PDUFA V Workload Adjuster Evaluation

Final Report

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Acronyms

BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
ERG	Eastern Research Group, Inc.
FDA	U.S. Food and Drug Administration
FTE	Full-Time Equivalent
FY	Fiscal Year (for U.S. government, October 1 to next September 31)
HDR	Human Drug Review
HQ	Headquarters; sometimes used interchangeably with the Office of the Commissioner
IND	Investigational New Drug
LOE	Level of Effort
NDA	New Drug Application
NME	New Molecular Entity
ORA	Office of Regulatory Affairs
PDUFA	Prescription Drug User Fee Act
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PY	PDUFA Year (for FDA HDR program, July 1 to next June 30)
QIDP	Qualified Infectious Disease Product
SME	Subject Matter Expert
SPA	Special Protocol Assessment
TSI	Tracked Safety Issue

Executive Summary

First enacted in 1992, the Prescription Drug User Fee Act (PDUFA) authorizes the U.S. Food and Drug Administration (FDA) to collect user fees that, combined with congressional appropriations, enable the Agency to review and act on prescription human drug/biologic submissions in a timely manner while maintaining its quality standards. Congress enacted PDUFA for a five-year term and has reauthorized the Act every five years thereafter. Due to increases in the numbers of prescription human drug/biologic submissions, FDA experienced a heavier workload under PDUFA II than under PDUFA I, and the user fee funding was not adequate to cover the associated review costs. To address this issue, PDUFA III introduced the PDUFA Workload Adjuster to estimate the change in human drug review (HDR) workload resulting from an increased volume of submissions to review; each year the government uses an estimated change in HDR workload to adjust the total PDUFA revenue amount to be collected in the Fiscal Year (FY). If an estimated increase in HDR workload calculated by the PDUFA Workload Adjuster is *xx%*, the total PDUFA revenue amount is adjusted accordingly:

(Starting total PDUFA revenue amount for FY)(1.xx) = Workload-adjusted total PDUFA revenue amount for FY

The PDUFA Workload Adjuster has been evaluated and refined a few times since its introduction. For PDUFA V, FDA committed to performing two independent evaluations of the Adjuster to determine whether it reasonably represents actual changes in workload volume and complexity in the HDR process. The first of the two evaluations, published in 2013, concluded that the PDUFA Workload Adjuster methodology was adequate — except that the complexity factor in the model did not adequately reflect workload per submission and should be removed and studied further. The second evaluation of the Adjuster, the subject of this report, has two main goals:

1. Evaluate the performance of the Adjuster methodology to determine if it reasonably represents actual changes in workload volume and complexity in the HDR process.
2. Make recommendations, if warranted, to discontinue, retain, or modify any elements of the Adjuster based on the evaluation results. If the recommendations include reintroducing a complexity factor, recommend inputs/algorithms to represent FDA workload volume and level of effort (LOE).

The Statement of Work specifies that the evaluation of the PDUFA Workload Adjuster should:

- Rely on the following resources: documents and data used for the Adjuster, interviews with FDA employees, and additional sources of workload and time reporting data made available by FDA.
- Examine the performance of the Adjuster from FY2009 through the most recently published version.
- Provide recommendations on inputs and algorithms if the contractor recommends the addition of a new complexity factor or other changes to the model to more effectively represent HDR workload — drawing only on information sources at FDA currently available for use.

Eastern Research Group, Inc. (ERG), the contractor that conducted this evaluation, evaluated the PDUFA Workload Adjuster against a set of acceptance criteria based on a combination of quantitative and qualitative analyses. This involved assessing the validity of the foundational assumptions that underlie

the Adjuster's methodology. Table ES-1 presents a summary of results. Based on evaluation results, ERG concludes that the current PDUFA Workload Adjuster is not optimal across several dimensions. Nevertheless, it could be the best feasible model currently available to FDA.

Table ES-1: Assessment of the PDUFA Workload Adjuster (as currently constructed) against acceptance criteria

Criterion*	Assessment	Justification for Assessment
Accurate	Not optimal	Quantitative and qualitative analyses suggest that: 1. Submission volume is not an accurate proxy for total HDR workload (review plus non-review workload). 2. Change in volume of the four submission types in the model is not an accurate proxy for change in total submission volume.
Defensible	Not optimal	Quantitative and qualitative analyses suggest that some of the foundational assumptions underlying the model are not valid, such as: *Assumption 1:* Prescription human drug/biologic submission volume is an adequate proxy for total HDR workload. • *Corollary 1*: Non-review HDR work varies in direct proportion to submission volume. • *Corollary 2*: The average LOE per submission is constant throughout a 5-year PDUFA authorization.
Feasible	Yes	The model works with existing tools and data sources. Use of model in previous years demonstrates feasibility.
Stable	Yes	Between Fiscal Year (FY) 2008 and FY2015, the mean annual change in the Adjuster (relative to year before, or 0 in first PDUFA year) is 2.2, the variance is 0.03, and the coefficient of determination is 83.1. FDA SMEs agree that this variance represents an acceptable level of stability in HDR workload adjustments.
Predictable	Not optimal	It is difficult for FDA to anticipate adjustments early enough to allocate resources (including hiring staff) in time to support adjustment-funded workload.
Straightforward	Not optimal	Although the model is simple conceptually, it relies on complex data pulls and processing.
Transparent	Not optimal	Details of methodology are not obvious to FDA staff not closely involved in implementing the workload adjustment calculations each year. Assumptions and justifications are not documented.
Flexible	No	Cannot accommodate future changes in HDR workload associated with new initiatives or requirements.

***Accurate** = Accurately represents changes in total HDR workload over time. **Defensible** = Is based on assumptions that can reasonably be expected to be valid. **Feasible** = Works with existing tools and data sources. **Stable** = Represents changes in HDR workload without exaggerating volatility. **Predictable** = Provides adjustments that FDA and industry can reasonably anticipate. For FDA, changes in HDR workload can be anticipated early enough to permit timely allocation of resources (including any hiring required) for the workload represented by the adjustment. **Straightforward** = Is based on a reasonably simple methodology with simple calculations, without relying on excessively complex statistical models or excessive data fields, variables, and components. **Transparent** = Has explicit, clearly documented methodologies, assumptions, rationales, data sources, and calculations. **Flexible** = Can accommodate future changes in HDR workload associated with new initiatives or requirements.

ERG conceptualized, built, tested, and assessed several alternatives to determine whether the current PDUFA Workload Adjuster is the best feasible model or whether alternatives might represent potential improvements. To do this, ERG identified the current model's main weaknesses, grouped them into categories, and developed strategies to overcome the weaknesses. The model's main weaknesses are:

- The Adjuster does not capture some types of HDR submissions (e.g., research investigational new drug submissions, labeling supplements, resubmissions, postmarket submissions). Contributions to HDR workload and temporal patterns in the volumes of these submission types vary; it is difficult to quantify the extent to which this weakness leads to imprecision in Adjuster outputs.
- In using submission volume to proxy workload, the model does not account for changes in average LOE per submission, which appears to have increased over time.
- The Adjuster does not capture non-review HDR activities (e.g., postmarket work, regulation and policy development, science and research, training, program management), which appear to represent an increasing proportion of total HDR workload.

In addition, the PDUFA Workload Adjuster does not capture unfulfilled HDR program demand, defined as HDR tasks that are in-house or requested but not being worked on. Verifying and quantifying unfulfilled demand is beyond the scope of this study, but might be of interest for future study.

To overcome PDUFA Workload Adjuster weaknesses, alternatives that ERG developed include:

- In the volume calculations, add submission/work types that meet criteria for importance, measurability, and feasibility (i.e., labeling supplements).
- In the volume calculations, weight submissions that have work-intensive attributes (LOE drivers) that meet criteria for importance, measurability, and feasibility.
- For the weighting factor calculations, use HDR hours from FDA time reporting systems instead of data from the PDUFA standard cost estimation process (to simplify calculations). If FDA decides to continue use of standard cost-based weighting factors, omit the normalization step (to simplify calculations).
- Replace the Adjuster with a static (fixed) adjustment to be applied throughout a 5-year PDUFA authorization.
- Add an optional catch-up estimate. In the future, FDA could create a method to identify, verify, quantify, and monetize unfulfilled HDR program demand to develop a "catch-up" estimate to bring resources and full HDR workload into alignment.

Note that some of these alternatives can be mixed and matched to work in combination with each other. Table ES-2 presents assessments of the alternatives for volume calculation, weighting factor calculation, and static adjustment calculation. The catch-up estimate is not included because it represents an option for future consideration.

Table ES-2: Assessment of potential PDUFA Workload Adjuster alternatives against acceptance criteria

Criterion	Current Model	Alternative Volume Calculations: Add Labeling Supplements	Alternative Volume Calculations: Weight by LOE Drivers	Alternative Weighting Factor Calculations: Use HDR Hours	Static Adjustment
Accurate	Not optimal	Improved, but still not optimal *(model will directly capture 46% instead of 43% of HDR workload; model indirectly captures some other work, but might be imprecise)*	Improved, but still not optimal *(increases workload adjustment, but selection of LOE drivers might not be scientifically valid and model still does not capture other types of workload)*	Improved, but still not optimal *(would permit inclusion of additional submission/work types in volume calculations, but important aspects of HDR workload still excluded)*	No *(accuracy cannot be assessed scientifically)*
Defensible	Not optimal	Not optimal *(methodological weaknesses remain)*	Not optimal *(methodological weaknesses remain)*	Not optimal *(no improvement)*	No *(has methodological weaknesses)*
Feasible	Yes	Yes	Yes	Yes	Yes
Stable	Yes	Yes	Yes	Yes	Yes
Predictable	Not optimal	Not optimal *(no improvement)*	Not optimal *(no improvement)*	Not optimal *(no improvement)*	Yes
Straight-forward	Not optimal	Not optimal *(adding labeling supplements does not increase complexity of model, but does add to data processing requirements)*	Less optimal *(weighting volume by LOE drivers* decreases *straightforwardness of model)*	Improved, but still not optimal *(weighting factor calculation more straightforward, but rest of model remains not optimal)*	Yes
Transparent	Not optimal	Not optimal *(no improvement)*	Not optimal *(no improvement)*	Improved, but still not optimal *(weighting factor calculations more transparent, but rest of model remains not optimal)*	Yes
Flexible	No	No	No	No	No

Based on all available evidence, ERG concludes that the choice between retaining some version of the current PDUFA Workload Adjuster and shifting to a new method is a subjective one. The current model is likely imprecise, but it is well-established, is well-known, and provides continuity with the past 13 years of PDUFA workload adjustment practice. Implementing a new approach to develop a static adjustment introduces uncertainties about its validity and how it will perform relative to the known approach of the current model – but it greatly improves the predictability of outputs. In light of these tradeoffs, ERG offers the following recommendations:

1. Retain the PDUFA Workload Adjuster (i.e., do not replace it with a static adjustment).
2. Refine the current version of the Adjuster by adding labeling supplements to the list of submission types included in the volume calculations.

   Note: ERG also provides an optional mechanism for periodically reassessing whether other submission or work types should be included in the volume calculations.

3. Do not weight submission volumes by LOE drivers because this will increase the complexity of the model without meaningfully improving the accuracy of workload adjustments.

4. Refine the current version of the Adjuster by using HDR hours instead of standard costs in weighting factor calculations because this simplifies the model while producing similar results – and facilitates inclusion of additional submission/work types (those without standard costs available) in volume calculations if FDA decides to do so.

ERG also recommends exploring the nature and scope of unfulfilled demand in the HDR program in order to identify, verify, quantify, and monetize each type of unfulfilled demand. Doing so will provide (1) a more complete picture of total HDR workload for management consideration and (2) a foundation for determining whether it would be beneficial to develop a catch-up estimate to fund efforts to address unfulfilled demand.

1. Introduction

1.1 Overview of PDUFA Workload Adjuster

As part of the prescription human drug/biologic development process, sponsors prepare submissions for Food and Drug Administration (FDA) review (Table 1-1). First enacted in 1992, the Prescription Drug User Fee Act (PDUFA) authorizes FDA to collect user fees that, combined with congressional appropriations, enable the Agency to review and act on submissions in a timely manner while maintaining its quality standards. Congress enacted PDUFA for a five-year term and has reauthorized the Act every five years thereafter.

Due to increases in the numbers of prescription human drug/biologic submissions, FDA experienced a heavier workload under PDUFA II than under PDUFA I, and the user fee funding was not adequate to cover the associated review costs. To address this issue, PDUFA III introduced the PDUFA Workload Adjuster to estimate changes in human drug review (HDR) workload resulting from an increased volume of submissions to review.

Table 1-1: Selected types of prescription drug/biologic submissions under PDUFA

Drug Submission	Biologic Submission	Associated with PDUFA User Fee	In PDUFA Workload Adjuster	Purpose of Submission
• Commercial Investigational New Drug (IND) submission	• Commercial IND	No	Yes	Permit investigational research across state lines (sponsor is usually a corporate entity or one of the institutes of the National Institutes of Health)
• Research IND	• Research IND	No	No	Permit research on an unapproved drug by a physician
• New Molecular Entity (NME) New Drug Application (NDA) • Non-NME NDA, with clinical data • Non-NME NDA, without clinical data	• Biologics License Application (BLA)	Yes (full fee) Yes (full fee) Yes (half fee)	Yes (NDAs/BLAs) Yes (NDAs/BLAs) Yes (NDAs/BLAs)	Permit marketing of drug or biologic for specified indications
• Efficacy supplement • Manufacturing supplement • Labeling supplement	• Efficacy supplement • Manufacturing supplement • Labeling supplement	Yes if includes clinical data (half fee)	Yes Yes No	Permit changes to an already approved marketing application

As originally implemented, the PDUFA Workload Adjuster estimated changes in HDR workload as follows:

1. For each submission type in Adjuster, calculate current 5-year rolling average number of new submissions and base 5-year rolling average.
2. For each submission type in Adjuster, calculate percent change in 5-year rolling average number of new submissions; this is percent change in volume.
3. For each submission type in Adjuster, multiply percent change in volume by a weighting factor to account for the proportion of total HDR work that each submission type represents.
4. Sum weighted percent change in volume for each submission type to estimate the total percent change in HDR workload based on submission volume.

In 2007, for PDUFA IV, FDA made two changes to the PDUFA Workload Adjuster. First, it changed the measurement of commercial Investigational New Drug (IND) submission volume from the number of *new* submissions to the number of *active* submissions[1] to account for the fact that a commercial IND can be active for many years. Second, it added a complexity factor to the PDUFA Workload Adjuster to account for changes in the *complexity* of reviews rather than just the *volume* of reviews. The complexity factor was based on counts of five specific activities in reviews of INDs and New Drug Applications (NDAs) and Biologics License Application (BLAs):

- **Commercial INDs:** Number of (1) meetings scheduled and (2) Special Protocol Assessments (SPAs) submitted. These were measured relative to the number of new INDs.
- **NDAs and BLAs:** Number of (3) meetings scheduled, (4) labeling supplements submitted, and (5) annual reports submitted. These were measured relative to the number of NDA/BLA submissions.

With each reauthorization of PDUFA, Congress has expanded the scope of FDA's review activities (Figure 1-1). The five activities represented in the complexity factor for the PDUFA Workload Adjuster do not reflect the full range of FDA's HDR responsibilities for submissions. A 2013 evaluation concluded that the complexity factor did not adequately represent total work per submission,[2] and that year FDA removed the complexity factor from the Adjuster. FDA also shifted from a 5-year rolling average to a 3-year rolling average of numbers of submissions in calculating the workload adjustment. Figure 1-2 illustrates the methodology of the current PDUFA Workload Adjuster, while Table 1-2 provides the numbers for the Fiscal Year (FY) 2015 PDUFA workload adjustment calculation.

[1] A commercial IND is considered active if FDA receives an amendment or correspondence during the year.

[2] U.S. Food and Drug Administration. (2013). An Evaluation of the Prescription Drug User Fee Act (PDUFA) Workload Adjuster Fiscal Years 2009 – 2013.

