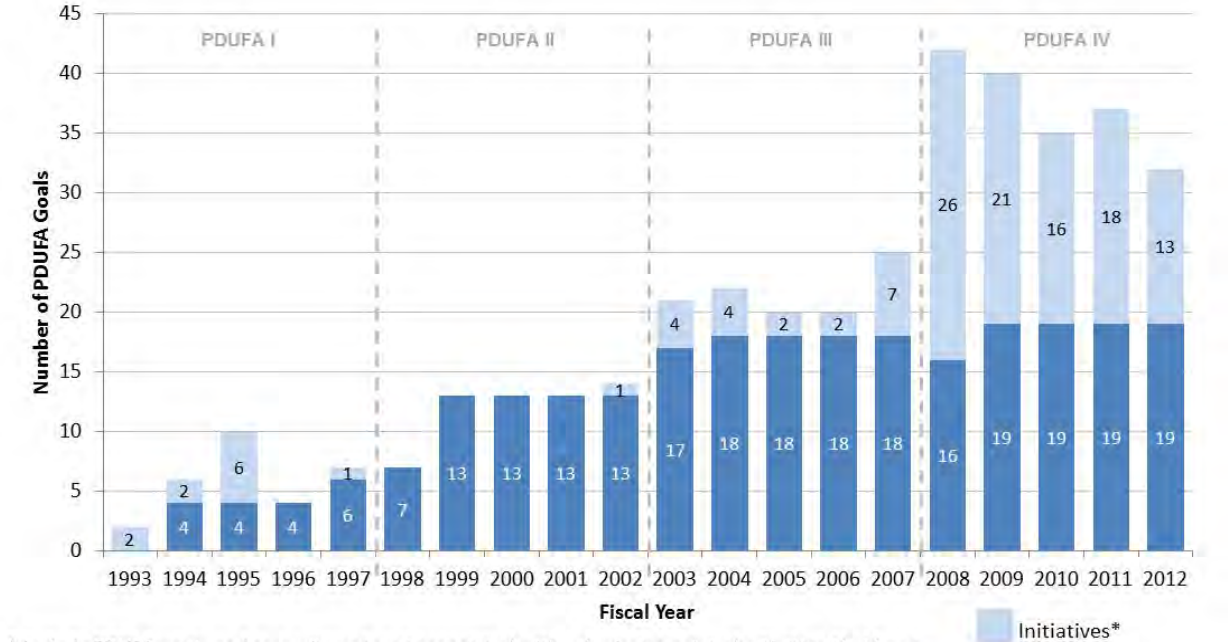
Since the selection of activities was completed in 2006, they predate the 2007 FDAAA legislation. We recognize that the significant impacts of FDAAA were not realized and therefore not incorporated into the adjustment. We discuss this in a more general sense in the next section.

5.5.2 The Complexity Factor as a Representation of Work per Submission

The methodology for calculating the Complexity Factor is not updated annually to account for newly required activities. As a model based on a fixed set of review activities, it is ill-suited to accurately capture workload in the FDA's dynamic environment. The current complexity factor suggests that the amount of work per submission is decreasing slightly. However, the quantity of mandated activities associated with the review of human drugs has increased significantly from PDUFA I to PDUFA V.

New PDUFA Performance Goals are generally associated with an increase in FDA responsibility, and thus, an increase in the amount of work per submission. So, with the goal of better understanding complexity of work from an unbiased, legislative perspective, we assessed the increase in PDUFA Performance Goals from original PDUFA passage in FY 1992 through FY 2012. In doing so, we confirmed that each PDUFA authorization has had a compounding impact on workload. Each subsequent reauthorization has amended the previous Act and added new requirements for the review of human drug submissions. Figure 10, below, quantifies these responsibilities, which include tasks such as review of original, standard and priority NDA/BLA submissions, and activities associated with meeting management, amongst many others identified through FDA's Annual PDUFA Performance Reports. A corresponding increase is seen in internal PDUFA related goals and tracked performance (Figure 11).

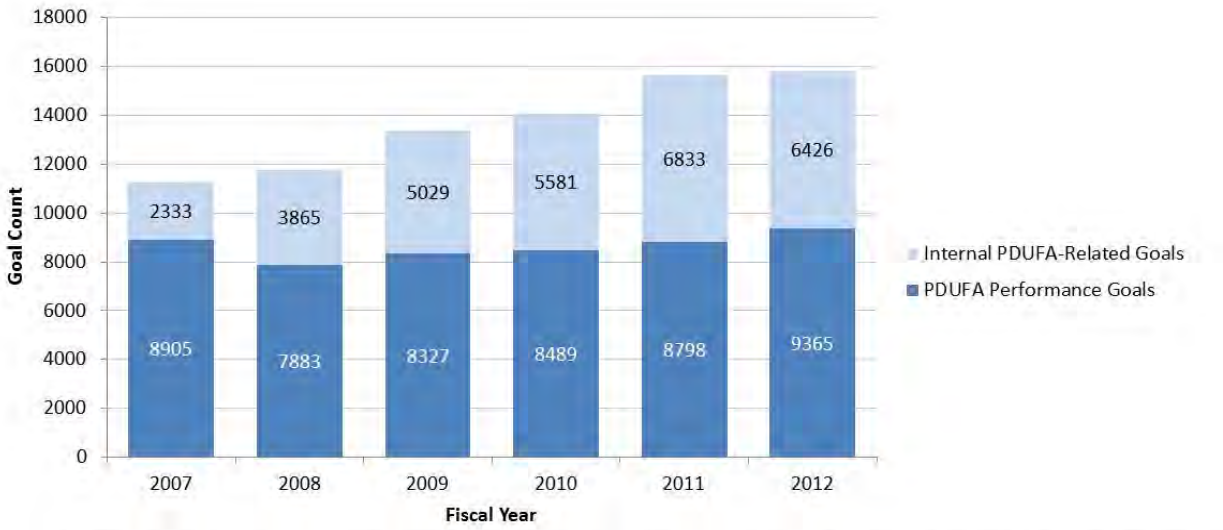
Figure 10: PDUFA Performance Goals[16]