Figure 1-1: Evolution of PDUFA and the Workload Adjuster

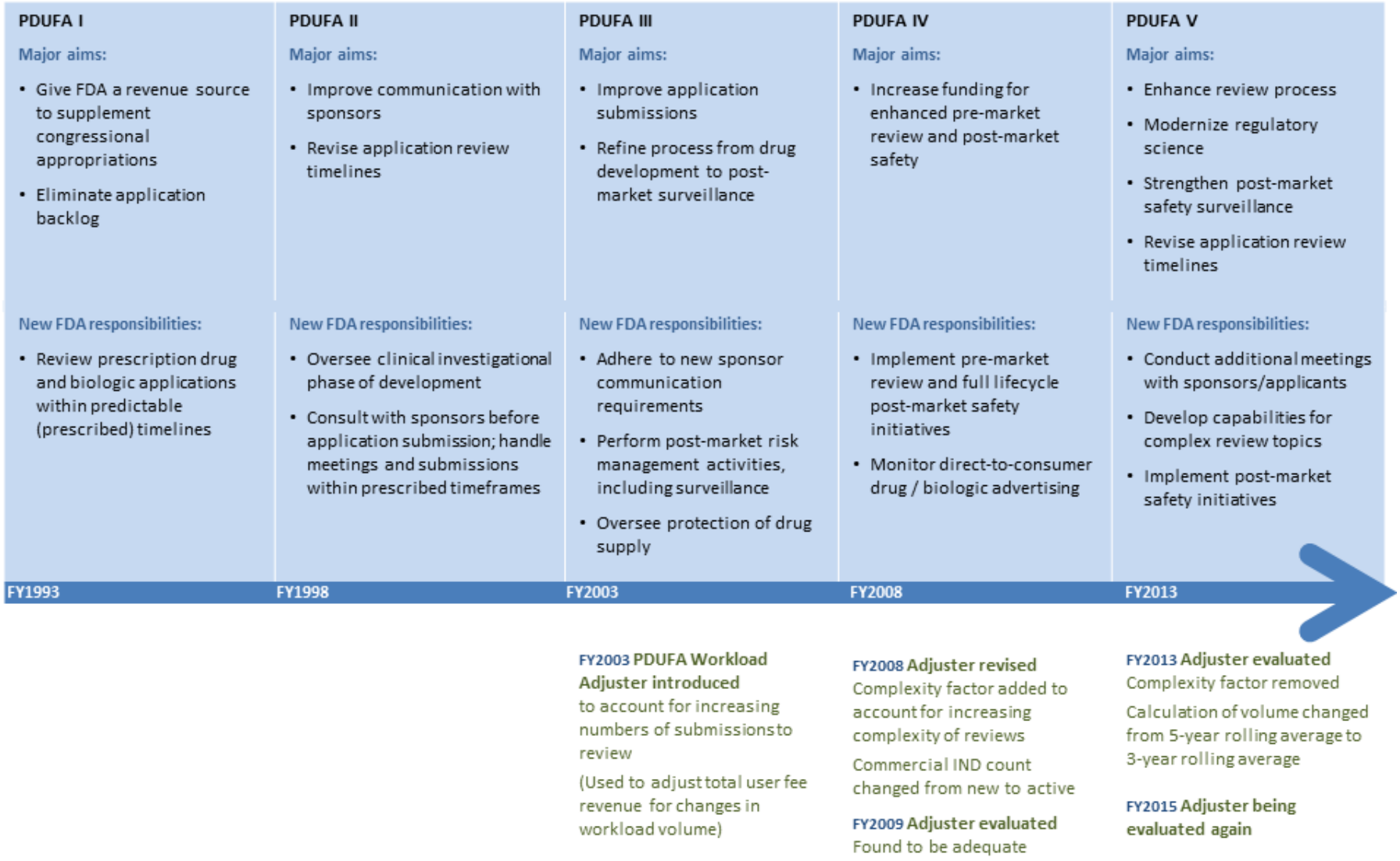


Figure 1-2: Current PDUFA Workload Adjuster methodology

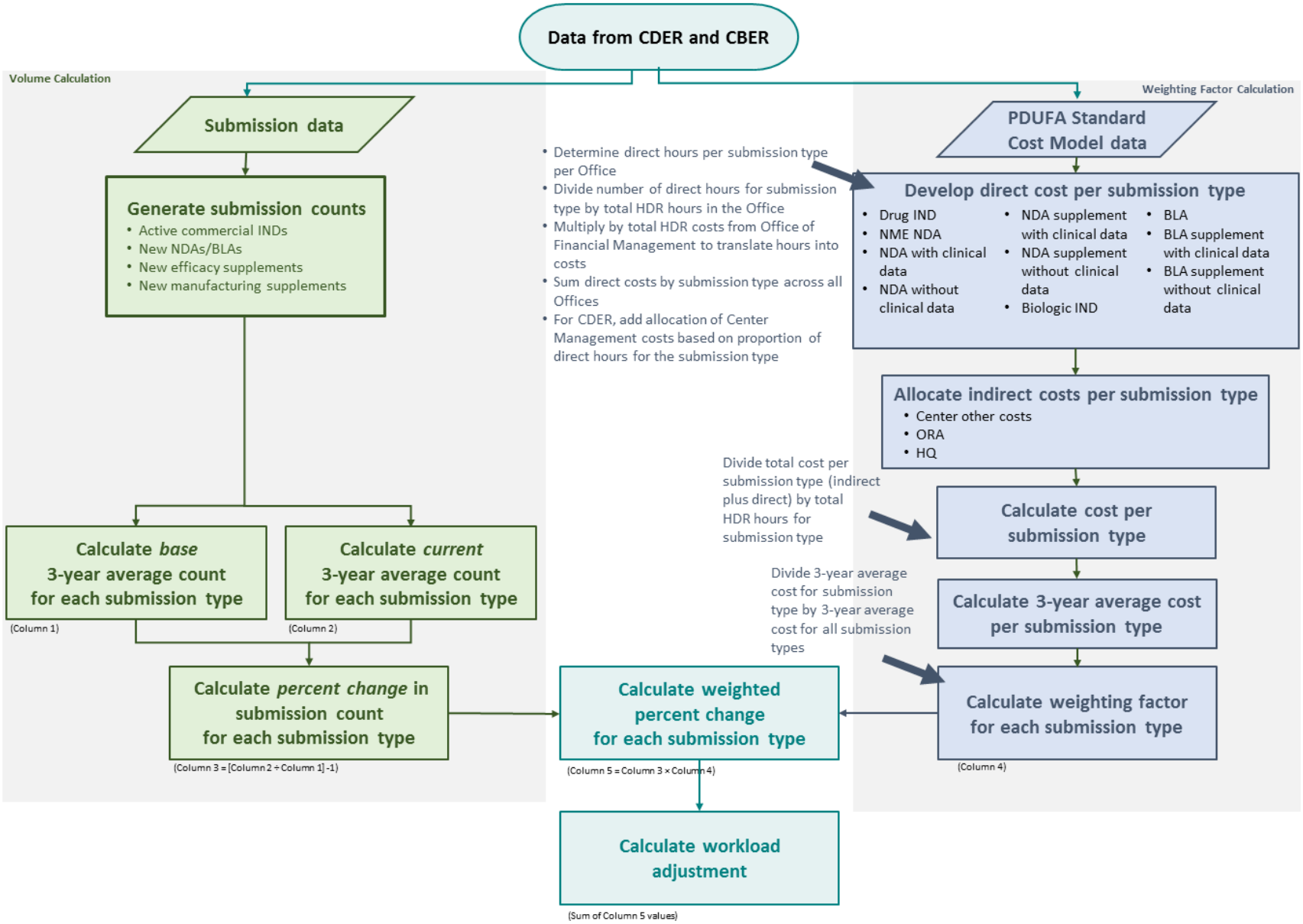


Table 1-2: Calculation of PDUFA workload adjustment for FY2015

Submission Type	3-Year average base years (2010-2012)	3-Year average 2012-2014	Percent change (Column 1 to Column 2)	Weighting factor (percent)	Weighted percent change
	Column 1	Column 2	Column 3	Column 4	Column 5
New NDAs/BLAs	124	141	13.68%	37.3%	5.11%
Active commercial INDs	6,830	7,141	4.56%	41.4%	1.88%
Efficacy supplements	136	157	14.97%	7.5%	1.13%
Manufacturing supplements	2,548	2,434	-4.50%	13.8%	-0.62%
FY2015 Workload Adjustment					**7.49%**

1.2 Evaluation Goals and Scope

During PDUFA IV, FDA enlisted an independent contractor to conduct an evaluation of the adjustment for changes in review activities (complexity factor) portion of the PDUFA Workload Adjuster. At that time, the results suggested that the Adjuster provided reasonable adjustments.[3] In 2012, for PDUFA V, FDA committed to performing two independent evaluations of the PDUFA Workload Adjuster to determine whether it reasonably represents actual changes in workload volume and complexity in the HDR process. The first of the two evaluations, published in 2013, concluded that the PDUFA Workload Adjuster methodology was adequate — except that the complexity factor did not adequately reflect workload per submission and should be removed and studied further. FDA accepted this recommendation and removed the complexity factor. The Agency also changed the calculation of submission volume from a 5-year rolling average to a 3-year rolling average.

The second evaluation of the PDUFA Workload Adjuster, the subject of this report, has two main goals:

1. Evaluate the performance of the Adjuster methodology to determine if it reasonably represents actual changes in workload volume and complexity in the HDR process.
2. Make recommendations, if warranted, to discontinue, retain, or modify any elements of the Adjuster based on the evaluation results. If the recommendations include reintroducing a complexity factor, recommend inputs/algorithms to represent FDA workload volume and level of effort (LOE).

[3] U.S. Food and Drug Administration. (2009). Evaluation of the Adjustment for Changes in Review Activities Applied to the Prescription Drug User Fee Act (PDUFA) IV Workload Adjuster for FY2009.

The Statement of Work for this evaluation also asks the contractor to propose changes to FDA's use of standard costs in the Workload Adjuster, if warranted.

In addition, the Statement of Work asks the contractor to develop a PDUFA workload inventory that catalogs and characterizes the bulk of activities that comprise the bulk of the HDR program. The purpose of this task is to inform the contractor's evaluation of the performance of the PDUFA Workload Adjuster in representing changes in HDR workload. ERG's methodology for this task is described in Section 2.

The Statement of Work specifies that the evaluation of the PDUFA Workload Adjuster should:

- Rely on the following resources: documents and data used for the Adjuster, interviews with FDA employees, and additional sources of workload and time reporting data made available by FDA.
- Examine the performance of the PDUFA Workload Adjuster from FY2009 through the most recently published version.[4]
- Provide recommendations on inputs and algorithms if ERG recommends the addition of a new complexity factor or other changes to the model to more effectively represent HDR workload – drawing only on information sources at FDA currently available for use.

[4] Where feasible, ERG examined the performance of the PDUFA Workload Adjuster from FY2008 (instead of FY2009) in order to include all of the PDUFA IV years in the analysis. In general, our evaluation of the Adjuster itself spans FY2008 to FY2015, which is the most recent published version of the Adjuster. Some other analyses (e.g., those identifying trends in counts or hours for submissions and HDR activities) run through FY2014, the most recent year for which complete data are available.

2. Methods

To evaluate the PDUFA Workload Adjuster, ERG established a set of "acceptance criteria" (Table 2-1) to assess the extent to which the Adjuster meets requirements for a successful model. The acceptance criteria represent typical standards, refined to reflect needs for this particular model. To evaluate the PDUFA Workload Adjuster against these criteria, ERG:

- Conducted quantitative analyses of Adjuster inputs and outputs.
- Developed a PDUFA workload inventory (catalog of the bulk of work in the HDR program), identified the portion of the inventory directly included in the Adjuster, and conducted quantitative analyses of types of HDR work not directly included in the Adjuster.
- Conducted qualitative analyses of the results of interviews with FDA experts.

Ideally, evaluation of the accuracy of a model (the first acceptance criterion) entails comparing model outputs with actual values or other credible standards. In the case of the PDUFA Workload Adjuster, actual values for total HDR workload are not available. Although FDA maintains data on counts of many HDR submissions and activities, many other types of HDR work are not easily countable, so the Agency has no way of measuring the *total* volume of HDR workload in terms of counts. Similarly, FDA maintains time reporting data or Full-Time Equivalent (FTE) levels broken out by certain types of HDR work, but these data do not necessarily correlate with workload because increases in hours or FTEs could reflect increases in staffing without increases in workload (see Section 2.2, Limitations). Therefore, ERG took

Table 2-1: Acceptance criteria and evaluation methods for the PDUFA Workload Adjuster

Acceptance Criterion	Definition
Accurate	Accurately represents changes in total HDR workload over time.
Defensible	Is based on assumptions that can reasonably be expected to be valid.
Feasible	Works with existing tools and data sources.
Stable	Represents changes in HDR workload without exaggerating volatility.
Predictable	Provides adjustments that FDA and industry can reasonably anticipate. For FDA, changes in HDR workload can be anticipated early enough to permit timely allocation of resources (including any hiring required) for the workload represented by the adjustment.
Straightforward	Is based on a reasonably simple methodology with simple calculations, without relying on excessively complex statistical models or excessive data fields, variables, and components.
Transparent	Has explicit, clearly documented methodologies, assumptions, rationales, data sources, and calculations.
Flexible	Can accommodate future changes in HDR workload associated with new initiatives or requirements.

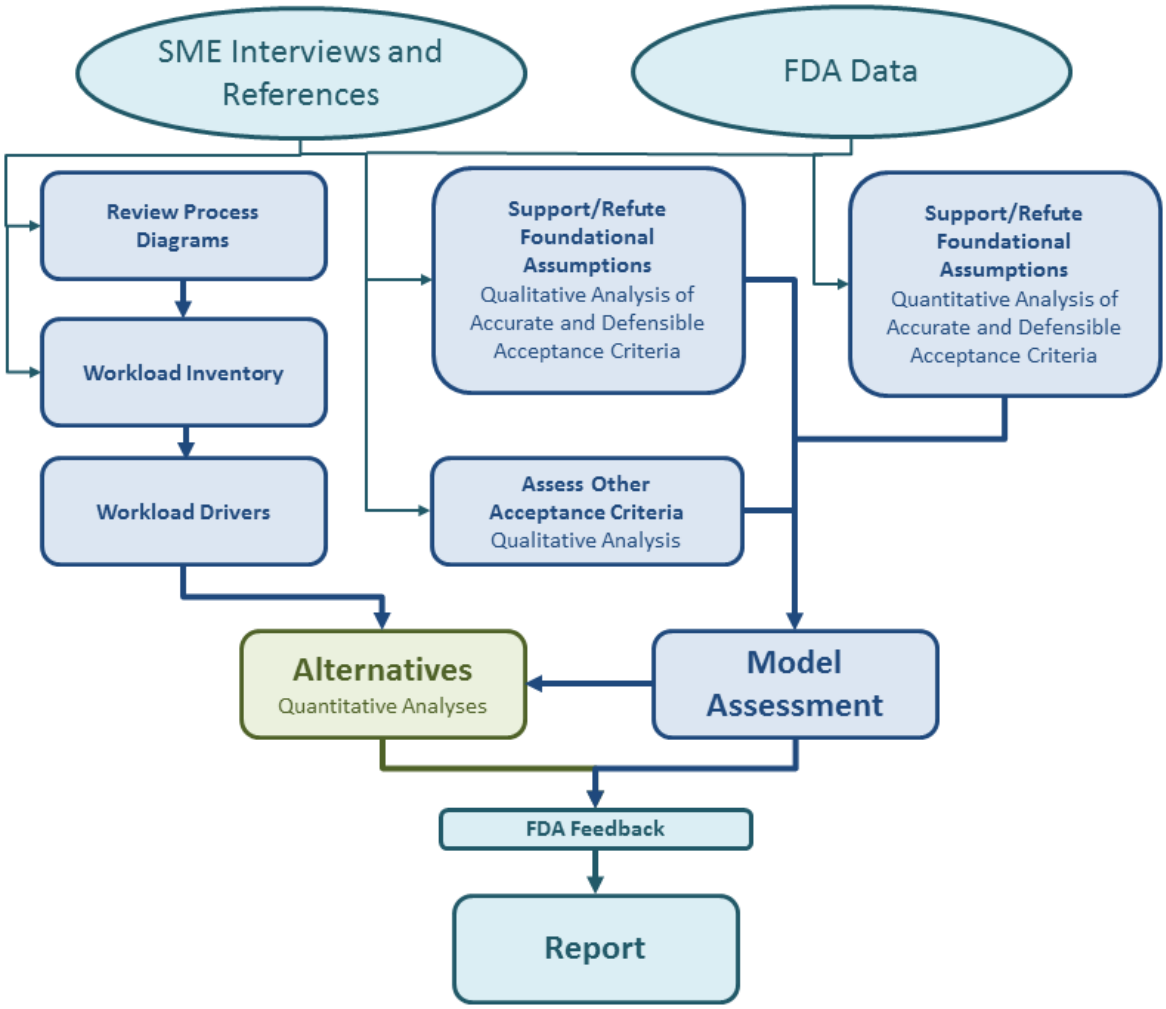
an alternative approach to assessing the accuracy of the PDUFA Workload Adjuster: identify the foundational assumptions on which the Adjuster is based (Table 2-2), assess the validity of those assumptions, and then draw conclusions about whether the Adjuster is likely to generate accurate results. This approach also enabled ERG to reach conclusions about the defensibility of the Adjuster (the second acceptance criterion).

Based on the evaluation of the PDUFA Workload Adjuster, ERG identified weaknesses of the current model and conceptualized potential strategies for overcoming those weaknesses. ERG then built and tested a series of alternatives accordingly (Figure 2-1). ERG assessed the alternatives against the same acceptance criteria used to evaluate the current PDUFA Workload Adjuster.

Table 2-2: Foundational assumptions underlying the PDUFA Workload Adjuster

Component of PDUFA Workload Adjuster	Foundational Assumption
Submission Volume as a Proxy for HDR Workload	*Assumption 1:* Prescription human drug/biologic submission volume is an adequate proxy for total HDR workload. • *Corollary 1*: Non-review HDR work varies in direct proportion to submission volume. • *Corollary 2*: The average LOE per submission is constant throughout a 5-year PDUFA authorization.
Measurement of Submission Volume	*Assumption 2:* Counts of active INDs, new NDAs/BLAs, new efficacy supplements, and new manufacturing supplements adequately represent total prescription human drug/biologic submission volume. • *Corollary 1*: Counts of other types of submissions vary in direct proportion to the counts listed above.
Calculation of Changes in Submission Volume	*Assumption 3:* Comparing the current 3-year rolling average to a base 3-year rolling average adequately balances the need for accurate calculation of submission volume changes and the need for stability and predictability of resulting adjustments.
	Assumption 4: Use of past submission counts can predict future HDR workload.
Weighting of Submission Volume Changes	*Assumption 5*: Use of one year of data to calculate work units adequately balances the need for accurate calculation of work units and the need for stability and predictability of resulting adjustments.
	Assumption 6: Standard cost values from the PDUFA Standard Cost Model accurately represent the relative proportion of total submission volume represented by each submission type.
	Assumption 7: Normalizing weighting factors by the NME NDA standard cost serves a purpose.

Figure 2-1: Overview of PDUFA Workload Adjuster evaluation and alternatives methods



2.1 Sources

2.1.1 Interviews

As shown in Table 2-3, ERG conducted interviews with Subject Matter Experts (SMEs) representing FDA offices involved in HDR work and PDUFA Workload Adjuster calculations across the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Office of Regulatory Affairs (ORA), and FDA Headquarters (HQ). ERG conducted a total of 45 interviews. The interviews focused on developing a detailed understanding of types and drivers of HDR workload in order to facilitate analysis of the adequacy of the PDUFA Workload Adjuster in estimating changes in workload, as well as to identify potential alternatives. Interview topics included:

- Types of review work and non-review work (e.g., postmarket work, regulation and policy development, science and research, training, program management) in the HDR program.
- Major activities that make up each type of work.
- Relative workload of the activities — and which might be considered "drivers" of HDR workload.

- How these types of work/activities have evolved over time and how they might continue to evolve in the future.
- Opinions about the current PDUFA Workload Adjuster (in terms of the acceptance criteria).
- Potential alternatives to the PDUFA Workload Adjuster.

ERG used interview results to contribute to our assessment of the PDUFA Workload Adjuster against the established acceptance criteria. ERG also used interview results to flesh out process diagrams for major categories of HDR work and develop an inventory of HDR activities funded by PDUFA.

Table 2-3: Center and discipline affiliations of FDA SMEs interviewed by ERG

Center	Discipline
HQ	Office of Commissioner – Economics Office of Commissioner – Financial Management
CDER	Program and Strategic Analysis
CDER	Program Overview & Performance Reports
CDER	Clinical (Medical) Regulatory Project Management
CDER	Clinical Pharmacology
CDER	Pediatric and Maternal Health
CDER	Biometrics (Statistics)
CDER	Product Quality – Small Molecule Product Quality – Biotechnology
CDER	Postmarket Safety *(initial and followup interviews)*
CDER	Policy
CBER	PDUFA Data Management
CBER	Review Management
CBER	Regulatory Project Management
CBER	Clinical PDUFA Regulatory Review: Non-Clinical Pharmacology/Toxicology
CBER	Pediatric and Maternal Health Medication Error/Proprietary Name Review & Drug Promotion Facilities Inspection – Clinical Facilities Inspection – Manufacturing
CBER	Biostatistics Premarket and Postmarket Review and Surveillance
CBER	Product Quality – Biotechnology
ORA	Inspections

2.1.2 PDUFA Workload Inventory

ERG created an inventory of HDR activities (the PDUFA workload inventory, or inventory) to serve as a reference for the scope of work that the PDUFA Workload Adjuster is intended to represent. The inventory lays out the various categories of HDR work and then lists the process steps and work activities that FDA implements to complete that work (see Appendix A). The inventory also provides a range of information for each work activity such as a description of the work activity, the hours spent to complete the activity, and interview findings that address that work activity.

To create the PDUFA workload inventory, ERG first developed a set of process diagrams for the major categories of HDR work based on publicly available information and other references provided by FDA. An example appears in Appendix B. ERG verified and elaborated on the activities within the process diagrams through additional research and interviews with FDA SMEs, then built the framework for the inventory (worksheets for major categories of work and rows for activities within the major categories). ERG then used a combination of interview results and FY2014 submission counts and FDA time reporting data to populate the inventory. ERG used the completed inventory to identify:

- Components or categories of HDR work that are and are not directly included in the PDUFA Workload Adjuster.
- Components or categories of HDR work that could potentially be added to an alternative version of the Adjuster to more accurately estimate changes in HDR workload.
- Drivers of work intensity that could potentially be used in an alternative version of the Adjuster to weight submissions that require a greater LOE than other submissions — again, to more accurately estimate changes in HDR workload.

2.1.3 Data

ERG used data provided by FDA to (1) analyze PDUFA Workload Adjuster inputs and outputs, (2) test the foundational assumptions underlying the methodology of the Adjuster, (3) populate an inventory of HDR activities with quantitative data on the LOE associated with HDR work at the aggregated and disaggregated levels, (4) identify potential drivers of HDR workload that are not currently captured in the Adjuster, and (5) build and test alternative PDUFA workload adjustment models.

FDA provided ERG with two main types of data:

- **Time reporting data.** FDA provided HDR-related time reporting data representing FY2007 to FY2014 for both CDER and CBER. ERG used these data to identify how the average LOE per submission for the four submission types in the PDUFA Workload Adjuster changes over time, how changes in the LOE for potential drivers of submission review workload compare to changes in submission volume, and whether the LOE for non-review activities (e.g., postmarket work, regulation and policy development, science and research, training, program management) varies directly with submission volume.
- **Counts of submissions and HDR activities.** FDA provided data on submissions, submission traits, and HDR activities for FY2007 to FY2014 or subsets of that period where appropriate (Table 2-4).

Table 2-4: HDR submission and activity data provided by FDA

Commercial IND Data	NDA/BLA Data	Supplements Data	Other
IND ID	In PDUFA V NME Program	Supplement ID	Research INDs
Receipt date	NDA/BLA ID	Established name	New labeling supplements
Clinical holds	Established name	Receipt date	Labeling supplements in backlog
Clinical hold releases	Receipt date	Goal date	Class 2 NDA/BLA resubmissions
Pre-NDA/BLA meetings	Filing date	Action date	Class 1 efficacy supplement resubmissions
Other meetings	Goal date	Action type	Class 2 efficacy supplement resubmissions
SPAs	Action date	Meetings	Manufacturing supplement resubmissions
Breakthrough Therapy	Action type	Review priority	Labeling supplement resubmissions
	Review priority	With clinical data	Annual reports requiring review
	With clinical data	Breakthrough Therapy	Tracked Safety Issues
	Breakthrough Therapy	Fast Track	
	Fast Track	Accelerated approval	
	Accelerated Approval		
	QIDP designation		
	Proprietary name review		
	REMS		
	Shared REMS		
	Postmarket requirements (PMRs)		
	Postmarket commitments (PMCs)		
	Application orientation meeting		
	Mid-cycle communication		
	Late-cycle meeting		
	Advisory committee meeting		
	Post-action feedback meeting		
	Other meetings		

ERG used these data to determine whether (1) other submission types (beyond the four included in the Adjuster) or other types of HDR work vary in direct proportion to submission volume as measured in the Adjuster, and (2) certain time-intensive review activities vary in direct proportion to submission volume.

2.2 Limitations

Following is a list of potential limitations of ERG's evaluation of the PDUFA Workload Adjuster.

Methodological Limitations

1. Workload is a somewhat vague and subjective term and cannot be directly measured. Two possible approaches for measuring workload are:

   ✓ **Identify and count all work activities performed.** Defining a comprehensive set of activities that capture the totality of FDA's HDR workload is very difficult given the wide-range of activities involved in the drug review process. While many activities are submission-based and therefore countable, other required HDR tasks are not directly tied to submissions and are more difficult to measure in terms of counts (e.g., regulation and policy development, science and research, training, program management).

   ✓ **Determine time spent on work activities comprising workload.** This approach cannot be relied upon alone for the HDR program because hours reflect time spent on tasks, which might not correlate with actual workload (e.g., more staff could be assigned to the same amount of work).

   Therefore, ERG used a combination of quantitative data (counts and hours) and qualitative data (SME interview responses and other references) to develop *suggestive* evidence concerning whether the PDUFA Workload Adjuster reasonably represents changes in HDR workload.

2. Due to the limitation cited above, no comprehensive measure of total HDR workload is available for comparison with model outputs. This is why ERG adopted the approach of testing the Adjuster against acceptance criteria and underlying foundational assumptions, using the PDUFA workload inventory as a reference for the scope of HDR work that the PDUFA Workload Adjuster is intended to represent.

3. It can be difficult to identify a temporal trend with confidence for a relatively short time period, such as the period we are considering, generally PDUFA Years (PYs) 2008-2014.[5] Additionally, temporal trends found in this timeframe might not hold for future years.

[5] For the HDR program, PY runs from July 1 to the next June 30. FDA tracks some activities by PY, so ERG displayed some results in this report by PY instead of FY.

4. The PDUFA Workload Adjuster, and therefore this evaluation, is designed to capture workload that is or can be completed. The Adjuster does not capture unfulfilled HDR program demand, such as backlogs of unreviewed supplements. Identifying, verifying, and quantifying all types of unfulfilled demand is outside the scope of this evaluation. ERG did, however, note when SMEs interviewed for this study spoke about unfulfilled demand, and we offer a preliminary concept for a method to estimate unfulfilled demand for future consideration.

Interview Limitations

1. Many of the SMEs interviewed for this study are Director and team lead-level FDA employees with a considerable depth and breadth of experience with the HDR program. These experts provided excellent information about HDR work within their areas of expertise and actual or potential concerns about the Adjuster. Nevertheless, they might not always have accurate information about the LOE required for specific HDR activities. This is why ERG examined both qualitative and quantitative information about HDR activities.
2. Many of the SMEs spoke to HDR workload in their Office or Division. Some HDR activities that are very important or represent a large share of work in one organizational unit are less important or voluminous in other organizational units. To help mitigate this limitation, ERG conducted numerous (45) interviews of a wide range of SMEs and identified common themes. Specific details provided by interviewees varied based on their areas of expertise, but the main themes were consistent across interviews and consistent with the results of quantitative analyses.

Time Reporting Data Limitations

1. CDER and CBER record time data 8 weeks per year (2 weeks every quarter). Because the data are samples, it is possible that they might not be representative of HDR work performed throughout the entire year.
2. ERG's analyses were limited to the time reporting categories reported by CDER and CBER. Therefore, ERG could not break out hours expended for all types of HDR activities or interest – or for all types of submission traits of interest. For example, disaggregated data for all types of FDA communications (both formal and informal) with sponsors/applicants were not available, nor were data broken out by review priority or other designations; these items are not tracked at that level of disaggregation in FDA's time reporting systems.
3. CDER changed time reporting systems in FY2013. Therefore, data before and after FY2013 are not strictly comparable. This is why graphs in this report show a trend break between FY2012 and FY2013 (for graphs showing hours) or between FY2013 and FY2014 (for graphs of PDUFA workload adjustments that rely on previous-year time reporting data).
4. Time reporting data might not accurately represent HDR workload. HDR hours could increase because FDA assigned more staff to perform the same amount of work, not because there was more work to be completed. In fact, we know that FDA hired additional staff during PDUFA IV to address understaffing issues. This is why ERG relied on both qualitative analyses (of FDA SME

interview responses) and quantitative analyses (of submission and activity counts as well as hours) when considering HDR workload associated with submission reviews and other activities.

5. Time reporting data for ORA and HQ are not used in the current PDUFA Workload Adjuster and were therefore unavailable for this evaluation. Nevertheless, FDA SMEs agree that CDER and CBER represent a large majority of HDR hours.

Data Count Limitations

1. As with time reporting data, ERG's analyses were limited to the types of submission and activity counts available in FDA's data systems.
2. In some cases, definitions of HDR submissions or activities might change, or measurement of counts might change. For example, CDER recently implemented a change in its internal business practice for how Tracked Safety Issues (TSIs), a type of postmarket safety work, are tracked. Such changes in definitions or measurement have the potential to skew results. This study did not measure the impact of such changes.

3. Evaluation of the PDUFA Workload Adjuster

Table 3-1 presents a summary of ERG's assessments of the PDUFA Workload Adjuster by the acceptance criteria established for this model. As shown, ERG concludes that the model is not optimal across several dimensions—most notably "Accurate" and "Defensible," but also "Predictable," "Straightforward," "Transparent," and "Flexible." Although we conclude that the model does not optimally meet these criteria, we also acknowledge that *it might be the best feasible model currently available to FDA.* ERG conceptualized, built, tested, and assessed several alternatives in an attempt to overcome the current Adjuster's weaknesses. These are described in Section 4. ERG's findings and recommendations regarding the current model and alternatives appear in Section 5.

Table 3-1: PDUFA Workload Adjuster acceptance criteria

Criterion	Assessment	Justification for Assessment
Accurate	Not optimal	Quantitative and qualitative analyses suggest that: 1. Submission volume is not an accurate proxy for total HDR workload (review plus non-review workload). 2. Change in volume of the four submission types in the model is not an accurate proxy for change in total submission volume. (See Table 3-2.)
Defensible	Not optimal	Quantitative and qualitative analyses suggest that some of the foundational assumptions underlying the model are not valid. (See Table 3-2)
Feasible	Yes	The model works with existing tools and data sources. Use of model in previous years demonstrates feasibility.
Stable	Yes	Between FY2008 and FY2015, the mean annual change in the Adjuster (relative to year before, or 0 in first PDUFA year) is 2.2, the variance is 0.03, and the coefficient of determination is 83.1. FDA SMEs agree that this variance represents an acceptable level of stability in HDR workload adjustments.
Predictable	Not optimal	It is difficult for FDA to anticipate adjustments early enough to allocate resources (including hiring staff) in time to support adjustment-funded workload.
Straightforward	Not optimal	Although the model is simple conceptually, it relies on complex data pulls and processing.
Transparent	Not optimal	Details of methodology are not obvious to FDA staff not closely involved in implementing the workload adjustment calculations each year. Assumptions and justifications are not documented.
Flexible	No	Cannot accommodate future changes in HDR workload associated with new initiatives or requirements.

As described in Section 2, Methods, ERG could not directly measure the performance of the PDUFA Workload Adjuster against actual or standard HDR workload values because FDA does not calculate such values. Therefore, we analyzed the model to identify the foundational assumptions on which the model is based and conducted a series of analyses to examine the validity of the foundational assumptions. This approach enabled us to assess (1) the likelihood that model outputs are accurate and (2) the defensibility of the methodology used in the model. Table 3-2 presents a high-level summary of the results of these analyses. We present further information about these results, grouped by category of foundational assumptions, as follows:

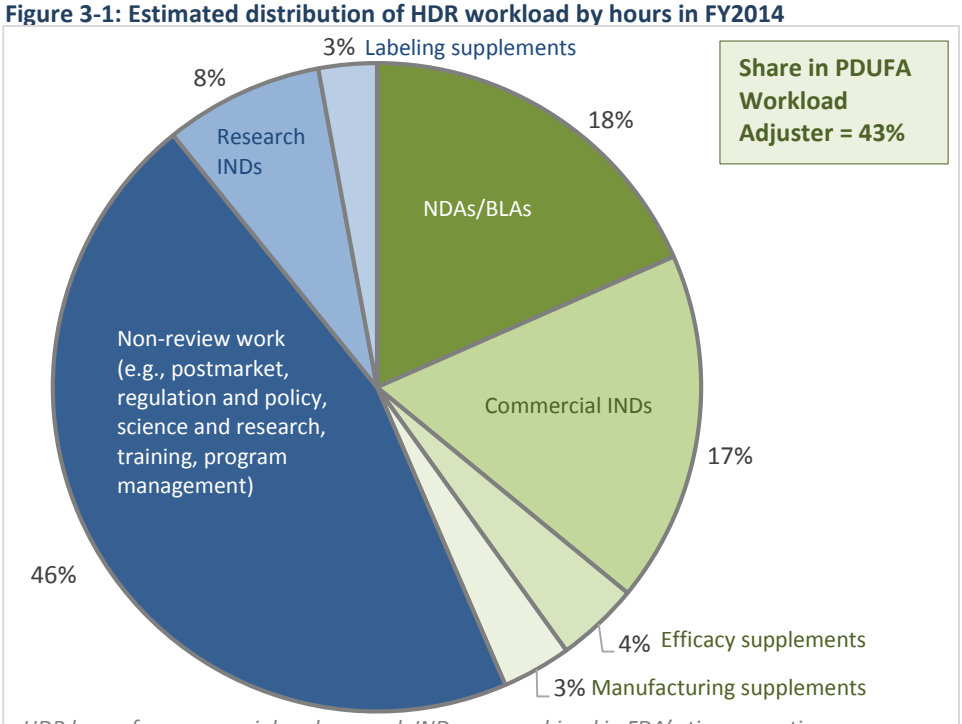
- Section 3.1, Submission volume as proxy for HDR workload
- Section 3.2, Measurement of submission volume
- Section 3.3, Calculation of changes in submission volume
- Section 3.4, Calculation of weighting factors

3.1 Submission Volume as Proxy for HDR Workload

Assumption 1: Prescription human drug/biologic submission volume is an adequate proxy for total HDR workload.

The PDUFA Workload Adjuster is predicated on the assumption that submission volume serves as an adequate proxy for total HDR workload — or at least the bulk of HDR workload. In FY2014, the four submission types included in the Adjuster (new NDAs/BLAs, commercial INDs, efficacy supplements, and manufacturing supplements) represented an estimated 43 percent of total HDR workload as measured by HDR hours recorded in CDER and CBER time reporting systems (Figure 3-1). For Assumption 1 to be true, these submission types must represent the types of work shown in Figure 3-1: the bulk of this workload must vary in direct proportion to submission volume. For Assumption 1 to

Figure 3-1: Estimated distribution of HDR workload by hours in FY2014



HDR hours for commercial and research INDs are combined in FDA's time reporting systems. ERG disaggregated the hours by (1) relative counts and (2) relative LOE estimates from FDA. Supplement hours broken out by type available only for CDER. ERG applied CDER distribution to CBER supplement hours to estimate total supplement hours by type.

Table 3-2: PDUFA Workload Adjuster foundational assumptions and evaluation results

Assumption	Analysis	Results	Interpretation
Submission Volume as Proxy for HDR Workload			
Assumption 1: Prescription human drug/biologic submission volume is an adequate proxy for total HDR workload	Compared PDUFA workload adjustments from current Adjuster with values calculated using HDR hours instead of submission counts (FY2008-FY2015)	As expected,* adjustments derived from HDR hours are substantially higher than those produced by the current Adjuster (based on submission counts)	Available evidence suggests that Assumption 1 and its corollaries are **not valid** In addition, currently no method exists to quantify unfulfilled HDR program demand
	Analyzed SME statements about rate of change of total HDR workload (actual workload, not just hours) relative to submission volume	Total HDR workload outpaces submission volume due to greater technical and communication demands for submission reviews and increasing non-review work Quantifications of HDR workload do not include unfulfilled demand (HDR tasks that are in-house or requested but not being worked on)	
Assumption1-Corollary 1: Non-review HDR workload varies in direct proportion to submission volume	Compared changes in non-review and review hours in HDR program (FY2008-FY2014)	Non-review work represents an increasing proportion of total HDR hours	
	Compared rate of change of non-review work relative to submission volume (FY2008-2014)	Mixed results: Some non-review work outpaces submission volume	
	Analyzed SME statements about rate of change of non-review work relative to submission volume	Uncertain: Non-review work might not vary in direct proportion to submission volume	
Assumption 1-Corollary 2: The average LOE per submission is constant throughout a 5-year PDUFA authorization	Calculated average hours per submission, by submission type (FY2008-2014)	As expected,* average hours per submission shows an upward trend	
	Compared rate of change of LOE-intensive submission activities/traits relative to submission volume (FY2008-2014)	Mixed results: Some LOE-intensive traits/activities outpace submission volume; results for some other traits/ activities are inconclusive	
	Analyzed SME statements about LOE per submission and factors that affect work intensity	Actual workload (not just hours) per submission has been increasing due to greater technical and communication demands	

Assumption	Analysis	Results	Interpretation
Measurement of Submission Volume			
Assumption 2: Counts of active commercial INDs, new NDAs/BLAs, new efficacy supplements, and new manufacturing supplements adequately represent total prescription human drug/biologic submission volume	Compared year-over-year changes in counts of submissions included and excluded from the Adjuster	Growth in counts of labeling supplements outpaces growth in counts of the four submission types in the Adjuster Rates of change in counts for other submission types (e.g., research INDs, resubmissions, amendments) and the proportion of NDAs that are NMEs are similar or trends are inconclusive	The four submission types in the Adjuster do not represent the volume of labeling supplements and it is unclear how well they represent some other submission types (where trends are inconclusive), suggesting that workload adjustments based only on the four submission types might be **imprecise**
Assumption2-Corollary 1: Counts of other types of submissions vary in direct proportion to the counts listed above			
Calculation of Changes in Submission Volume			
Assumption 3: Comparing current 3-year rolling average to a base 3-year rolling average adequately balances need for accurate calculation of submission volume changes and need for stability/predictability of resulting adjustments	Compared Adjuster outputs using 5-year, 4-year, 3-year, 2-year, and 1-year averages	Adjuster outputs vary substantially based on number of years used in rolling averages	Choice of rolling average **depends on FDA and stakeholder preferences** regarding the balance between stability and sensitivity
Assumption 4: Use of past submission counts can predict future HDR workload	Compared predicted submission counts (based on rolling averages used in Adjuster) to actual next-year submission counts	Predicted and actual submission counts differ substantially (by 5-27 percent), depending on type of submission and year	Available evidence suggests that past submission counts are **imprecise** predictors of future HDR workload (in terms of submission volume)

Assumption	Analysis	Results	Interpretation
Calculation of Weighting Factors			
Assumption 5: Use of one year of data to calculate work units adequately balances the need for accurate calculation of work units and need for stability/predictability of resulting adjustments	Compared Adjuster outputs based on use of 1-year versus 3-year rolling averages	Results are similar	Assumption is **valid**
Assumption 6: Standard cost values from the PDUFA Standard Cost Model accurately represent the relative proportion of total submission volume represented by each submission type	Calculated weighting factors using HDR hours rather than standard costs	Results in a negligible to modest difference; active commercial INDs share increases slightly when HDR hours are used	**HDR hours can be used** instead of standard costs
Assumption 7: Normalizing weighting factors by the NME NDA standard cost serves a purpose	Compared weighting factors calculated with and without division by standard cost for an NME	Results are similar in PY2007 and PY2008 and exactly the same from PY2009 onward	Available evidence **refutes assumption** that this normalization step serves a purpose

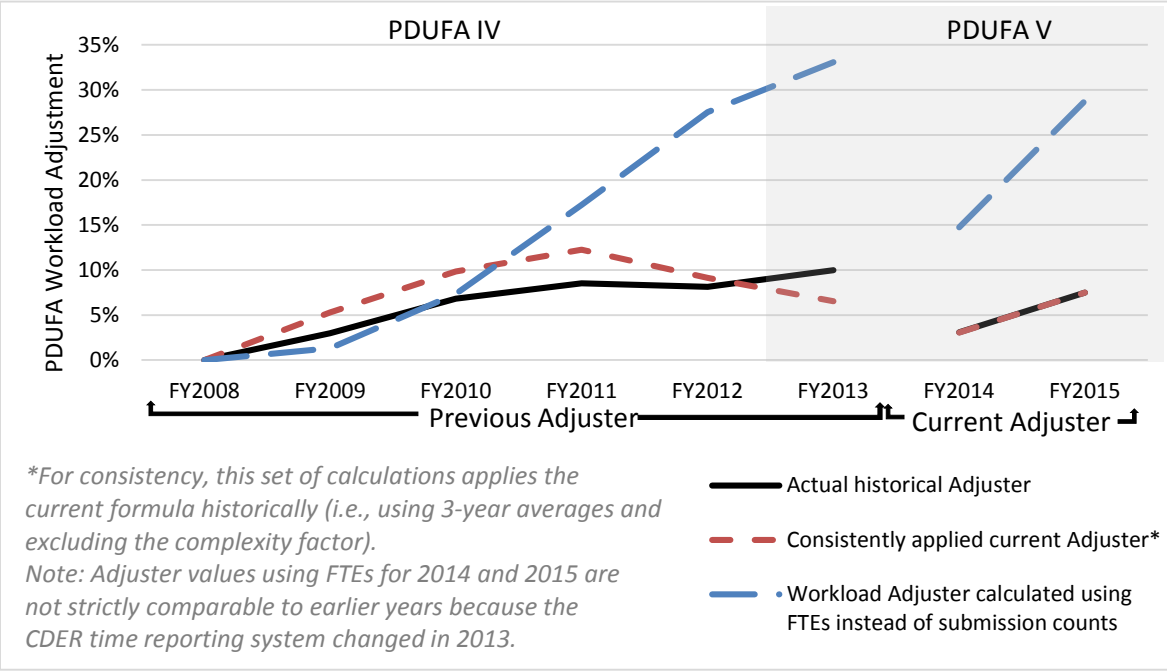
*ERG expected workload adjustments based on HDR hours to be higher than those based on submission volume, and for hours per submission to increase during PDUFA IV, due to increases in FDA staffing that occurred in PDUFA IV. To determine whether *part* of the increase in HDR hours reflects an increase in actual workload (not just FTEs), ERG conducted a qualitative analysis of SME interview results (next row in table).

be true, two other conditions must also hold. Non-review HDR workload must vary in direct proportion to review workload (Corollary 1) and, for review work, the average LOE per submission must remain constant throughout a 5-year PDUFA authorization (Corollary 2). Thus, ERG conducted analyses to test the validity of these corollaries (pages 23-27) as a means of evaluating Assumption 1. ERG also conducted some analyses to provide suggestive evidence to support or refute Assumption 1 directly (below).