** Include PDUFA goals and commitments not associated with submission-related activities that have corresponding timeframes. ** Represent a count of discrete FDA commitments to perform an activity, in response to a submission, within a specified timeframe.*
Notes: Goals developed for increased granularity in reporting and interim goals used during transition to new goals were not counted.
Source: Annual PDUFA Performance Reports, FY 1997 – FY 2012.

[16] Appendices A, of Annual PDUFA Performance Reports to Congress, for FY 1997 – FY 2012, were reviewed for goals corresponding to performance measures set forth in commitment letters for each PDUFA reauthorization. Source: http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/default.htm

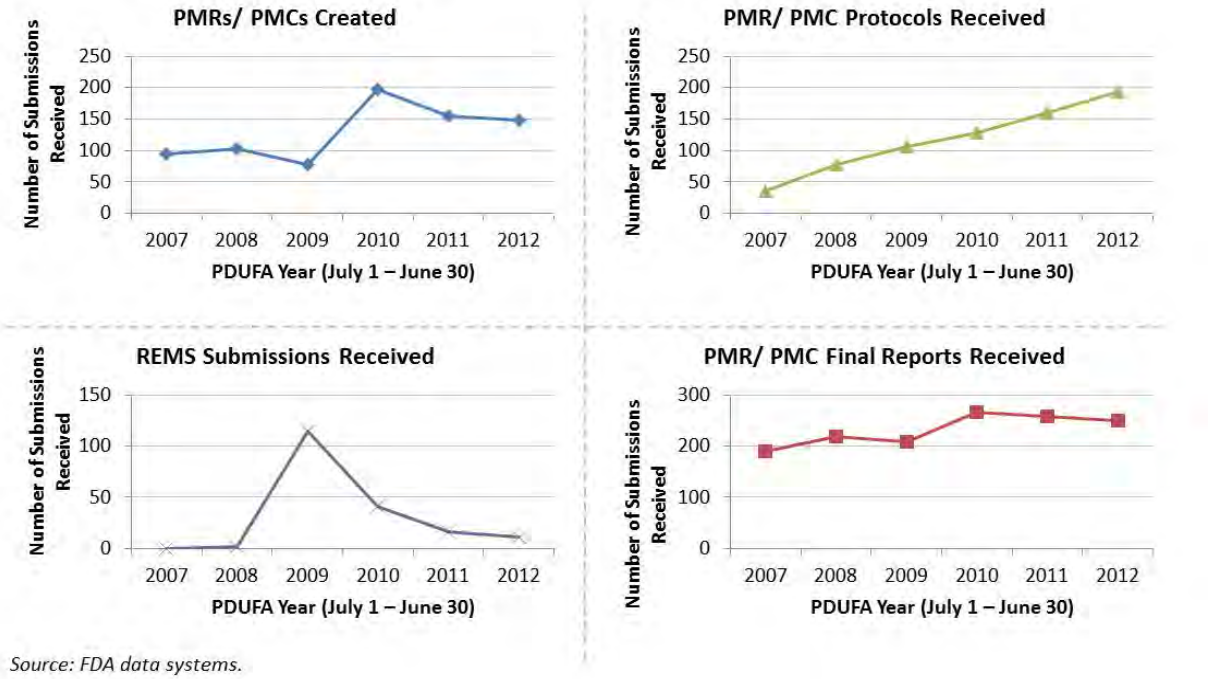
Figure 11: Tracked PDUFA Performance and Internal PDUFA-related Goals, FY 2007 – FY 2012



Notes: FY2011 and FY2012 data is captured as of September 30, 2012. Number of tracked goals will increase further under PDUFA V for NME Program, etc.
Source: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM331454.pdf

The four submission types represent most, but not all, of the volume of work in the postmarket phase of the Human Drug Review Program. Since the first PDUFA authorization, there has been a significant increase in postmarket activities, including newer activities associated with FDAAA that are not adequately captured in the current Workload Adjuster. These newer activities include REMS and PMRs and the development of a supportive operating model (e.g., regulations, policies), additional coordination and correspondence during review of NDAs/BLAs and applicable efficacy supplements, and increased postmarket tracking. For example, prior to FDAAA, the FDA utilized RiskMAPs to manage risks after approval of a drug. RiskMAPs did not require the same amount of effort as compared to REMS, which were established under FDAAA. After the passage of FDAAA, the FDA experienced both a need to establish a REMS-related supportive operating model, and also saw a surge in the number of REMS submissions, as shown in Figure 12, below.

Figure 12: Trend Analysis of Postmarket Activities



Source: FDA data systems.