Compare PDUFA workload adjustments from current Adjuster with values calculated using HDR hours instead of submission counts. For this analysis, ERG constructed estimates of workload adjustments based on total hours instead of counts for the four submission types. Specifically, ERG determined total HDR FTEs (as reported by CDER and CBER) each year, calculated 3-year rolling averages, and then used the percent change between current and base 3-year rolling averages as the workload adjustment for each year. The resulting adjustments are substantially higher than those produced by the current model (Figure 3-2). ***As noted in Section 2.2, Limitations, these results are unsurprising due to increases in FDA staffing that took place during PDUFA IV. Thus, increases in hours might not signify increased workload.*** Nevertheless, the higher workload adjustments based on HDR hours could *in part* reflect actual increases in workload in addition to increases in FTEs. To investigate this possibility further, ERG analyzed SME interview responses and conducted additional analyses (for Corollaries 1 and 2 below) to provide more evidence.

For this and other quantitative analyses, ERG used the current PDUFA Workload Adjuster to calculate adjustments for all years of the analysis. This is because ERG is tasked with evaluating the performance of the current *Adjuster, not the previous version (that used 5-year rolling averages and a complexity factor for volume calculations) used during PDUFA IV and the first year of PDUFA V. Nevertheless, we also show actual historical adjustments published in the Federal Register for reference.*

Figure 3-2: PDUFA Workload Adjustments calculated using HDR hours versus current model



**For consistency, this set of calculations applies the current formula historically (i.e., using 3-year averages and excluding the complexity factor).*
Note: Adjuster values using FTEs for 2014 and 2015 are not strictly comparable to earlier years because the CDER time reporting system changed in 2013.

Analyze SME statements about rate of change of total HDR workload relative to submission volume.
Nearly all of the FDA SMEs interviewed for this study (41 of 45)[6] stated directly or indirectly that total HDR workload probably outpaces the volume of the four types of submissions included in the PDUFA Workload Adjuster. To that end, many SMEs cited:

- Types of work not in the Adjuster where changes in workload appear to outpace submission volume. For example:
  - ✓ Review of labeling supplements
  - ✓ Postmarket work (e.g., annual reports, PMRs/PMCs, safety, certain types of surveillance)
  - ✓ Policy and guidance work related to mandates outside of FDA control, such as the Breakthrough Therapy pathway included in the Food and Drug Administration Safety and Innovation Act (FDASIA) but not negotiated in PDUFA V
  - ✓ Responses to complex, urgent safety issues and emerging threats/health crises
- Submission traits and review activities that have driven up the average LOE per submission review, thereby causing changes in submission review workload to outpace submission volume. For example:
  - ✓ Increased demand for meetings and other communications (both formal and informal)
  - ✓ Increased proportion of submissions involving complex or novel science and technology
  - ✓ Increased proportion of submissions with special designations (Breakthrough Therapy, Fast Track, Qualified Infection Disease Product or QIDP, priority review) that increase workload on a per-submission basis due to greater demands for communication, need for specialized expertise, or staffing requirements to meet compressed schedules

In addition, some SMEs commented that quantifications of HDR workload do not take into account unfulfilled program demand, such as backlogs of unreviewed labeling supplements. As demand for communication with sponsors and applicants increases, expanding overall workload, such unfulfilled demand might increase as well – without being captured in the PDUFA Workload Adjuster.

The evidence presented thus far suggests that review workload might be increasing at a faster rate than submission volume, and non-review workload is not directly linked to submission volume; in turn, these phenomena suggest that submission volume might not be an adequate proxy for total HDR workload. To develop further evidence to support or refute this hypothesis, ERG conducted additional analyses for Assumption 1, Corollaries 1 and 2 (below).

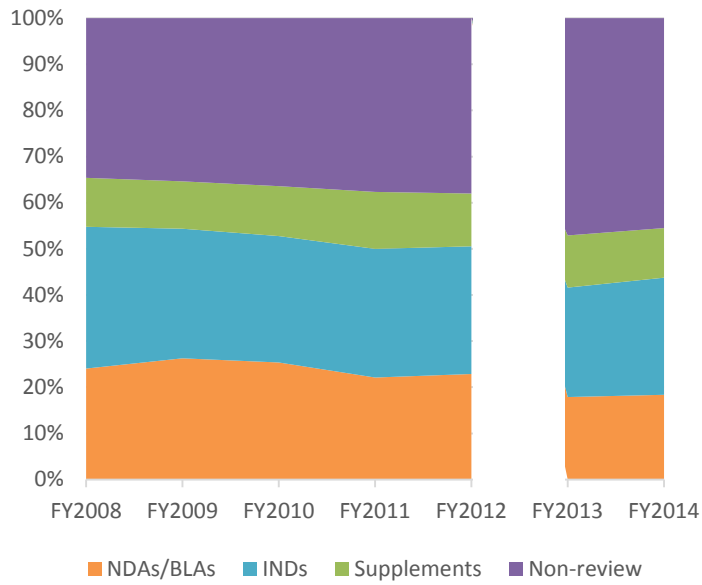
[6] The few remaining FDA SMEs expressed various degrees of uncertainty about whether total HDR workload tracks with submission volume.

Assumption 1, Corollary 1: Non-review HDR work varies in direct proportion to submission volume.

As noted above, the validity of Assumption 1 depends, in part, on the notion that non-review HDR workload varies in direct proportion to submission volume. The results described above for Assumption 1 suggest this might not be true. ERG conducted additional analyses focused on this corollary to Assumption 1 to gather additional information.

Compare rates of change of review and non-review HDR hours. ERG used CDER and CBER time reporting data to determine the number of hours expended each year, between FY2008 and FY2014, on review and non-review work. In general, non-review HDR hours rose at a greater pace than review HDR hours. Figure 3-3 shows the contributions of non-review work and review work (for the four submission types in the PDUFA Workload Adjuster, with hours for different types of supplements being combined because that is how the hours were provided to ERG for most years in this analysis). The results demonstrate that the share of time spent on non-review work increased between FY2008 and FY2013, then decreased slightly, although that could be an artifact of the change in CDER time reporting system.

Figure 3-3: Share of CDER and CBER HDR hours by submission/ work type

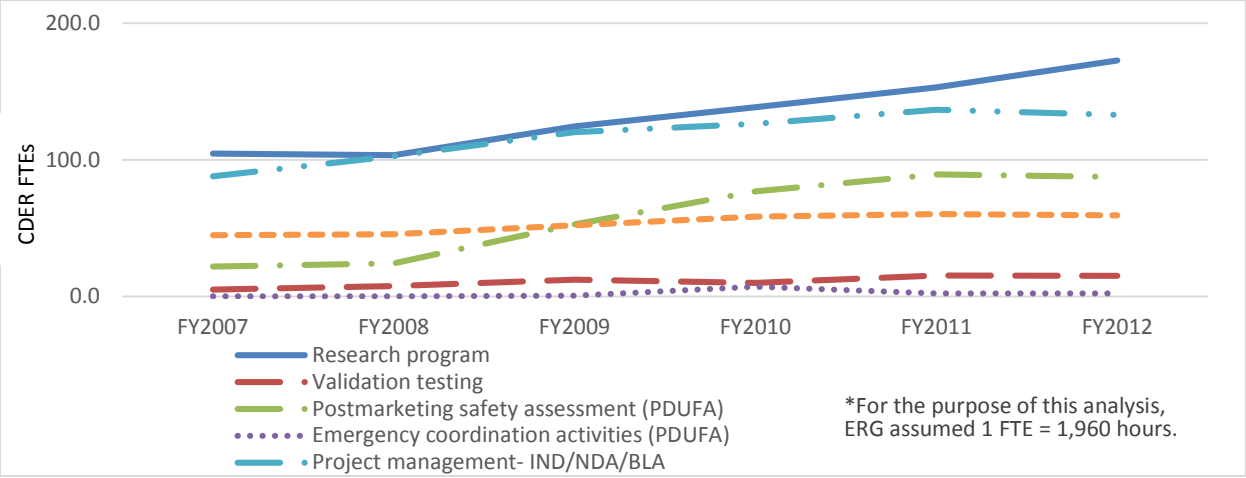


Note: CDER data not comparable before and after 2013 change in time reporting system.

***Test whether specific types of non-review workload vary in direct proportion to submission volume*.** ERG examined the extent to which specific types of non-review workload (as opposed to non-review workload as a whole) vary in direct proportion to submission volume, using two methods:

- **Measure workload by hours.** From FY2007 to FY2015, HDR hours (reported as FTEs) have increased by more than 100 percent for several non-review activities, such as research, validation testing, and postmarket safety assessment. Figure 3-4 shows representative data through FY2012.
- **Measure workload by activity counts.** ERG compared changes in the counts of some specific non-review activities (e.g., annual reports, TSIs, non-submission information requests and meetings) to changes in submission volume as measured in the PDUFA Workload Adjuster. In general, the rates of change were similar or inconclusive due to volatility or limitations in the data. Furthermore, analysis of the PDUFA workload inventory developed for this study reveals that activities for which counts are available represent only a portion of non-review workload.

Figure 3-4: CDER FTEs* for selected types of non-review HDR work



As a result, the available data were insufficient to sum activity-based workload to develop a profile of non-review workload as a whole.

Although the analysis of hours suggests the possibility that non-review workload outpaces submission volume, ERG considers the results to be inconclusive due to limitations in the data.

Analyze SME statements about rate of change of non-review HDR workload relative to submission volume. As indicated in the findings for Assumption 1 above, SMEs identified some types of non-review work not included in the Adjuster that outpace current HDR submission volume. For example:

- Postmarket work
- Policy and guidance work related to mandates outside of FDA control
- Responses to complex, urgent safety issues and emerging threats/health crises

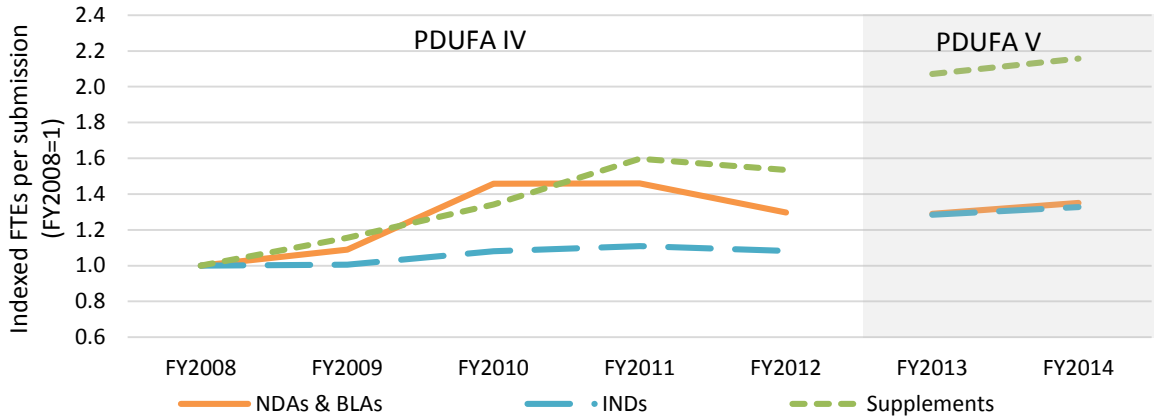
Combined with the results described above, these findings suggest that non-review HDR workload probably does not vary directly with submission volume – in which case submission volume might not accurately represent total HDR workload.

Assumption 1, Corollary 2: The average LOE per submission is constant throughout a 5-year PDUFA authorization.

As noted above, the validity of Assumption 1 depends in part on the notion that the average LOE per submission is constant throughout a 5-year PDUFA authorization period. ERG conducted analyses to estimate the average LOE per submission from FY2008 to FY2014.

Compare the average number of FTEs per submission each year. ERG used CDER and CBER time reporting data to calculate the average number of FTEs per submission for each submission type between FY2008 and FY2014. The results show increases in the average number of FTEs per submission ranging from 5 percent per year (INDs) to 19 percent per year (supplements); Figure 3-5 shows these results as indexed values to depict relative changes in average FTEs per submission as clearly as possible.

Figure 3-5: Indexed FTEs* per submission, by submission type

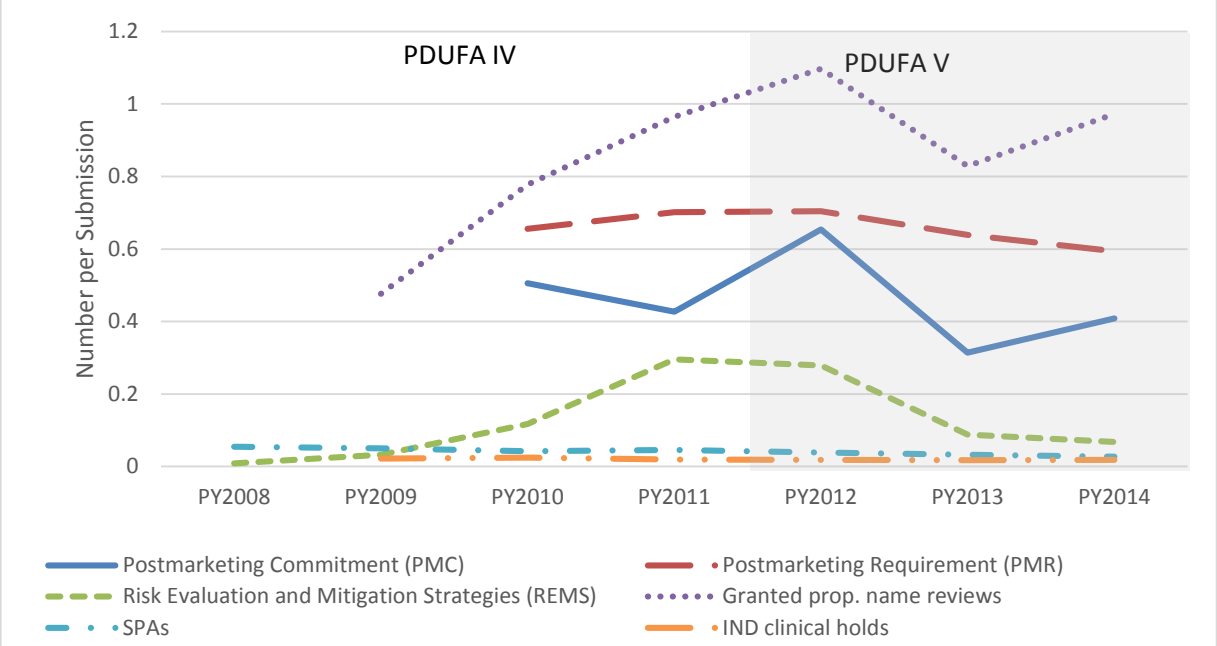


*Note: In 2013 CDER switched to a new time reporting system; therefore, data pre and post are not strictly comparable. *For the purpose of this analysis, ERG assumed 1 FTE = 1,960 hours.*

As noted previously, these results are unsurprising due to increases in FDA staffing that took place during PDUFA IV. Nevertheless, it is possible that the increases in average FTEs per submission represent increases in actual workload as well as staffing. To investigate that possibility further, ERG examined trends in the counts of time-intensive review activities as well as information from SMEs.

Test whether the volume of time-intensive submission activities/traits vary in direct proportion to submission volume. ERG identified a set of specific submission review activities that are time-intensive according to SMEs and our own analyses. Where counts were available, we then calculated activity counts per submission per year to determine whether the volume of time-intensive activities varies directly with submission volume (Figure 3-6). The results are inconclusive due to the high degree of variability in the numbers.

Figure 3-6: Number of time-intensive activities per submission per PDUFA Year (PY)



ERG also identified submission traits that are associated with increased work intensity (LOE) according to SMEs. We determined whether the volume of these traits varies in direct proportion to submission volume:

- For active commercial INDs, **Fast Track designations** outpaced submission volume by an average of 28% per year (in CDER) between PY2008 and PY2014. For NDAs/BLAs, on average Fast Track designations outpaced submission volume by 10% per year, but the data were too volatile to consider this result conclusive.
- For INDs and NDAs/BLAs, **Breakthrough Therapy designation** became available in 2013, so temporal trends cannot be identified. Nevertheless, this designation is believed by SMEs to be associated with a greater work intensity due to the associated increases in communications with sponsors. Therefore, use of this designation likely increases actual workload on a per-submission basis.
- For INDs and NDAs/BLAs, **QIDP designation** became available in July 2012, so temporal trends cannot be identified. Like the Breakthrough Therapy designation, the QIDP designation is likely to be associated with a greater work intensity, so use of this designation might increase actual workload on a per-submission basis. However, this designation is likely to impact only one CDER review division (which accounts for about 1% of FDA work hours), so ERG did not include this for consideration in potential alternatives to the current PDUFA Workload Adjuster.
- For NDAs/BLAs, **orphan designations** have been somewhat volatile relative to submission volume, revealing no clear trend.
- For NDAs/BLAs, the proportion of submissions with **NME status** has remained fairly stable, revealing no clear trend.
- For NDAs/BLAs, **priority reviews** outpaced submission volume by an average of 15% per year between PY2009 and PY2014.
- For NDAs/BLAs, the number of **accelerated approvals** has shown too much volatility to identify a clear trend relative to submission volume.

These results show that two time-intensive submission traits (Fast Track and priority review) have outpaced submission volume, and SMEs anticipate that Breakthrough Therapy will as well, suggesting that actual workload per submission might be increasing.

Determine whether communication-related workload varies directly with submission volume. FDA communicates with sponsors/applicants in many ways throughout the drug/biologic development process. Measurable types of communications include meetings (several types), written response only communications (in lieu of certain meetings), consults, and information requests. Other types of communications (e.g., informational telephone calls, emails, and other informal communications) are not readily measurable. ERG examined whether the volume of *measurable* communications varies directly with submission volume. The results generally show the volume of these communication types vary directly with submission counts. In recent years, a greater share of meeting requests have resulted in written responses only (which are counted as granted/completed meetings). Opinions vary on whether written responses only require similar or lower LOEs than meetings. We therefore consider the results for CDER IND meetings to be inconclusive. On the other hand, as described further below, FDA SMEs generally agree that demand for informal (non-measurable) communications is increasing.

Analyze SME statements about trends in workload per submission. Many SMEs interviewed for this study believe that actual workload per submission is increasing over time, primarily due to:

- Increased proportion of submissions involving complex or novel science and technology, which often require a greater LOE for review. (Of 45 FDA SMEs interviewed for this study, including those not involved in review work, 25 spontaneously identified this as a trend impacting workload.)
- Increased proportion of submissions with special designations — Breakthrough Therapy, Fast Track, priority review — that increase LOE on a per-submission basis. (Of 45 FDA SMEs, 20 spontaneously identified this as a trend impacting workload.)
- Increased demand for meetings and other communications, especially informal and other communications that are not measured, that add to total LOE per submission. (Of the 13 interviewees who spoke about communication demand, all 13 identified increased demand for communications as a trend impacting workload.)

Collectively, increases in certain LOE-intensive review designations and an apparent increase in demand for FDA-sponsor communications suggest that actual workload for submissions is probably increasing — in which case submission volume might not accurately represent total HDR workload.

3.2 Measurement of Submission Volume

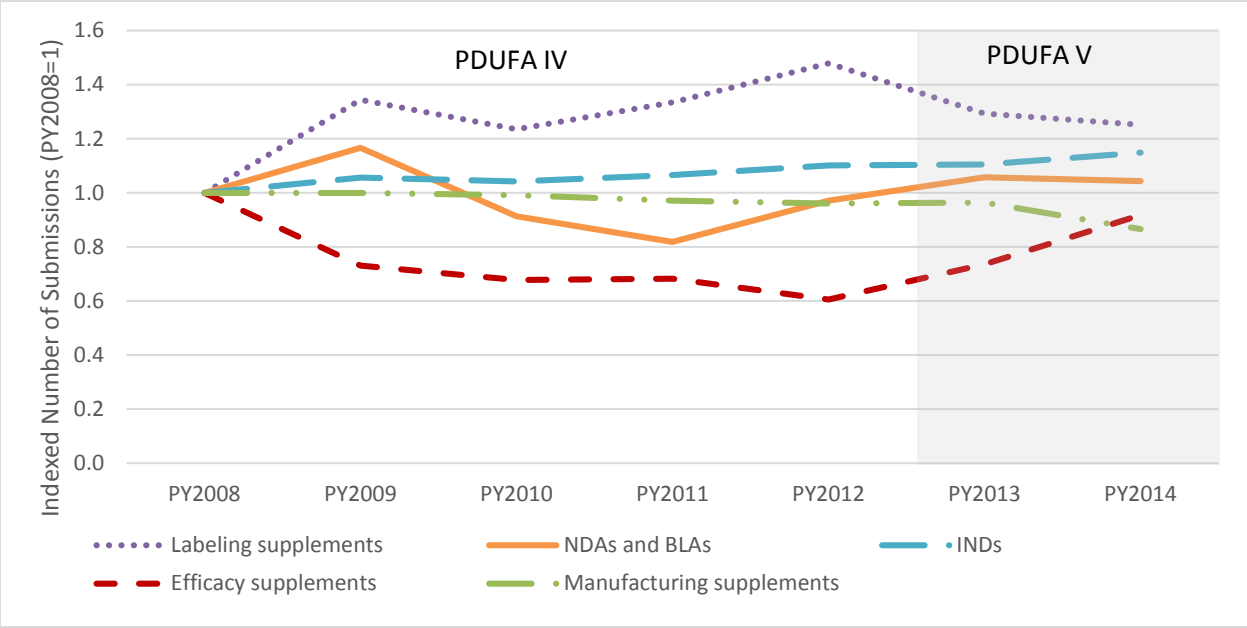
Assumption 2: Counts of active INDs, new NDAs/BLAs, new efficacy supplements, and new manufacturing supplements adequately represent total prescription human drug/biologic submission volume.

SMEs interviewed for this study indicated that the four submission types currently counted in the Adjuster probably do not fully represent prescription human drug/biologic submission volume. They suggested examining several other types of submissions: labeling supplements, research INDs, resubmissions, and amendments. ERG examined the submission types suggested by SMEs as part of our analysis for the corollary to Assumption 2 (below).

Assumption 2-Corollary 1: Counts of other types of submissions vary in direct proportion to the counts listed above.

Test whether the volume of other submission types varies in direct proportion to the volume of submission types in PDUFA Workload Adjuster. ERG compared temporal trends in the volume of labeling supplements, research INDs, resubmissions, and amendments with those for submission types represented in the Adjuster. We found that research IND volume tracks with commercial IND volume and that the volume of resubmissions and amendments are too volatile to identify a clear trend relative to original submission volume. On the other hand, the volume of labeling supplements has greatly outpaced the volume of other submission types between PY2008 and PY2014. Figure 3-7 shows indexed values to depict relative changes in submission volume as clearly as possible. Like manufacturing supplements, which are included in the PDUFA Workload Adjuster, labeling supplements comprise 3% of total HDR workload. This finding suggests that workload adjustments based only on four submission types might be imprecise.

Figure 3-7: Indexed submission counts, by submission type



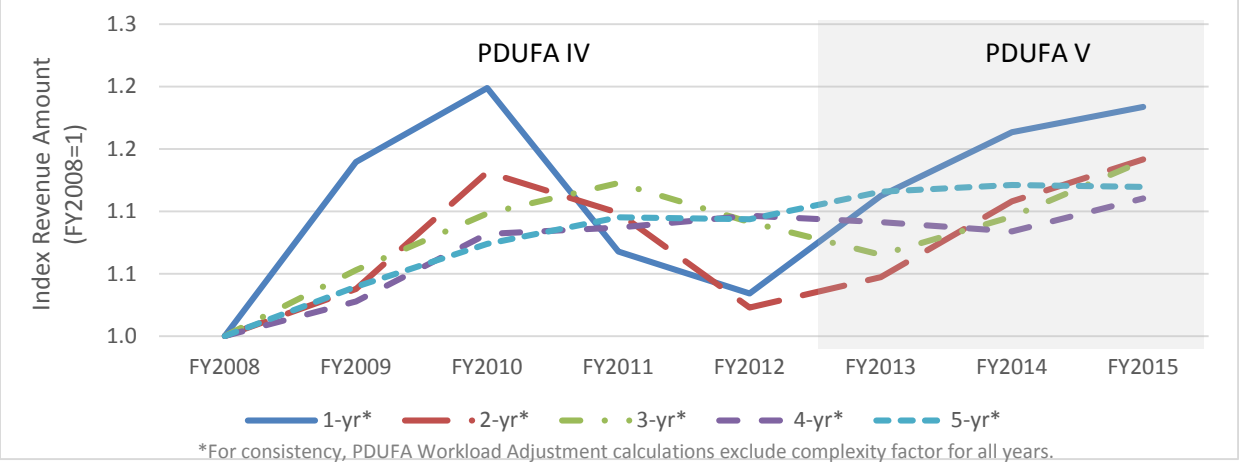
3.3 Calculation of Changes in Submission Volume

Assumption 3: Comparing a current 3-year rolling average to a base 3-year rolling average adequately balances the need for accurate calculation of submission volume changes and need for stability/predictability of resulting adjustments.

The PDUFA Workload Adjuster uses 3-year rolling averages for submission counts to smooth volatility. Using rolling averages can help to prevent revenue levels from being too influenced by short-run trends. In general, the larger the number of years in the rolling average, the lower the volatility – and vice versa.

Compare Adjuster results based on different rolling averages. ERG compared PDUFA Workload Adjuster outputs using 5-year, 4-year, 3-year, 2-year, and 1-year rolling averages. The resulting revenue amounts vary widely (Figure 3-8). Therefore, the choice of number of years in the rolling averages depends on stakeholder preferences regarding the tradeoff between sensitivity and stability.

Figure 3-8: Indexed revenue amounts from workload adjustments, by number of years in rolling average volume



*For consistency, PDUFA Workload Adjustment calculations exclude complexity factor for all years.

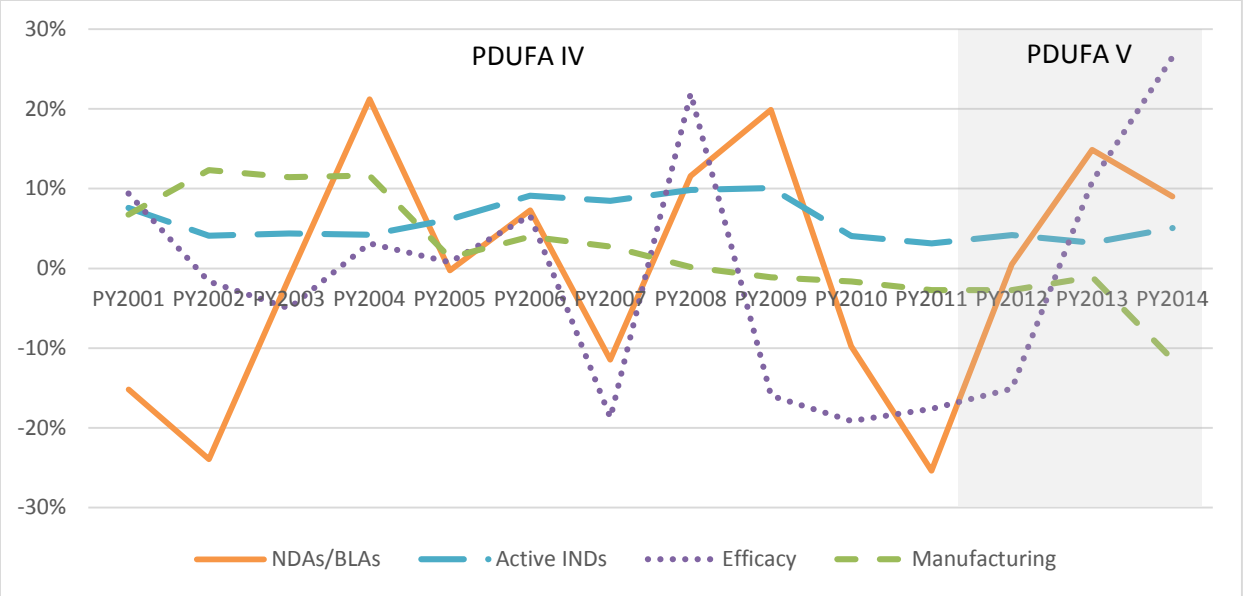
Analyze SME statements about the adequacy of comparing current 3-year rolling average to a base 3-year rolling average. SMEs interviewed for this study support the use of 3-year rolling averages in the PDUFA Workload Adjuster workload calculation.

Together, these findings suggest that use of a 3-year rolling average in volume calculations reasonably balances the need for sensitivity against the need for stability.

Assumption 4: Use of past submission counts can predict future HDR workload.

The PDUFA Workload Adjuster uses 3-year rolling averages of past (lagging) submission counts to approximate expected workload (measured by submission volume) the following year. To assess whether past submission counts can predict future submission volume, we compared 3-year rolling average submission counts ("predicted volume") with the actual submission counts for the next year. On average, the predicted volume per submission type is between 5 and 12 percent different from the actual submission count value, but the predicted volume can be up to 27 percent different from the actual value (Figure 3-9). The 3-year rolling average submission counts are closest to actual next-year counts for active commercial INDs and manufacturing supplements, with much greater variances observed for NDAs/BLAs and efficacy supplements. These results suggest that past submission counts are an imprecise predictor of future HDR workload volume.

Figure 3-9: Difference between lagging 3-year submission counts (predicted volume) and actual submission counts



3.4 Calculation of Weighting Factors

Assumption 5: Use of one year of data to calculate work units adequately balances the need for accurate calculation of work units and need for stability/predictability of resulting adjustments.

The submission counts and weighting factors used in the PDUFA Workload Adjuster are 3-year rolling averages. An early step in the weighting factor calculation – calculation of work units (standard cost weighting factors multiplied by submission counts) – is based on one year of data rather than rolling averages. For consistency in balancing the sensitivity and stability of workload adjustments, using 3-year rolling averages for work unit calculations might be a reasonable choice.

ERG calculated weighting factors and workload adjustments using 3-year rolling averages for work units. The results were similar to those generated by the current Adjuster (which uses one year of data for work units). This suggests that use of one year of data to calculate work units adequately balances needs for sensitivity and stability in workload adjustments, validating this assumption.

Assumption 6: Standard cost values from the PDUFA Standard Cost Model accurately represent the relative proportion of total submission volume represented by each submission type.

The Statement of Work for this contract asks ERG to consider whether changes in the use of standard costs (from the PDUFA Standard Cost Model) are warranted. To that end, ERG calculated weighting factors using HDR hours, then compared the resulting workload adjustments with those generated by the current Adjuster (which uses standard costs to calculate weighting factors). The results were similar (see Section 4.3), suggesting use of HDR hours is a reasonable choice if FDA should decide to discontinue reliance on the PDUFA Standard Cost Model. Use of HDR hours also simplifies the calculation of weighting factors.

Assumption 7: Normalizing weighting factors by the NME NDA standard cost serves a purpose.

When calculating weighting factors for the PDUFA Workload Adjuster, each weighting factor is normalized relative to the weight for NME NDAs. SMEs interviewed for this study stated that the rationale for normalizing standard costs by the NME NDA standard cost is unknown. They stated that any reasonable action to simplify the model, such as eliminating an unnecessary step, is desirable. Therefore, ERG compared weighting factors calculated with and without normalizing standard costs to an NME. Results are identical from PY2009 forward. Therefore, this normalization step is not needed (refuting the assumption that it serves a purpose), and the PDUFA Workload Adjuster could be simplified by its elimination.

4. PDUFA Workload Adjuster Alternatives

The PDUFA Workload Adjuster evaluation suggests that the model is not optimal across several dimensions. ERG conceptualized, built, tested, and assessed several alternatives to test whether the current Adjuster is the best feasible model available or whether alternatives might represent improvements. To do this, ERG identified the current model's main weaknesses, grouped them into categories, and developed strategies to overcome the weaknesses (Table 4-1). Many of the resulting alternatives, described further in the sections below, can be mixed and matched to work in combination with each other. Section 5 presents ERG's conclusions about the best feasible model available to FDA.

Table 4-1: PDUFA Workload Adjuster weaknesses and strategies to overcome them

Weakness of Current Model	Strategy to Overcome Weakness
The volume calculation does not capture: 1. Some important submission/work types (e.g., certain submissions, non-review work) 2. Changes in average LOE per submission	Alternative methods of calculating submission volume: 1. Add submission/work types that meet criteria for importance, measurability, and feasibility (labeling supplements)* 2. Weight submissions with measurable LOE drivers *ERG was unable to identify scientifically valid ways to add non-review work types due to measurability and feasibility issues. ***Or*** alternative method of calculating adjustments
The volume calculation is not flexible to accommodate changes in HDR workload based on submission/work types or LOE drivers that become important, measurable, and feasible	Optional mechanism to update submission volume calculation: 1. Add measurable submission/work types 2. Change/add measurable, feasible LOE drivers
Model is simple conceptually, but relies on complex data pulls and processing	Simpler methods of calculating weighting factors:* 1. Use HDR hours instead of standard costs 2. If retain standard costs, omit normalization step *ERG was unable to identify ways to simplify volume calculations because the *methodology* is already simple (but relies on complex data pulls and processing). ***Or*** alternative method of calculating adjustments
Model outputs (revenue adjustments) are not predictable enough for FDA to easily make timely resource allocation (and hiring) decisions to support adjustment-funded workload	Alternative method of calculating adjustments
Model does not account for unfulfilled demand	Optional addition of catch-up estimate for unfulfilled demand
Details of methodology and associated assumptions/justifications are not well documented	Clear documentation for any new model

4.1 Alternative Volume Calculations

The PDUFA Workload Adjuster currently measures workload in terms of volume – more specifically, in terms of submission volume. This results in two weaknesses, which require different strategies to overcome (Table 4-2).

Table 4-2: Alternatives to address weaknesses in PDUFA Workload Adjuster volume calculations

Weakness in Volume Calculation	Alternative Volume Calculation To Overcome Weakness
Does not include all important submission/work types	Add submission/work types to list of items included in model
Within the four types of submissions included, does not take into account differences in LOE for submissions with work-intensive attributes (LOE drivers)	Within each submission type, weight individual submissions with LOE drivers (multiply number of submissions with each LOE driver by an LOE factor that represents the additional workload associated with the driver)

To determine what submission/work types and LOE drivers to include in these alternatives, ERG analyzed our PDUFA workload inventory to identify items that:

- Represent an important contribution to workload, as determined by quantitative measures (contribution to total HDR hours) or qualitative assessments (of SME interview responses).
- Do not vary directly with the submission types in the Adjuster in terms of volume (because items that do very with these submission types are indirectly represented in the Adjuster).
- Are measurable (countable).
- Can feasibly be included in a volume calculation.

The PDUFA workload inventory items that meet these criteria are:

- Submission/work types: labeling supplements.
- LOE drivers: priority review, Breakthrough Therapy designation, Fast Track designation.

Appendix A provides more information about identification of submission/work types and LOE drivers to include in alternatives. ***We note that a major limitation of this approach is that we can include only PDUFA workload inventory items that are measurable and feasible based on data sources currently available to FDA.*** This problem is an important reason why the current PDUFA Workload Adjuster includes only four submission types and not other submission/work types – and why the complexity factor introduced to the Adjuster in PDUFA IV did not reflect all types of LOE drivers and was ultimately removed. Nevertheless, ERG explored alternative volume calculations with the identified submission/work types and LOE drivers to assess whether they might represent improvements over the current model.

Note: Currently, submission/work types may be included in volume calculations only if they have a standard cost from the PDUFA Standard Cost Model because standard costs are used to calculate weighting factors. If FDA adopts use of HDR hours instead of standard costs to calculate weighting factors (Section 4.3), it will be feasible to include submission/work types without standard costs.

We present the alternative volume calculations as follows:

- **Change 1: Add submission/work types that meet inclusion criteria.** Figure 4-1 illustrates the alternative volume calculation with labeling supplements as an additional submission/work type (Change 1 only). Note that other submission/work types could be added in similar fashion if they meet the inclusion criteria (and FDA adopts use of HDR hours to calculate weighting factors as noted above). Table 4-3 shows the workload adjustment calculations for FY2015 with this change. Addition of labeling supplements increases the workload adjustment from 7.49% (current model) to 7.68% (alternative).
- **Change 2: Add LOE drivers that meet inclusion criteria**. Figure 4-1 also illustrates the alternative volume calculation with weighting of submissions with LOE drivers: priority review, Breakthrough Therapy designation granted, and Fast Track designation granted (Change 2 only). To do this, we divided submission type counts into submissions with and without an LOE driver, then multiplied the number of submissions with an LOE driver by the LOE factor for that driver. Submissions with multiple LOE drivers are grouped with the LOE driver with the highest LOE factor. ERG used FDA workload estimates to derive the LOE factors.[7] ERG used the weighted submission counts to calculate current and base rolling averages to complete the volume calculation (Table 4-4, Table 4-5). Note that other LOE drivers could be added in similar fashion if they meet the inclusion criteria. For FY2015, weighting submission counts by LOE drivers increases the workload adjustment from 7.49% (current model) to 8.16% (alternative).
- **Changes 1 and 2 combined: Add both submission/work types and LOE drivers.** Figure 4-1 illustrates the alternative volume calculation with both labeling supplements added as a submission/work type and the submission counts weighted with LOE drivers (both Change 1 and Change 2). Table 4-6 shows the resulting calculations for FY2015: the workload adjustment increases from 7.49% (current model) to 8.24% (alternative).

Figure 4-2 shows workload adjustments from the current model and the volume calculation alternatives above for FY2008-FY2015.

Although the alternative volume calculations take into account measurable submission/work types and LOE drivers, they suffer from several limitations:

- They do not reflect submission/work types and LOE drivers that are not easily measurable or feasible to include in the model based on data sources currently available to FDA.
- Like the current model, they rely on lagging indicators of workload (past submission counts).
- They do not improve the predictability of model outputs.
- They make the model less straightforward rather than more straightforward.

ERG's assessment of these alternative volume calculations is summarized in Table 4-7.

[7] These LOE factors are based on expert FDA judgment and are used internally. They have not been validated.