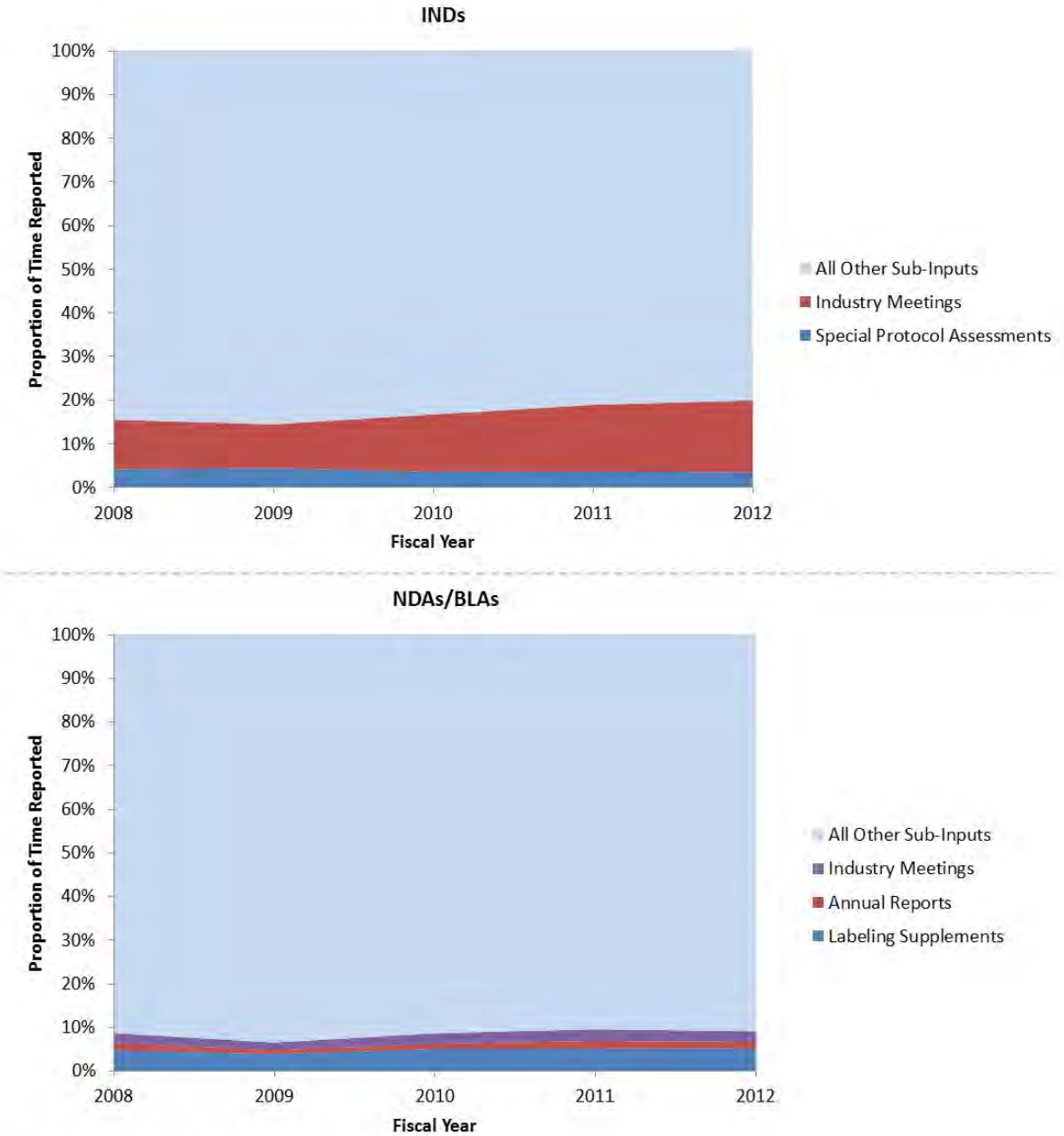
The number of PMR/PMC submissions increased after 2007. Although the increase in submissions may not serve as a suitable proxy for workload, the work associated with these submissions increased because of the new requirements associated with the enforcement of PMR timelines. The new requirements necessitated the coordination of multiple offices outside of CDER's Office of New Drugs (OND) (e.g., Office of Chief Counsel, Office of Compliance) and additional staff dedicated to the tracking of the PMR milestones established by the NDA/BLA approval letter.

5.5.3 Technical Concerns with the Complexity Factor

Our analyses suggest that the Complexity Factor is directionally inaccurate and thus results in a bias to the overall workload adjustment factor. To explain this divergence, we explored inherent features of the methodology responsible for this weakness.

First, the five review activities that make up the Complexity Factor represent a small fraction rather than the full scope of the human drugs review process. As shown in Figure 13 below, the current Complexity Factor only accounts for 9.2% of time spent on NDAs/BLAs and 19.9% of time on INDs.

Figure 13: Current Complexity Factors as Percent of Time



Source: FDA provided Workload Adjuster tool.