Figure 4-1. PDUFA Workload Adjuster with alternative volume calculation: Add labeling supplements as another submission/work type

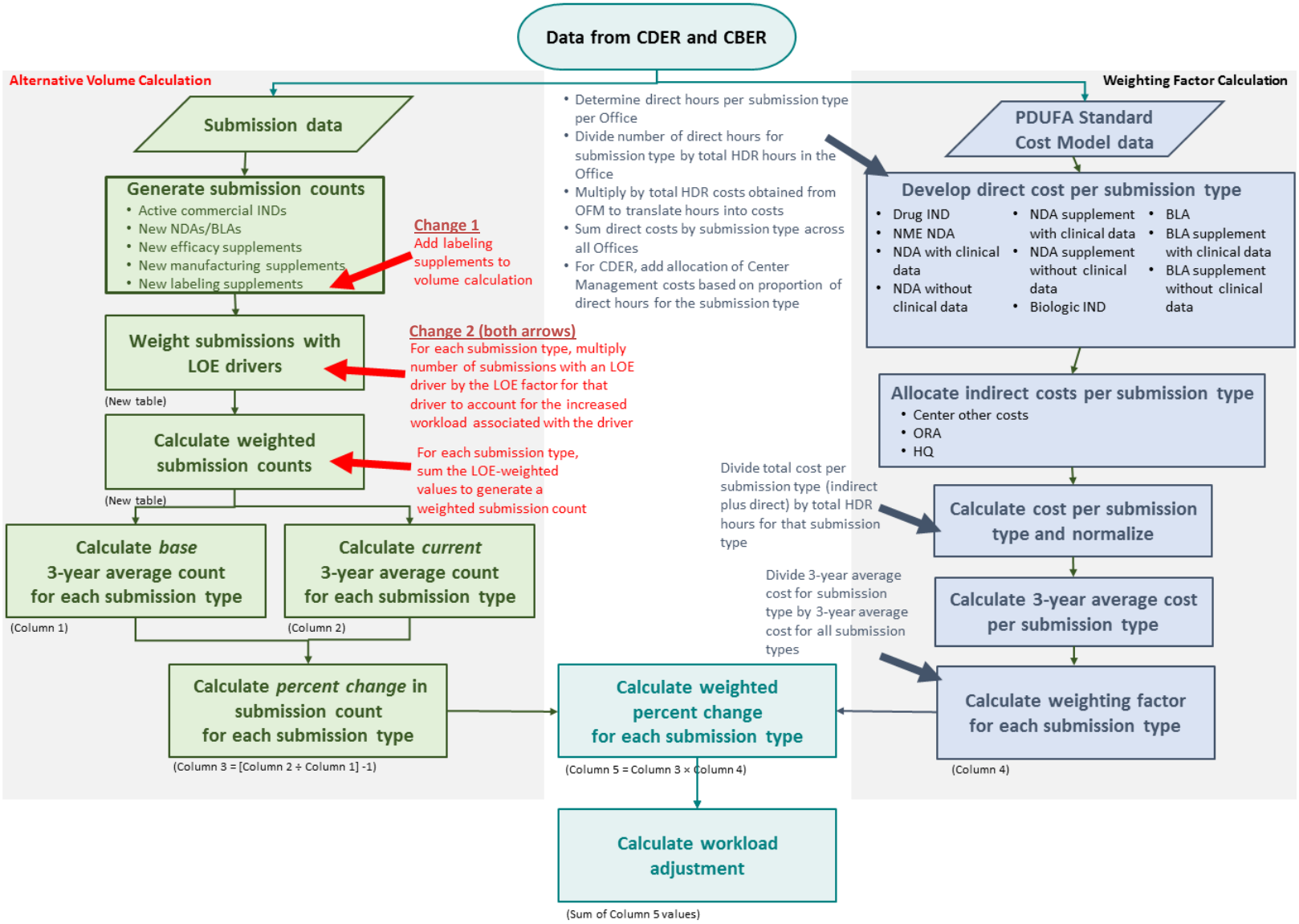


Table 4-3: FY2015 PDUFA workload adjustment with alternative volume calculation: Add submission/work types that meet inclusion criteria

Submission Type	3-Year average base years (2010-2012)	3-Year average 2012-2014	Percent change (Column 1 to Column 2)	Weighting factor (percent)	Weighted percent change
	Column 1	Column 2	Column 3	Column 4	Column 5
New NDAs/BLAs	124	141	13.68%	37.30%	5.11%
Active commercial INDs	6,830	7,141	4.56%	41.40%	1.89%
Efficacy supplements	136	157	14.97%	7.50%	1.13%
Manufacturing & labeling supplements [a]	3,782	3,659	-3.23%	13.80%	-0.45%
FY2015 Workload Adjustment					**7.68%**

[a] The PDUFA Standard Cost Model does not provide a separate standard cost for labeling supplements. Therefore, ERG used the standard cost for "supplements without clinical" as a *conservative* value for weighting factor calculation. Since this standard cost is also used for manufacturing supplements, we combined manufacturing and labeling supplements. *If FDA adopts use of HDR hours instead of standard costs for weighting factor calculations, use of an inaccurate standard cost for labeling supplements can be avoided.*

Table 4-4: FY2015 PDUFA workload adjustment with alternative volume calculation: Add LOE drivers* that meet inclusion criteria

Submission Type	Adjusted 3-Year average base years (2010-2012)	Adjusted 3-Year average 2012-2014	Percent change (Column 1 to Column 2)	Weighting factor (percent)	Weighted percent change
	Column 1	Column 2	Column 3	Column 4	Column 5
New NDAs/BLAs	128	147	15.25%	37.30%	5.69%
Active commercial INDs	6,836	7,159	4.73%	41.40%	1.96%
Efficacy supplements	139	159	14.99%	7.50%	1.13%
Manufacturing supplements	2,548	2,434	-4.50%	13.80%	-0.62%
FY2015 Workload Adjustment					**8.16%**

*Priority review, Breakthrough Therapy designation, Fast Track designation.

Table 4-5: Supporting table: Calculation of weighted submission counts (for columns 1 and 2)

Designation	Submissions		LOE Factor (Ratio of LOE with des. : without des.)	Adjusted Value	
	Base Years 2010-2012	Latest Years 2012-2014		Base Years 2010-2012	Latest Years 2012-2014
NDAs/BLAs					
No designation	93.7	103.0	1.00	93.7	103.0
Breakthrough Therapy	0.0	3.3	1.60	0.0	5.3
Priority review [a]	23.7	28.0	1.11	26.2	31.1
Fast Track [a]	7.0	7.0	1.11	7.8	7.8
Total				**127.7**	**147.1**
Active Commercial INDs [b]					
No designation	6,779.3	7,059.7	1.00	6,779.3	7,059.7
Breakthrough Therapy	0.0	17.3	1.60	0.0	27.7
Priority review	N/A	N/A	N/A	N/A	N/A
Fast Track [a]	50.7	64.7	1.11	56.2	71.7
Total				**6,835.5**	**7,159.1**
Efficacy Supplements					
No designation	107.0	121.7	1.00	107.0	121.7
Breakthrough Therapy [c]	N/A	N/A	N/A	N/A	N/A
Priority review [d]	29.3	35.0	1.08	31.6	37.7
Fast Track	N/A	N/A	N/A	N/A	N/A
Total				**138.6**	**159.4**
Manufacturing & Labeling Supplements [e]					
No designation	3,781.6	3,659.4	1.00	3,781.6	3,659.4
Breakthrough Therapy [c]	N/A	N/A	N/A	N/A	N/A
Priority review [d]	N/A	N/A	N/A	N/A	N/A
Fast Track	N/A	N/A	N/A	N/A	N/A
Total				**3,781.6**	**3,659.4**

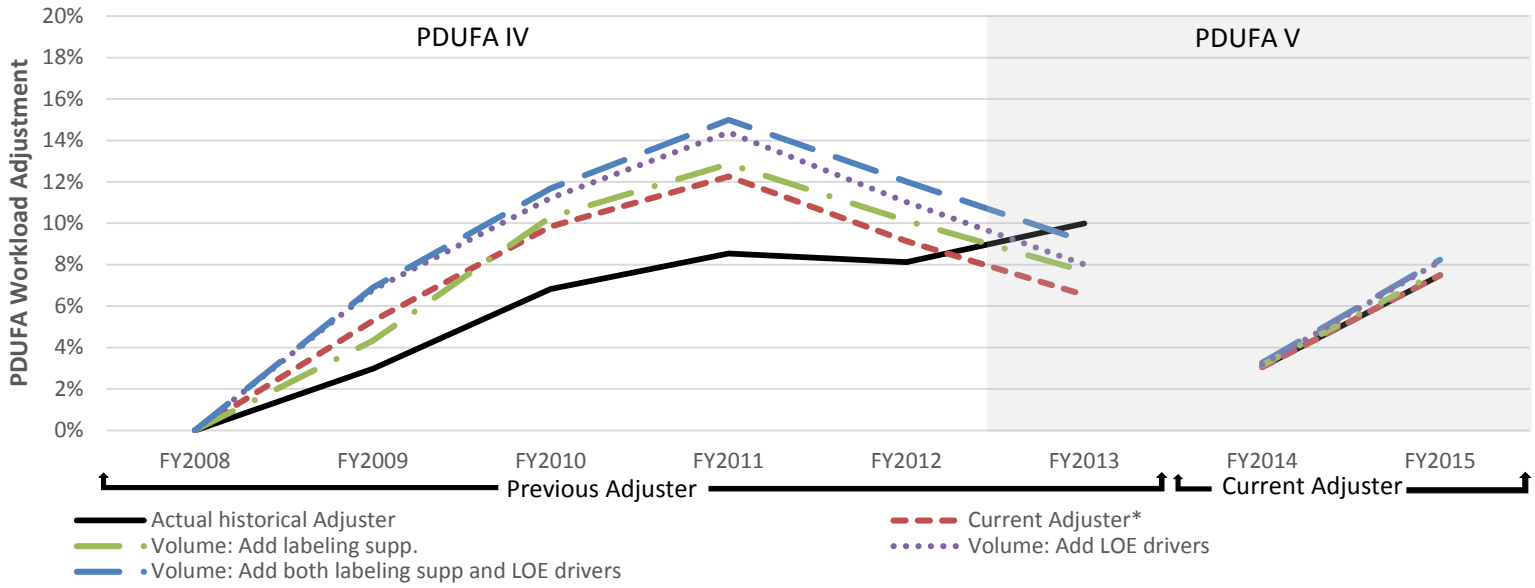
Note: If a submission has multiple designations, apply only one LOE factor in this order: Breakthrough Therapy, priority review, Fast Track.
[a] For Fast Track and priority, average ratios for NME and non-NME.
[b] IND counts with special designations might be underestimated because CBER data on Breakthrough Therapy and Fast Track designations for INDs are unavailable. NDA/BLA counts with special designations might be underestimated because they might not include those that received designations during IND stage.
[c] Some supplement may have Breakthrough Therapy designation; however, the additional LOE is relatively small and so we do not include these.
[d] For supplement with priority review, use ratio for non-NME.
[e] ERG combined manufacturing and labeling supplements as noted in Table 4-3.

Table 4-6: FY2015 PDUFA workload adjustment with alternative volume calculation: add both submission/work type and LOE drivers

Submission Type	Adjusted 3-Year average base years (2010-2012)	Adjusted 3-Year average 2012-2014	Percent change (Column 1 to Column 2)	Weighting factor (percent)	Weighted percent change
	Column 1	Column 2	Column 3	Column 4	Column 5
New NDAs/BLAs	128	147	15.25%	37.30%	5.69%
Active commercial INDs	6,836	7,159	4.69%	41.40%	1.94%
Efficacy supplements	139	159	13.71%	7.50%	1.03%
Manufacturing & labeling supplements [a]	3,782	3,659	-3.23%	13.80%	-0.45%
FY2015 Workload Adjustment					**8.24%**

[a] ERG combined manufacturing and labeling supplements as noted in Table 4-3.
Note: See Table 4-5 for supporting table for adjusted counts.

Figure 4-2: PDUFA workload adjustments using current model versus alternative volume calculations, FY2008 to FY2015



**For consistency, this set of calculations applies the current formula historically (i.e., using 3-yr averages and excluding complexity factor).*

Table 4-7: Acceptance criteria for PDUFA Workload Adjuster with alternative volume calculations

Criterion	Assessment: Current Model	Alternative Volume Calculations: Add Labeling Supplements	Alternative Volume Calculations: Weight by LOE Drivers	Justification for Assessment
Accurate	Not optimal	Improved, but still not optimal *(model will directly capture 46% instead of 43% of HDR workload)*	Improved, but still not optimal *(increases workload adjustment, but selection of LOE drivers might not be scientifically valid)*	Important aspects of HDR workload are still excluded from the model due to data limitations.
Defensible	Not optimal	Not optimal	Not optimal	Alternative volume calculations do not resolve all of the weaknesses related to the model's foundational assumptions.
Feasible	Yes	Yes	Yes	Model works with existing tools and data sources.
Stable	Yes	Yes	Yes	Between FY2008 and FY2015, the mean annual change in Adjuster outputs (relative to year before, or 0 in first PDUFA year) is 2.1, the variance is 0.11, and the coefficient of determination is 18.8 -- smaller than that with the current model (83.1). Adjustments are more stable with the alternative volume calculations than with the current model.
Predictable	Not optimal	Not optimal	Not optimal	No improvement over current model.
Straightforward	Not optimal	Not optimal	Less optimal *(weighting volume by LOE drivers* slightly adds to model complexity*)*	Although alternatives are still simple conceptually, they rely on complex data pulls and processing – even more so than with the current model.
Transparent	Not optimal	Not optimal	Not optimal	Details of methodology would still not be obvious to FDA staff not closely involved in implementing workload adjustment calculations.
Flexible	No	No	No	Still cannot accommodate future changes in HDR workload associated with new initiatives or requirements unless optional update mechanism is used (Section 4.2).

4.2 Optional Mechanism for Updating Volume Calculations

This evaluation of the PDUFA Workload Adjuster underscores that workload for various types of HDR work, and LOE drivers for those types of work, can change over time. Therefore, it might be useful for FDA to have a mechanism for updating (1) the submission/work types included in the volume calculation and (2) the LOE drivers used to weight submissions or counts of other types of work. In terms of model mechanics, it would be straightforward to update the list of submission/work types and LOE drivers in the model. More challenging would be the task to decide whether, when, and how to make such changes. If FDA wishes, the Agency could do so by:

- Maintaining the PDUFA workload inventory developed for this evaluation.
- Regularly updating the tables of submission/work types and LOE drivers.
- Regularly analyzing the results to determine whether any other submission/work types or LOE drivers meet the inclusion criteria (or whether any no longer meet the inclusion criteria).
- Vetting the identified submission/work types and LOE drivers to obtain consensus that it is reasonable and feasible to update the submission/work types and LOE drivers accordingly.
- For LOE drivers, developing LOE factors based on expert estimates and judgment.
- Testing the updated volume calculations to ensure they perform as expected.

ERG poses this as an option for future consideration. As noted above, this option will be feasible only if FDA adopts use of HDR hours instead of standard costs to calculate weighting factors (Section 4.3). This is because the PDUFA Standard Cost Model does not produce standard costs for other submission/work types in the HDR program.

4.3 Alternative Weighting Factor Calculations

The PDUFA Workload Adjuster currently adjusts submission volumes by weighting factors to account for the contribution of each submission type to total submission review work. The weighting factors are calculated based on standard costs from the PDUFA Standard Cost Model. This method contributes to the complexity of the data pulls and processing required for the current Adjuster. ERG identified alternatives to address this issue (Table 4-8).

Table 4-8: Alternatives to address weakness in PDUFA Workload Adjuster weighting factor calculations

Weakness in Weighting Factor Calculation	Alternative Weighting Factor Calculation To Overcome Weakness
Model is simple conceptually, but relies on complex data pulls and processing	Simpler methods of calculating weighting factors: 1. If retain standard costs, omit normalization step 2. Use HDR hours instead of standard costs

We present the alternative weighting factor calculations as follows:

- **Omit normalization step.** As explained in Section 3, standard costs for submission types in the Adjuster are normalized by the NME NDA standard cost as part of weighting factor calculations.

Omitting this step produces the same results from FY2009 forward. Because this is a simple change, we do not provide a diagram for this alternative (simply omit normalization step in current model) or a workload adjustment calculation table (values same as current model).

- **Use HDR hours instead of standard costs.** We note that the PDUFA Standard Cost Model relies on time reporting data to produce standard costs for submission types; therefore, both the current PDUFA Workload Adjuster and this alternative ultimately rely on time reporting data. This alternative simplifies weighting factor calculation by removing the steps associated with standard costs. Figure 4-3 illustrates the alternative weighting factor calculation using HDR hours (CDER and CBER time reporting data) instead of standard costs. Table 4-9 shows the FY2015 workload adjustment produced using the alternative weighting factors; the adjustment decreases from 7.49% (current model) to 7.08% (alternative). Figure 4-4 shows PDUFA workload adjustments for the current model versus this alternative for FY2008 to FY2015.

The first weighting factor calculation alternative (omitting normalization step) simplifies the PDUFA Workload Adjuster slightly, while the second alternative (use HDR hours) significantly simplifies the weighting factor portion of the model, making it more straightforward and transparent. It also provides a method of calculating weighting factors in case the PDUFA Standard Cost Model is discontinued. In addition, use of HDR hours instead of standard costs permits inclusion of additional submission/work types in volume calculations (Section 4.1) because submission/work types will no longer be limited to those associated with a standard cost from the PDUFA Standard Cost Model. Even labeling supplements do not have a separate standard cost, so use of HDR hours instead of standard costs would avoid the need to use an inaccurate standard cost (that for manufacturing supplements) for labeling supplements.

ERG's assessment of these alternative volume calculations is summarized in Table 4-10.