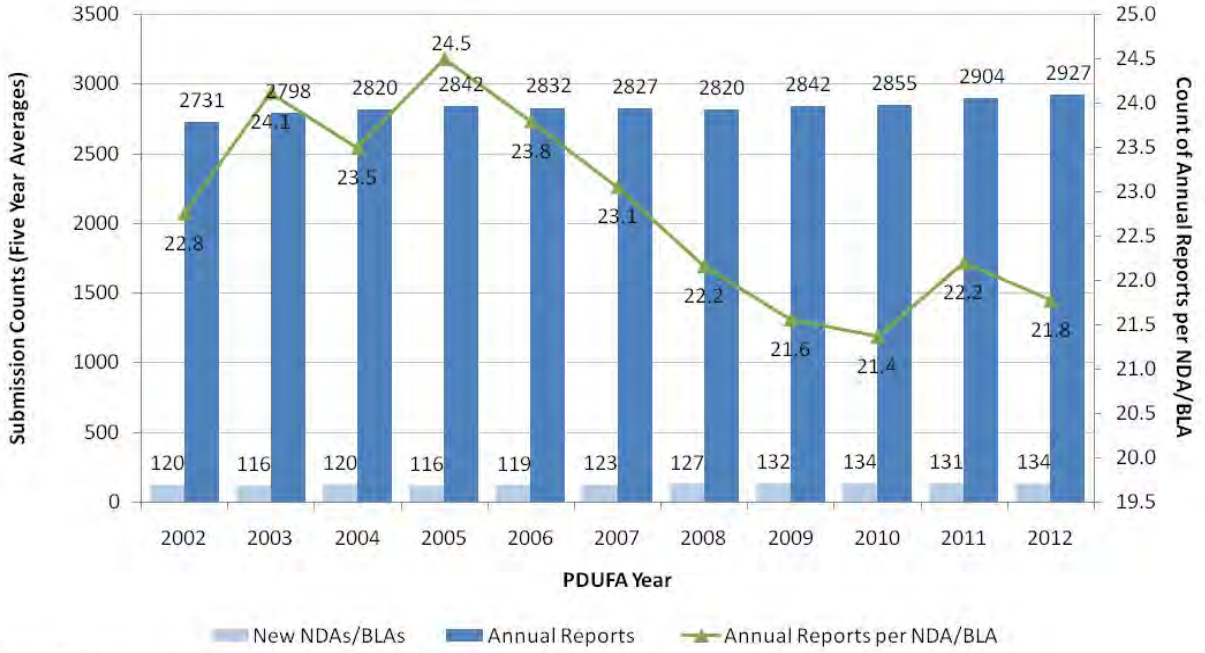
Second, chosen proxies do not necessarily reflect the directionality of total workload activities. The FDA's internal analyses suggested that for INDs, the complexity factor activities were decreasing while most activities were increasing.

Third, the proxies chosen are not robust compared to competing priorities. As noted, labeling supplements and annual report reviews do have associated backlog. Since time reporting is a

weighting factor applied to the activity counts, they may be underweighted when a backlog exists.

Lastly, the Complexity Factor is calculated using ratios, which are sensitive to change in the relative rates of growth between numerator and denominator. This may lead to a counterintuitive overall negative factor where activities increase at a slower pace than submissions. Even while the number of activities is growing, it may not grow as fast as total submissions, resulting in a declining ratio of activity to volume. Figure 14 illustrates one of the examples. Between FY 2008 and FY 2009, the five year rolling averages of labeling supplements over NDA/BLAs increased from from 127 to 131. Similarly, the five year rolling average of the denominator, new NDA/BLAs increased, from 936 to 973. The change in the relative proportions, however, resulted in a counterintuitive result of -0.079% growth when time weighted, which was added with other complexity factor inputs to contribute to an overall negative adjustment.

Figure 14: Labeling Supplements per NDA/BLA, for PDUFA Year 2002 – 2012



Notes: Submission counts are provided based on 5-year rolling averages.
Source: FDA provided Workload Adjuster tool.

6 Recommendations

This evaluation assessed whether the Workload Adjuster reasonably represents actual changes in workload in the human drug review process from FY 2009 – FY 2013. The conclusion is that the Workload Adjuster does reasonably represent change in workload volume but not workload complexity. Therefore, we recommend removing the current Complexity Factor and conducting a study on possible methods for accounting for complexity that are methodologically sound and stable. Recommendations were grouped into short term alternatives, which may be implemented as part of the FY 2014 Workload Adjuster, and long term considerations which require additional time to fully evaluate and implement. Table 3 describes the list of alternatives.

Table 3: Final List of Alternatives

Time Frame	Adjustment Activities	Implications / Advantages & Disadvantages
Short term	Status Quo	Advantages • Uses a familiar model • Represents the volume dimension of workload • Accounts for some of the work per submission Disadvantages • Does not reasonably represent current workload complexity Implications • Decreases the accuracy of the workload adjustment made in FY 2014
	Remove the Current Complexity Factor*	Advantages •Simplifies forecasting (i.e., an increase in submission counts results in an increase in the Workload Adjustment Factor) •Does not require regular reconfiguring Disadvantages • Provides a linear model based on volume of submissions • Does not capture changes in work per submission • Is not impacted by changes in business process or FTE Implications • Assumes all complexity stays the same over time, an inaccurate assumption
Long Term	Further study the representation of PDUFA related activities, specifically postmarket and implementation*	Advantages •Enables the Workload Adjuster to accurately represent the full human drug review program •Assesses the impact of periodic implementation needs, as well as policy and guidance and other activities currently not quantified Disadvantages •Does not result in an immediate improvement to the Workload Adjuster •Introduces potentially the same risk of misrepresenting or under-representing work per submission through the use of multiple, highly dynamic variables Implications •Presumes that relevant activities can be discretely identified and counted or otherwise quantified

Time Frame	Adjustment Activities	Implications / Advantages & Disadvantages
	Consider Options for a replacement measure of Complexity	Advantages •Balance the value of measuring amount of work over time, rather than just once at PDUFA negotiations •Determine alternative measures that represent the full activities required in the review of human drugs

** indicates recommended activities*

The selected short and long term recommendations are described below.

6.1 Short-Term Recommendation: Remove Complexity Factor

The short-term recommendation is to remove the Complexity Factor (Column 2b of the Workload Adjuster) for FY 2014 due to its technical weaknesses. Our evaluation found that the current Complexity Factor is not representative of overall time per submission; further, FDA experts confirmed that it consists of activities that are not representative of all the review work associated with their corresponding submission types.

6.2 Long-Term Considerations for Further Study

In the long term, the FDA has an opportunity to significantly improve the representation of the Workload Adjuster, to capture a full picture of PDUFA-related activities throughout the human drug review program. Although the current Complexity Factor is biased, its removal leaves the model without a representation of complexity. To address this, the FDA should continue to consider whether there is potential to account for increasing workload complexity every five years, during PDUFA negotiations. Alternatively, if the FDA determines that an annual complexity factor is necessary, the team recommends a comprehensive evaluation to determine the most appropriate metrics of complexity. We recommend that future measure of actual changes in workload account for postmarket activities and implementation activities (e.g., infrastructure development).

Postmarket activities are not well accounted for in the Workload Adjuster. The model adjusts new NDA/BLA submissions received within the given fiscal year through Annual Reports and Labeling Supplement metrics. However, research found that there has been an increase in the amount and complexity of other postmarket safety activities. We recommend that the FDA assess appropriate proxies/metrics to account for workload changes associated with PDUFA postmarket activities.

Policy activities also should be considered for inclusion in the model. We recommend that the FDA determine how to quantify these activities through samples and data collection.

This evaluation has the potential to provide meaningful insights to the FDA and support the enterprise in fully quantifying the workload associated with the critical human drug review program.

Appendices

Appendix A Key Abbreviations and Terms

BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Acts of 2007
FDAMA	Food Drug and Administration Modernization Act
FDASIA	Food and Drug Administration Safety and Innovation Act
FTE	Full Time Equivalent
FY	Fiscal Year
IBM	International Business Machines
IND	Investigational New Drug
NDA	New Drug Application
OND	Office of New Drugs
PDUFA	Prescription Drug User Fee Act
PMC	Post marketing Commitment
PMR	Post marketing Requirement
REMS	Risk Evaluation and Mitigation Strategies
SPA	Special Protocol Assessment

Appendix B Reference Documents

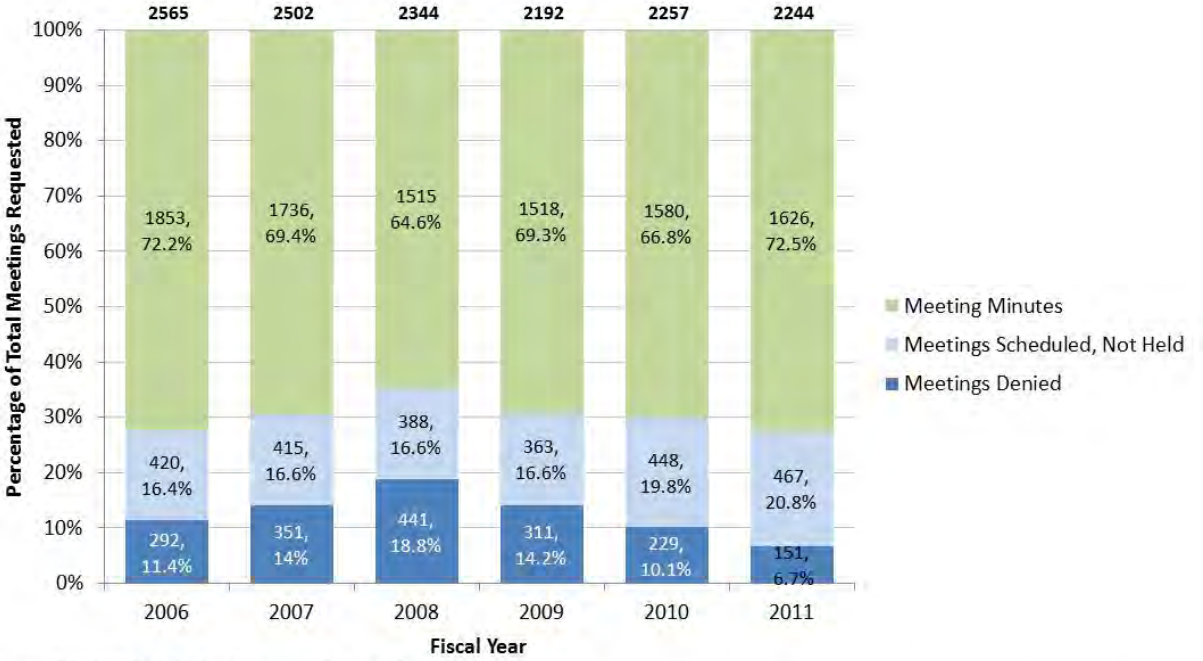
1. Booz Allen Hamilton, (January, 2008). Post marketing Commitments Study Final Report.
2. Booz Allen Hamilton, (September 9, 2011). Assessment of the Impact of the Electronic Submission and Review Environment on the Efficiency and Effectiveness of the Review of Human Drugs – Final Report.
3. Booz Allen Hamilton (April 29, 2011). Planned Review Timelines Assessment.
4. Deloitte & Touche, LLP (March 31, 2009). Evaluation of the adjustment for changes in review activities applied to the prescription drug user fee act (PDUFA) IV Workload Adjuster for FY 2009 -- Final Report. Retrieved from http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm164339.htm
5. FDA, Annual PDUFA Performance Reports to Congress, for FY 1997 – FY 2012, Appendices A. Retrieved from http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/ PDUFA/default.htm.
6. FDA, CDER Manual of Policies and Procedures. MAPP 4121.2 Tracking of Significant Safety issues in Marketed Drugs – Use of the DARRTS Tracked Safety Issues.
7. FDA-internal presentations related to the Complexity Factor presented to the PDUFA IV Finance Committee, "Proposed Workload Adjuster Methodology Revisions" dated June 16, 2006 and "Workload Adjuster Discussion" dated July 21, 2006.
8. FDA-internal narrative describing changes proposed for the Workload Adjuster, "Proposed PDUFA IV Workload Adjuster Modification" dated November 1, 2006.
9. FDA, Prescription drug user fee act (PDUFA). (December 13, 2012). Retrieved from http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.
10. FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017. Retrieved from http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf.
11. FDA, PDUFA V Workload Adjuster Evaluation Kickoff Meeting (Jan 31, 2013).
12. FDA, Workload Adjuster for FY 2013, Microsoft Excel Workbook.
13. KPMG Consulting, (March 29, 2002). Re-analysis of 1993 standard costs for the process for the review of human drug submissions as required under the prescription drug user fee act.