Figure 4-3: Workload Adjustments with alternative weighting factor calculations

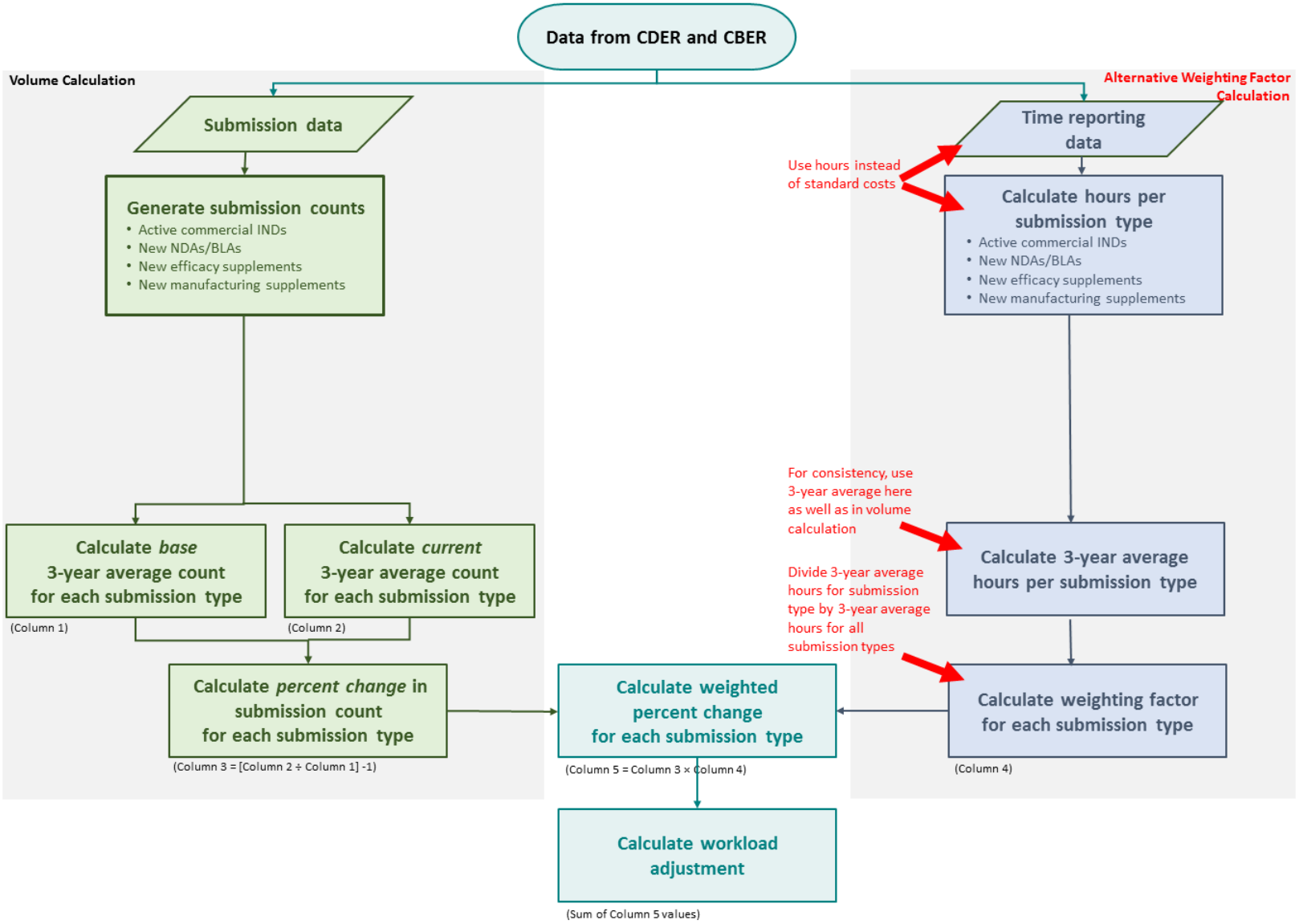
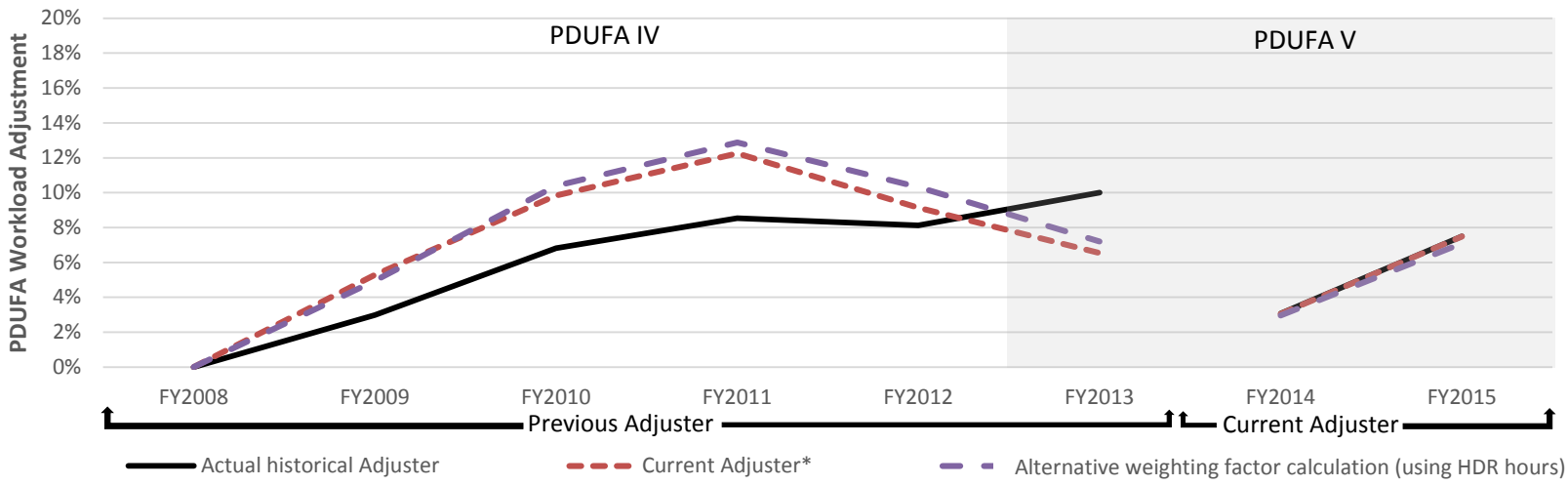


Table 4-9: FY2015 PDUFA workload adjustment with alternative weighting factor calculations: Use HDR hours instead of standard costs

Submission Type	3-Year average base years (2010-2012)	3-Year average 2012-2014	Percent change (Column 1 to Column 2)	Weighting factor (percent)	Weighted percent change
	Column 1	Column 2	Column 3	Column 4	Column 5
New NDAs/BLAs	124	141	13.68%	45.4%	6.20%
Active commercial INDs	6,830	7,141	4.56%	34.6%	1.58%
Supplements [a]	2,685	2,590	-3.51%	20.1%	-0.70%
FY2015 Workload Adjustment					**7.08%**

[a] ERG combined efficacy and manufacturing supplement hours because they are combined in the CBER time reporting data made available to us. CDER time reporting data disaggregate hours by supplement types. If disaggregated hours from CBER become available, it will be possible to have a separate line item for each supplement type.

Figure 4-4: PDUFA workload adjustments using current model versus alternative weighting factor calculations (use HDR hours instead of standard costs), FY2008 to FY2015



**For consistency, this set of calculations applies the current formula historically (i.e., using 3-yr averages and excluding complexity factor).*

Table 4-10: Acceptance criteria for PDUFA Workload Adjuster with alternative weighting factor calculations

Criterion	Assessment: Current Model	Assessment: Omit Normalization	Assessment: Use HDR Hours Instead of Standard Costs	Justification for Assessment
Accurate	Not optimal	Not optimal	Improved, but still not optimal	Use of HDR hours would permit inclusion of additional submission/work types in volume calculations, if FDA decides to do so. However, important aspects of HDR workload are still excluded from the model due to data limitations.
Defensible	Not optimal	Not optimal	Not optimal	Some of the foundational assumptions underlying the model are still not valid.
Feasible	Yes	Yes	Yes	The model works with existing tools and data sources.
Stable	Yes	Yes	Yes	Stability is very similar to current model.
Predictable	Not optimal	Not optimal	Not optimal	No improvement over current model.
Straightforward	Not optimal	Slightly improved, but still not optimal	Improved, but still not optimal	Although the alternatives simplify weighting factor calculation slightly (omit normalization) or substantially (use HDR hours), the model as a whole still relies on complex data pulls and processing.
Transparent	Not optimal	Slightly improved, but still not optimal	Improved, but still not optimal	Although the weighting factor calculation would be more transparent, details of methodology as a whole would still not be obvious to FDA staff not closely involved in adjustment calculations unless FDA develops clear documentation.
Flexible	No	No	No	No improvement over current model.

4.4 Static Approach

The alternative volume and weighting factor calculations presented above do not resolve most of the weaknesses identified with the current PDUFA Workload Adjuster. Another alternative would be to replace the current PDUFA Workload Adjuster with a fixed (or static) adjustment to be used throughout a 5-year PDUFA authorization. The main challenge associated with this alternative is selecting an appropriate value for the workload adjustment.

ERG tested three methods of determining a static workload adjustment value, all based on *marginal* PDUFA workload adjustments from FY2003 to FY2015. As shown in Table 4-11, the PDUFA workload adjustment is cumulative throughout a 5-year PDUFA authorization because the adjustment is always relative to the base year. To calculate a static adjustment that can be applied every year throughout a

5-year PDUFA cycle, ERG used marginal adjustments (difference between current FY adjustment and previous FY adjustment) as the basis for calculations. The three methods of determining a static workload adjustment value that ERG tested are:

- **Method 1:** Calculate the mean marginal workload adjustment.
- **Method 2:** Calculate the mean marginal workload adjustment, excluding the high and low values to mitigate the impact of outliers.
- **Method 3:** Calculate the median marginal workload adjustment.

Table 4-11 shows these calculations, while Figure 4-5 compares the resulting static adjustments with historical adjustments.

Use of a static PDUFA workload adjustment to be used throughout an entire 5-year PDUFA authorization offers two advantages compared to the current PDUFA Workload Adjuster: it sidesteps challenging accuracy and defensibility issues that stem from limitations in available data, and it is a feasible method of greatly improving stability, predictability, straightforwardness, and transparency. On the other hand, this alternative has significant weaknesses: it separates PDUFA workload adjustments from any measure of HDR workload, it assumes that HDR workload will continually trend in the same direction, and it creates a circular reference (because calculation of the adjustment refers back to calculated adjustments). Table 4-12 presents ERG's assessment of this alternative.

Table 4-11: Calculation of a static workload adjustment

Fiscal Year	Year in PDUFA Authorization	Workload Adjustment for FY	Marginal Workload Adjustment
2003	1	N/A	N/A
2004	2	-1.39%	-1.39%
2005	3	1.47%	2.86%
2006	4	1.43%	-0.04%
2007	5	6.30%	4.88%
2008	1	11.72%	5.42%
2009	2	2.98%	2.98%
2010	3	6.82%	3.84%
2011	4	8.54%	1.72%
2012	5	8.12%	-0.42%
2013	1	10.00%	1.88%
2014	2	3.07%	3.07%
2015	3	7.49%	4.42%
		Method 1: Mean marginal workload adjustment	2.43%
		Method 2: Mean marginal workload adjustment, excluding high and low values	2.52%
		Method 3: Median marginal workload adjustment	2.92%

Figure 4-5: PDUFA workload adjustments: historical versus alternative static values

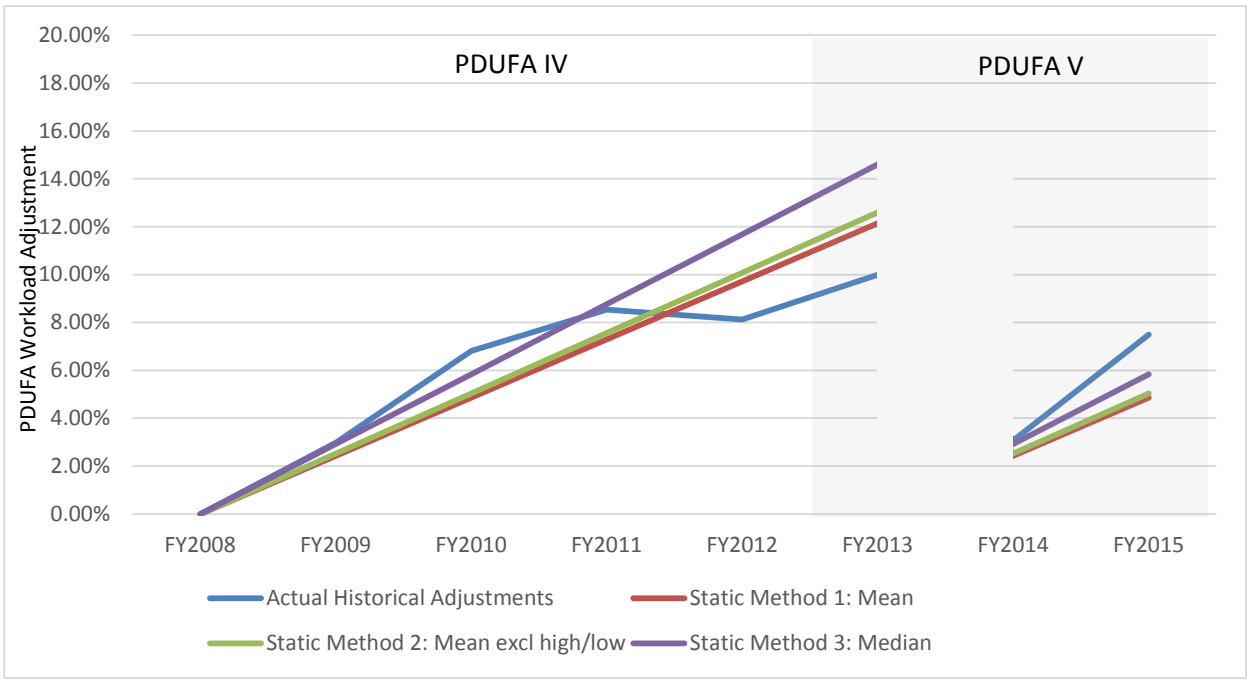


Table 4-12: Acceptance criteria for calculation of static workload adjustments

Criterion	Assessment: Current Model	Assessment: Static Alternative	Justification for Assessment
Accurate	Not optimal	No	Accuracy cannot be assessed scientifically, except in comparison to historical values or other alternatives.
Defensible	Not optimal	No	Method has methodological weaknesses.
Feasible	Yes	Yes	Based on readily available data and tools.
Stable	Yes	Yes	Would result in same adjustment each year.
Predictable	Not optimal	Yes	Adjustments for 5 years would be known at beginning of a new PDUFA authorization.
Straightforward	Not optimal	Yes	Calculation is simple, without reliance on complex methods, data pulls, or data processing.
Transparent	Not optimal	Yes	Calculation is clear and easily explained.
Flexible	No	No	Static value would be updated only every 5 years.

4.5 Optional Catch-Up Estimate

In interviews, a few FDA SMEs raised the issue of accounting for unfulfilled HDR work demand. They noted that the current PDUFA Workload Adjuster does not count unfulfilled demand, such as backlogs of unreviewed labeling supplements that do not have PDUFA goal dates as part of the current workload. Identifying, verifying, and quantifying all types of unfulfilled demand in the HDR program was outside the scope of this evaluation. Nevertheless, ERG conceptualized a basic approach to monetizing unfulfilled demand to develop a catch-up estimate — or added amount of funding — to help realign resources to reflect actual HDR workload, including unfulfilled demand:

- **Step 1: Identify categories** of unfulfilled demand in the HDR program, based on further study.
  Example: Unreviewed labeling supplements in backlog.
- **Step 2: Quantify each type** of unfulfilled demand, based on available data or expert estimates.
  Example: Number of labeling supplements in backlog.
- **Step 3: Monetize each type** of unfulfilled demand on a per unit basis.
  Example: Number of labeling supplements in backlog multiplied by average review cost per labeling supplement.

Conceptually, this approach provides a method of adding PDUFA funding to meet unfulfilled HDR program demand – and it is flexible to incorporate any type of unmet demand that can be measured or estimated. On the other hand, adding an optional catch-up estimate could increase concern about the stability of PDUFA revenue adjustments and increase concern about the defensibility of the results if catch-up calculations require additional assumptions and estimates.

5. Findings and Recommendations

In this PDUFA Workload Adjuster evaluation, ERG found that the current model is not optimal across several dimensions: "Accurate," "Defensible," "Predictable," "Straightforward," "Transparent," and "Flexible." Nevertheless, it could be the best feasible model available to FDA if alternatives do not represent meaningful improvements along these dimensions.

Based on all available evidence, ERG concludes that the choice between retaining some version of the current PDUFA Workload Adjuster and shifting to an entirely new method is a subjective one. The current model is likely imprecise, but it is well-established, well-known, and provides continuity with the past 13 years of PDUFA workload adjustment practice. Implementing a new approach to develop a static adjustment introduces uncertainties about its validity and how it will perform relative to the known approach of the current model – but it greatly improves the predictability of outputs. In light of these tradeoffs, ERG offers the following recommendations:

1. Retain the PDUFA Workload Adjuster (i.e., do not replace it with a static adjustment).
2. Refine the current version of the Adjuster by adding labeling supplements to the list of submission types included in the volume calculations.

   Note: ERG also provides an optional mechanism for periodically reassessing whether other submission or work types should be included in the volume calculations.
3. Do not weight submissions with measurable LOE drivers. Although this alternative would likely capture more HDR workload, it would increase the complexity of the model without accounting for all types LOE drivers. Selecting LOE drivers that are measurable and feasible — while omitting other LOE drivers because they are not measurable or feasible — has the potential to skew results.
4. Refine the current version of the Adjuster by using HDR hours instead of standard costs in weighting factor calculations because this simplifies the model while producing similar results — and facilitates inclusion of additional submission/work types in volume calculations if FDA decides to do so.

ERG also recommends exploring the nature and scope of unfulfilled demand in the HDR program in order to identify, verify, quantify, and monetize each type of unfulfilled demand. Doing so will provide (1) a more complete picture of total HDR workload for management consideration and (2) a foundation for determining whether it would be beneficial to develop a catch-up estimate to fund efforts to address unfulfilled demand.

Appendix A: Workload Inventory

The PDUFA workload inventory is a workbook that includes several components encompassing major categories of HDR work:

- Review of active commercial INDs
- Review of research INDs
- Review of NDA/BLAs
- Review of efficacy supplements
- Review of manufacturing supplements
- Review of labeling supplements
- Additional work associated with special designations: Fast Track, Breakthrough Therapy, accelerated approval, priority review, QIDP, orphan drug, NME NDA or original BLA (the Program).
- Other drug/biologic development support outside of submissions
- Postmarket work: PMRs/PMCs, post-approval review of labeling and advertising, clinical trial phase IV commitments, postmarket safety surveillance, lot release, postmarket reporting.
- Non-review activities: Center/program management, enforcement activities, regulatory science activities, science and research, training, other non-review activities.

For each major category of HDR work, rows represent specific work activities at three levels of granularity (primary, secondary, tertiary) where appropriate. For each activity or row, columns provide information about the activity:

- Activity name
- Purpose
- Responsible FDA office/division
- Contribution to overall LOE for the category of work
- Contribution to overall LOE for all of HDR work
- Whether the activity meets criteria for being considered a workload driver
- Whether the activity is measurable and whether it could feasibly be incorporated into an alternative version of the PDUFA Workload Adjuster

To create the PDUFA workload inventory, ERG first developed a set of process diagrams for the major categories of HDR work based on publicly available information and other references provided by FDA. We verified and elaborated on the activities within the process diagrams through additional research and interviews with FDA SMEs, then built the framework for the inventory (worksheets for major categories of work and rows for activities within the major categories). ERG then used a combination of interview results and FY2014 submission counts and FDA time reporting data to populate the inventory.

For this appendix, ERG has not provided a list of activities (rows) in the PDUFA workload inventory for each major category of HDR work because they are too numerous. Instead, we provide an example process map (Appendix B) that shows work activities at a high level of aggregation to illustrate basic types of process steps and activities included.

In the PDUFA workload inventory, three criteria contribute to a determination that an activity might be a driver of HDR workload:

- Do interview results indicate that the activity is a workload driver?

  FDA SMEs interviewed for this study identified an activity as being a potential workload driver if it represents a large proportion of HDR work, increases review LOE on a per-submission basis, and/or is not included as a type of work in the PDUFA Workload Adjuster. To err on the side of inclusiveness, ERG listed all such activities, even if they were associated with a low level of confidence on the part of SMEs.

- Do time reporting data indicate that the activity is a workload driver?

  ERG determined that an HDR activity might be a workload driver if it represents over 9% of total HDR hours. ERG used the 9% value as a general barometer (not a strict rule) based on patterns in the time reporting data (natural breaks in distributions of hours for larger or smaller contributors to total HDR hours).

- Does workload for the activity change at a rate that differs from submission volumes?

  Some categories of HDR work, or activities within the categories, might not be included in the PDUFA Workload Adjuster, but could be represented indirectly if the associated workload changes at the same rate as the submission types in the Adjuster. ERG considered HDR work categories/activities to be potential workload drivers if the associated workload changes at a different rate than the submission types already included in the Adjuster.

For potential workload drivers, ERG added more information to determine whether the activity could be included in an alternative version of the PDUFA Workload Adjuster: Is the activity measurable? If so, is it feasible to include the measurement in an alternative model (based on methodological requirements)?

Analysis of the data in the PDUFA workload inventory revealed two types of potential workload drivers that should be treated differently in any alternative version of the PDUFA Workload Adjuster:

- LOE drivers that increase LOE per submission
- Types of work that are not currently represented in the Adjuster

Table A-1 and Table A-2 provide information about workload drivers that ERG determined could be included in an alternative version of the PDUFA Workload Adjuster. A list of additional potential workload drivers follows in Tables A-3 and A-4.