Appendix C Additional Figures Regarding Workload

The section below provides additional analyses in support of statements provided in Sections # - # of this report.

In seeking quantitative evidence in support of qualitative feedback indicating that, in times of a constrained workforce, Industry Meetings may be denied, the evaluation team reviewed relevant information available in the FY 2011 PDUFA Performance Report. The findings, presented in Figure 15, below, indicate that the number of meetings denied did in fact increase from FY 2006 to FY 2008, peaking in FY 2008 and decreasing through FY 2011. This general trend coincides with the overall peaks demonstrated in Figures 15 – 17 of this section.

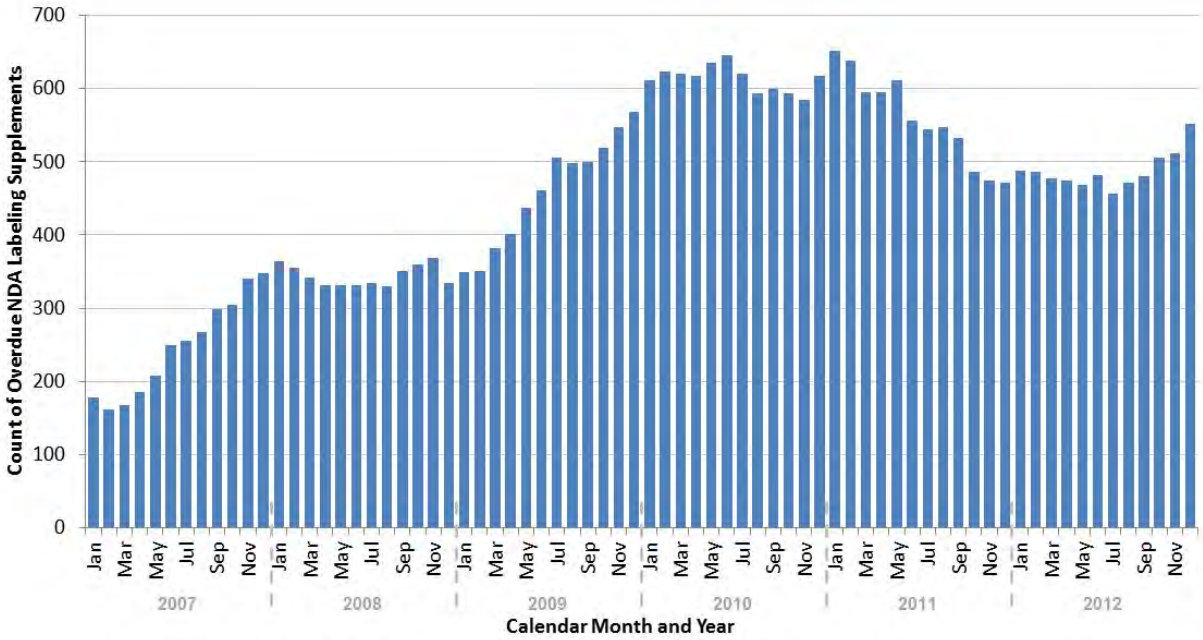
Figure 15: CDER and CBER, IND and NDA/BLA Meeting Status, FY 2006 – FY2011



Source: FY 2011 PDUFA Performance Report, Page 30. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM294101.pdf

Similarly, in support of interview statements indicative of a growing backlog of labeling supplements, the team reviewed available data. A backlog labeling supplement is one that has not been reviewed within six months of FDA receipt. Data for January 2007 – December 2012 shows a variable shift in the labeling supplement backlog, peaking throughout 2010 and into the beginning of 2011.

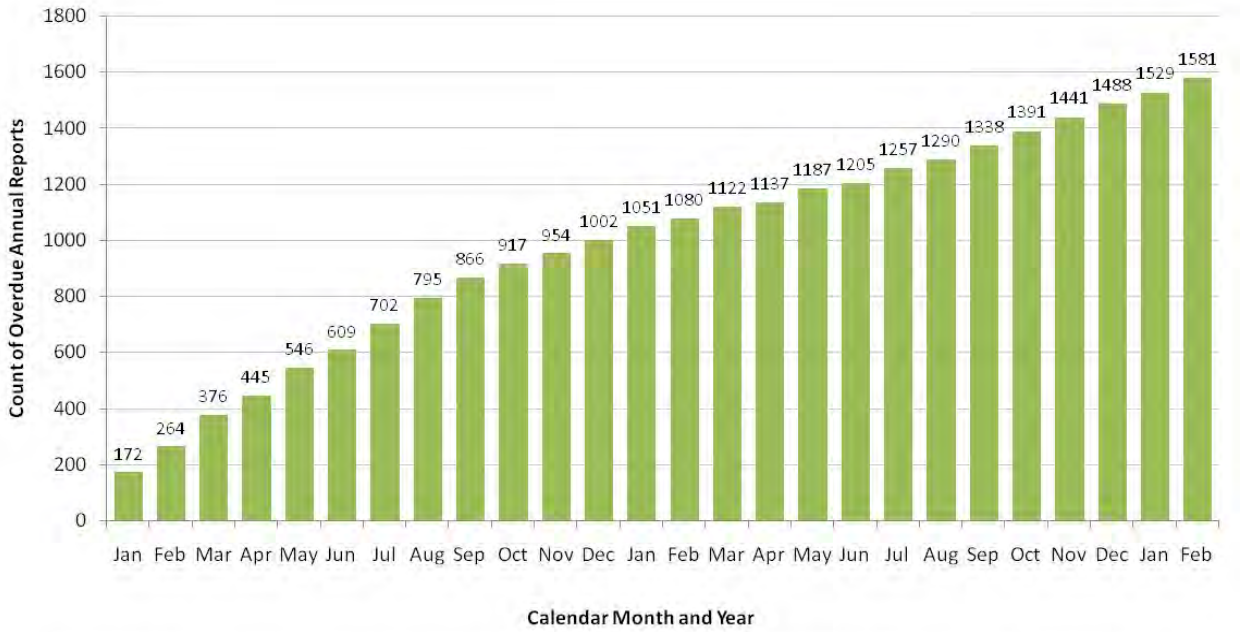
Figure 16: CDER NDA Labeling Supplement Backlog Trends, 2007 – 2012



Note: Backlog is defined as a Labeling Supplement that has not been reviewed within 6 months of FDA receipt, as indicated by FDA data systems.
Source: FDA provided.

Annual Reports procedural and processing data was similarly reviewed. CDER The annual reports data assessed for January 2011 – February 2013 is presented in Figure 17, below. CDER sets an internal goal for validating the content of an annual report within 90 days of receipt. The annual report backlog is defined here as consisting of annual reports that have not been indicated as having completed this initial validation step within this 90 day period. The figure below suggests that there may be certain annual reports throughout 2011, 2012, and into 2013 experiencing process delays.

Figure 17: CDER NDA Annual Report Validation Backlog

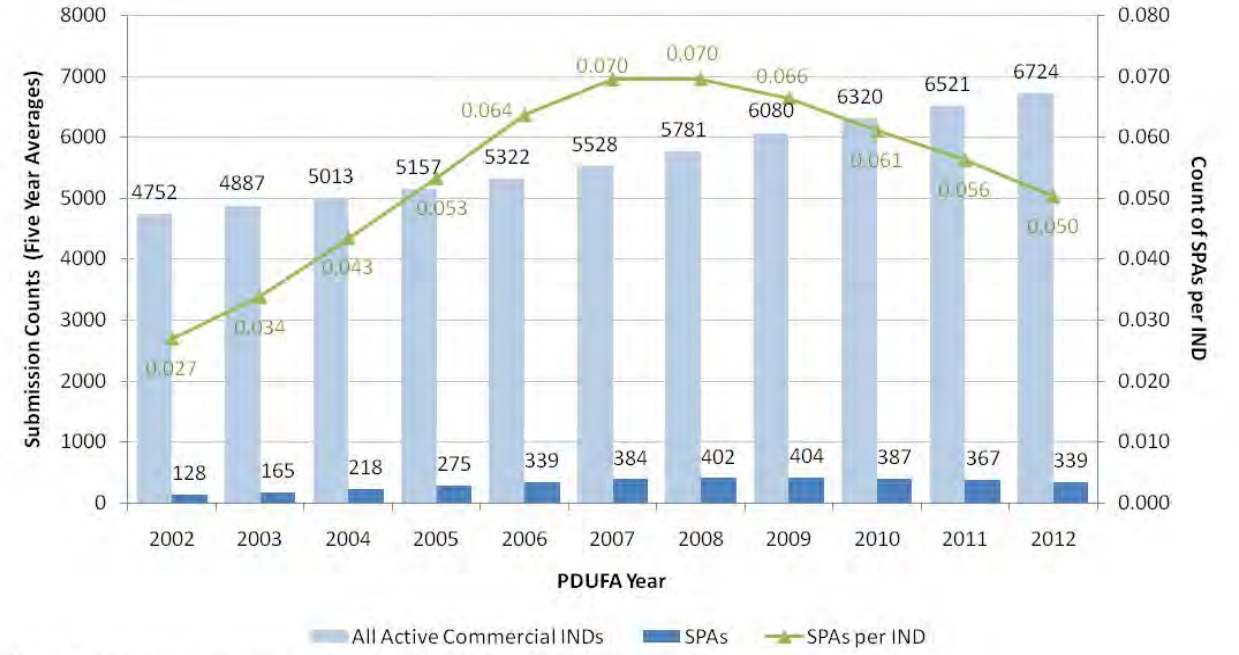


Notes: Backlog is defined as Annual Reports that do not have a corresponding 'Annual Status Report Review: Postmarketing Requirements and Commitments Summary' form available in the FDA data system, 3 months after Annual Report receipt.
Source: FDA provided.

Appendix D Figures Illustrating Complexity Factor Activities over Time

The figures below depict the performance of the five activities that comprise the complexity factor. Even while the number of activities is growing, it may not grow as fast as total submissions, resulting in a declining ratio of activity to volume. For INDs, the two activities currently in the Workload Adjuster to represent complexity are SPAs and Industry Meetings. The average ratio of SPAs per active commercial IND has dropped from 0.066 in FY 2009 to 0.050 in FY 2012.

Figure 18: SPAs per Active Commercial IND, for PDUFA Year 2002 – 2012



Notes: Submission counts are provided based on 5-year rolling averages.
Source: FDA provided Workload Adjuster tool.

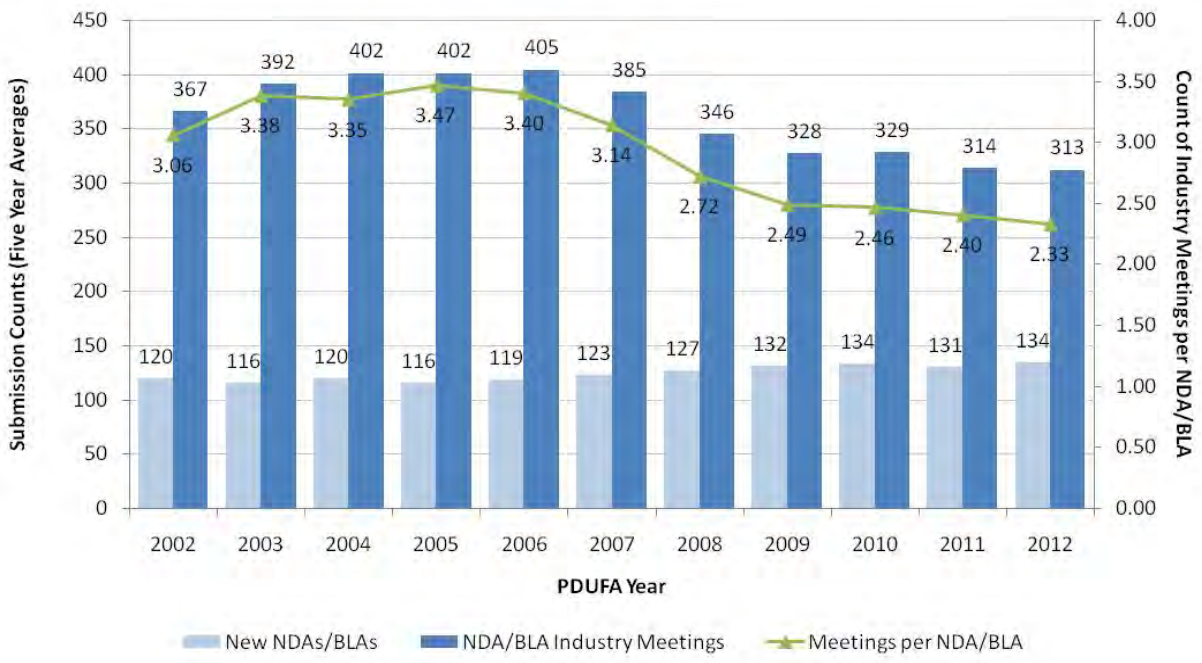
The average ratio of Meetings per active commercial IND has dropped from 0.29 in FY 2009 to 0.26 in FY 2012.

Figure 19: IND Industry Meetings per Active Commercial IND, for PDUFA Year 2002 – 2012

For NDA/BLAs, the three activities are Meetings, Labeling Supplements and Annual Reports. The average ratio of Meetings per NDA/BLA has dropped from 2.49 in FY 2009 to 2.33 in FY 2012. Since 2009, the FDA has fewer meetings denied (14.2% in FY 2009 to 6.7% in FY 2011) although the number of meetings scheduled, but not held, has been increasing (69.3 in FY 2009 to 72.5% in FY 2011).[17] In general, fewer meetings can be a desirable outcome when the issue can be resolved without a meeting. However, the issue resolution can still require work, suggesting that meetings scheduled may be a poor proxy for workload.

[17] FY 2011 PDUFA Performance Report, Page 30. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/UCM294101.pdf

Figure 20: NDA/BLA Industry Meetings per New NDA/BLA, for PDUFA Year 2002 – 2012



The average ratio of Annual Reports was 21.56 in FY 2009 and 21.78 in FY 2012. The annual reports had declined from FY 2006 to FY 2009.

Figure 21: Annual Reports per NDA/BLA, for PDUFA Year 2002 – 2012