Table A-1: Workload drivers: LOE

Potential Driver	LOE Driver as Determined by			Driver?	Measurable?	Feasible?	In Alternative?
	SME Interviews	Contribution to Total HDR Hours	Outpaces Submission Volume				
Breakthrough Therapy	Y	NA	NA	Y	Y	Y	Y
Fast Track	Y	NA	Y	Y	Y	Y	Y
Priority Review	Y	NA	Y	Y	Y	Y	Y

NA = data not available or insufficient for analysis

Table A-2: Workload drivers: Work types

Submission or Work Type	Volume Driver as Determined by			Driver?	Measurable?	Feasible?	In Alternative?
	SME Interviews	Contribution to Total HDR Hours	Outpaces Submission Volume				
Labeling Supplements	Y	NA	Y	Y	Y	Y	Y

NA = data not available or insufficient for analysis

Table A-3: Workload drivers: LOE

Potential LOE Driver	FDA Interviews (2015): Activity Is Workload Driver? (Y/N/Mixed/ Not Mentioned/ Inconclusive)	CDER/CBER Time Data (FY2013-14) Indicate Activity Is Workload Driver? (Y/N) [a]	Activity Change Over Time Differs from Submission Volumes? (Y/N/Not analyzed/ Inconclusive) [b]	HDR Workload Driver? (Y/N) [c]	Explanation [d]	Is Driver Measureable? (Y/N) [e]	Can Be Feasibly Added to Model? (Y/N/NA) [f]	Alternative
Active Commercial INDs [g]								
Conduct pre-submission support activities	Y	N	Inconclusive	N	--	--	--	--
Conduct application review (general)	Not mentioned	Y	Y	Y	Constitutes significant portion of activity hours (>9%). Hours spent on average IND submission review has increased relative to submission volume.	Y	NA	No, already included in Adjuster
Conduct initial review of original IND submission	Y	N	Not analyzed	N	--	--	--	--
Conduct safety review	Y	N	N	N	Interviews suggest activity is workload driver; constitutes significant portion of activity hours (>9%); CDER meetings related to safety volatile over time.	Y	N	
Clinical holds	Not mentioned	N	Y	N	--	--	--	--
Original submission and amendment review [h]	Y	Y	Y	Y	Constitutes significant portion of activity hours (>9%); interviews indicate activity as workload driver; hours spent on average submission review have increased.	Y	N	

Potential LOE Driver	FDA Interviews (2015): Activity Is Workload Driver? (Y/N/Mixed/ Not Mentioned/ Inconclusive)	CDER/CBER Time Data (FY2013-14) Indicate Activity Is Workload Driver? (Y/N) [a]	Activity Change Over Time Differs from Submission Volumes? (Y/N/Not analyzed/ Inconclusive) [b]	HDR Workload Driver? (Y/N) [c]	Explanation [d]	Is Driver Measureable? (Y/N) [e]	Can Be Feasibly Added to Model? (Y/N/NA) [f]	Alternative
Process protocol amendment	Inconclusive	N	Not analyzed	N	--	--	--	--
Evaluate and respond to SPA request	Y	N	Y	N	--	--	--	--
Proprietary name review	Y	N	N	N	--	--	--	--
NDAs/BLAs								
Pre-Submission Activities (optional)	Y	N	Not analyzed	N	--	--	--	--
Process submission and conduct scientific/regulatory review of application [h]	Not mentioned	Y	Y	Y	Constitutes significant portion of activity hours (>9%); hours spent on average NDA/BLA submission review has increased relative to submission volume.	Y	NA	No, already included in Adjuster
Review management	Y	N	Not analyzed	N	--	Y	N	--
Develop final labeling, REMS, PMRs/PMCs and communicate any issues and/or completion information to applicant.	Y	N	N	N	--	Y	--	--

Potential LOE Driver	FDA Interviews (2015): Activity Is Workload Driver? (Y/N/Mixed/ Not Mentioned/ Inconclusive)	CDER/CBER Time Data (FY2013-14) Indicate Activity Is Workload Driver? (Y/N) [a]	Activity Change Over Time Differs from Submission Volumes? (Y/N/Not analyzed/ Inconclusive) [b]	HDR Workload Driver? (Y/N) [c]	Explanation [d]	Is Driver Measureable? (Y/N) [e]	Can Be Feasibly Added to Model? (Y/N/NA) [f]	Alternative
Proprietary name review	Y	N	N	N	--	Y	--	--
Efficacy supplements								
Process Submission	Not mentioned	Y	Not analyzed	Y	Constitutes significant portion of activity hours (>9%).	Y	NA	No, already included in Adjuster
Conduct scientific/regulatory review of application	Not mentioned	Y	Y	Y	Constitutes significant portion of activity hours (>9%). Average number of hours spent on review has increased.	Y	NA	No, already included in Adjuster
Manage amendments to application (if applicable)	Not mentioned	N	Y	N	--	--	--	--
Manufacturing supplements								
Review of product quality supplements	Not mentioned	Y	Not analyzed	Y	Constitutes significant portion of activity hours (>9%).	Y	NA	No, already included in Adjuster
Meetings (Types A, B, C) [i]	**Y**	**N**	**Y**	**N**	**--**	**--**	**--**	**--**
Meetings (Advisory Committee) [i]	**Y**	**N**	**Y**	**Y**	**Interviews and time data suggest activities are workload driver; Advisory Committee Meetings have changed relative to submission volume.**	**--**	**--**	**--**

Potential LOE Driver	FDA Interviews (2015): Activity Is Workload Driver? (Y/N/Mixed/ Not Mentioned/ Inconclusive)	CDER/CBER Time Data (FY2013-14) Indicate Activity Is Workload Driver? (Y/N) [a]	Activity Change Over Time Differs from Submission Volumes? (Y/N/Not analyzed/ Inconclusive) [b]	HDR Workload Driver? (Y/N) [c]	Explanation [d]	Is Driver Measureable? (Y/N) [e]	Can Be Feasibly Added to Model? (Y/N/NA) [f]	Alternative
Special pathways/designations								
Review Fast Track designation	Y	N [h]	Y	Y	Interviews suggest activity is workload driver; constitutes significant portion of activity hours (>9%)	Y	Y	Alternative volume calculation
Comply with Breakthrough Therapy designations [k]	Y	Inconclusive	Inconclusive	Y	Constitutes significant portion of activity hours (>9%); while time period too short to identify time trend (inconclusive analysis), activity identified in interviews as workload driver.	Y	Y	Alternative volume calculation
Comply with priority review designation	Y	N [h]	Y	Y	Interviews indicate accelerated approval as workload driver; Increase in count of priority relative to standard.	Y	Y	Alternative volume calculation
Other [l]								
Concurrent review submissions	Y	N	Not analyzed	N	--	--	--	--
CBER submissions	Y	N	Not analyzed	N	--	--	--	--
Combination products	Y	N	Not analyzed	N	--	--	--	--
Product novelty / complexity	Y	N	Not analyzed	N	--	--	--	--
Market factors	Y	N	Not analyzed	N	--	--	--	--

Table References

[a] 9% of the total time spent on a given type of HDR work was used as a general barometer to indicate workload drivers. The determination of a driver was derived from professional judgment based on the available data presented.
[b] This column informs whether an activity is captured in the current Adjuster model (which determines whether it might be considered as an element in a new model alternative). An activity is considered to be indirectly incorporated into the model if it varies in direct proportion to submission volumes counted in the current model (i.e., submission counts serve as a good proxy for the workload of the activity). If an activity does not change in proportion to the submission volume, it is not considered to be incorporated into the current model.
[c] "Y" indicates that either: 1) two of the three data sources (interviews, time data, analysis of change relative to submission volume) indicate that the activity is a workload driver OR 2) one of the three data sources very strongly indicates a workload driver. "N" indicates that either: 1) no data source indicated that the activity is a workload driver OR 2) the data source indicating a workload driver only provided weak evidence. Expert judgment was used to make a determination when data sources had conflicting results.
[d] Response only provided when activity identified as workload driver.
[e] Column only completed if driver is measurable.
[f] Column only completed if driver can feasibly be added to the model.
[g] Unless otherwise noted, active INDs refers to commercial INDs.
[h] The time data categories for processing and reviewing submissions/applications overlap, and therefore they are grouped into one driver category.
[i] Combines meeting type(s) for all review processes in Adjuster. While time reporting data do not reflect SME interview responses with regard to the time intensity of meetings, the range of meeting-related data captured in hours reported is unclear. For example, it is unclear whether meeting preparation is included in the hours reported or simply the time used to conduct the meetings. The type of meeting-related activities included/excluded in time reporting data might help explain the mismatch between interview findings and hours reported.
[j] Data is based on Advisory Committee meeting data, and this activity falls under "Obtain Expert Advice" in the workload inventory.
[k] Breakthrough Therapy designations were only type of special designation/expedited pathway included in time reporting data, so determining if it was a workload driver relative to the other HDR special designations was not possible. Interviewees generally did not distinguish explicitly between Breakthrough Therapy designation requests and designation granted, but most spoke about the additional effort associated with increased communications for submissions granted this designation.
[l] This category of drivers originates from FDA SME interviews. The suggested drivers span across multiple HDR review categories and activities do not neatly fall into one of the HDR workload categories listed.

Table A-4: Workload drivers: Work type

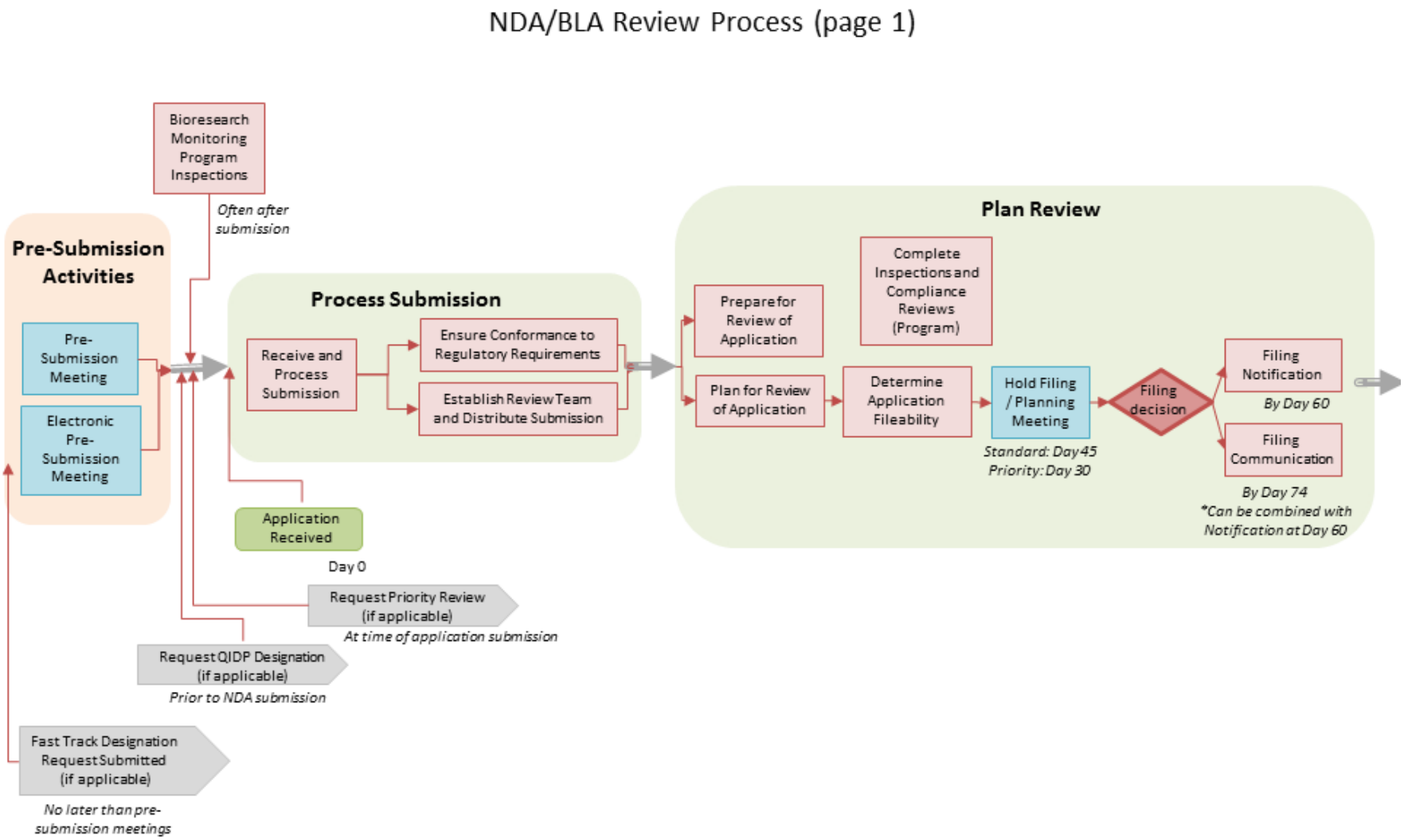
Work Type	FDA Interviews (2015): Work Type Is Workload Driver? (Y/N/Mixed/ Not Mentioned/ Inconclusive)	CDER/CBER Time Data (FY2013-14) Indicate Work Type Is Workload Driver? (Y/N) [a]	Work Type Change Over Time Differs from Submission Volumes? (Y/N/Not analyzed/ Inconclusive) [b]	HDR Workload Driver? (Y/N) [c]	Explanation [d]	Is Driver Measureable? (Y/N) [e]	Can Be Feasibly Added to Model? (Y/N/NA) [f]	Alternative
Labeling supplements								
Application review	Y	N [g]	Y	Y	Interviews suggest labeling supplements are workload driver/contributor to workload submission volume; Growth in labeling supplements has greatly outpaced growth in other submission types.	Y	Y	Alternative volume calculation
Research INDs								
Review of research IND submissions (entire process)	Y	N [g]	N	N	--	--	--	--
Other Drug Cycle Support								
Manage initial contacts	Not mentioned	N [g]	Y	N	--	--	--	--
Non-review work (combined activities)	**Y**	**Y**	**Y**	**Y**	**Interviews and time data suggest activities are workload driver.**	**Y**	**N**	**--**
Provide center/program management	Y	Y	Not analyzed	Y	Interviews suggest contributor to workload volume; constitutes significant portion of activity hours (>9%).	Y	N	--
Manage application processes [h]	Y	Y	Not analyzed	Y	Interviews suggest contributor to workload volume; constitutes significant portion of activity hours (>9%).	Y	N	--

Work Type	FDA Interviews (2015): Work Type Is Workload Driver? (Y/N/Mixed/ Not Mentioned/ Inconclusive)	CDER/CBER Time Data (FY2013-14) Indicate Work Type Is Workload Driver? (Y/N) [a]	Work Type Change Over Time Differs from Submission Volumes? (Y/N/Not analyzed/ Inconclusive) [b]	HDR Workload Driver? (Y/N) [c]	Explanation [d]	Is Driver Measureable? (Y/N) [e]	Can Be Feasibly Added to Model? (Y/N/NA) [f]	Alternative
Conduct regulatory science activities	Y	Y	Not analyzed	Y	Interviews suggest contributor to workload volume; constitutes significant portion of activity hours (>9%).	Y	N	--
Regulation and policy development and implementation [i]	Y	Y	Not analyzed	Y	Interviews suggest contributor to workload volume; constitutes significant portion of activity hours (>9%).	Y	N	--
Conduct/participate in training	Y	Y	Y	Y	Interviews suggest contributor to workload volume; constitutes significant portion of activity hours (>9%). Hours spent on training increased moderately relative to submission volume.	Y	N	--
Postmarket (combined activities)	**Y**	**Y**	**Y**	**Y**	**Interviews suggest activities are workload driver.**	**Y**	**N**	
Conduct postmarket safety activities	Y	Y	Not analyzed	Y	Interviews suggest contributor to workload volume; constitutes significant portion of activity hours (>9%).	--	--	--
Lot release	Y	Y	Not analyzed	Y	Interviews suggest contributor to workload volume; constitutes significant portion of activity hours (>9%).	--	--	--

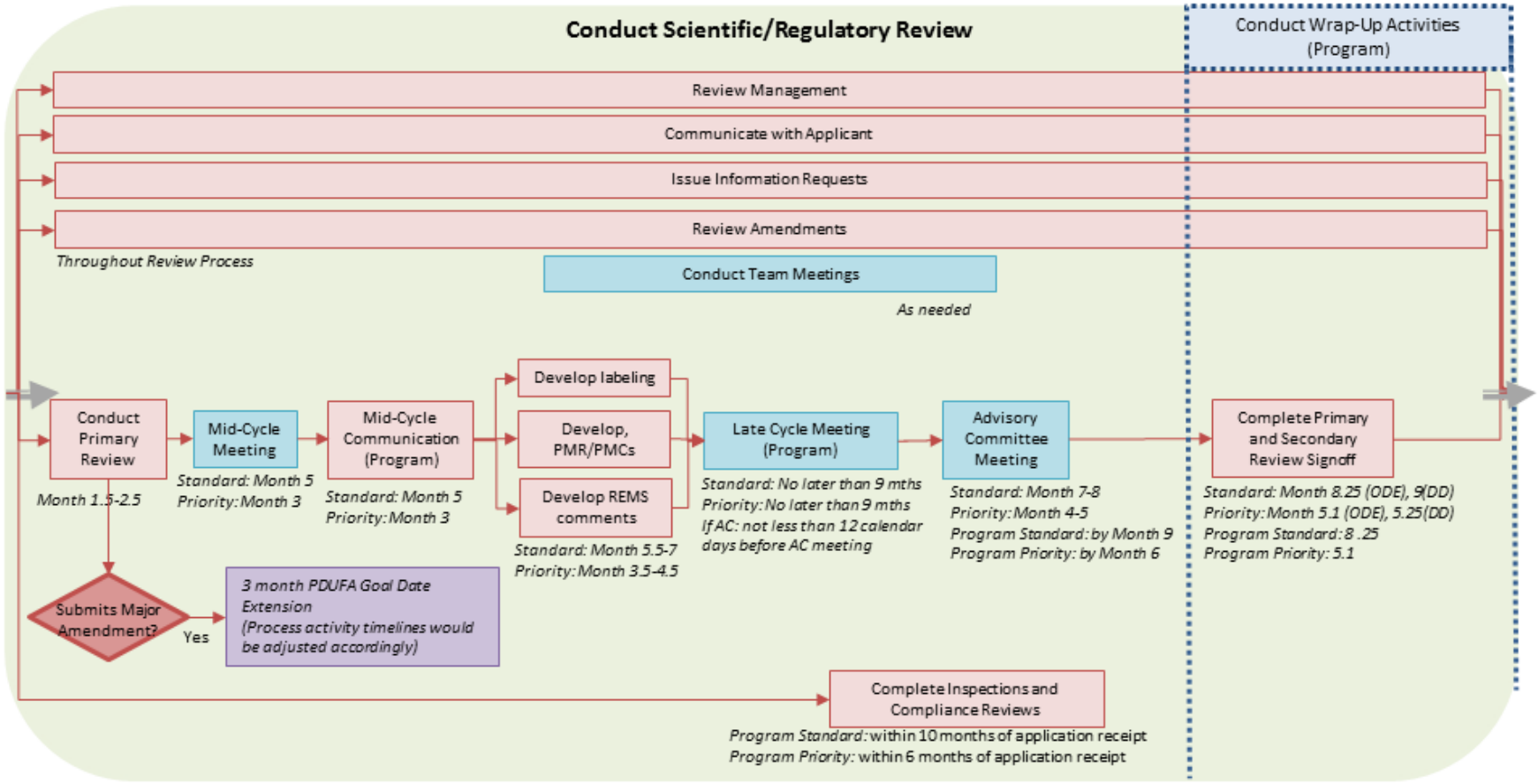
Table References

[a] 9% of the total time spent on a given type of HDR work was used as a general barometer to indicate workload drivers. The determination of a driver was derived from professional judgemnt based on the available data presented.
[b] This column informs whether an activity is captured in the current Adjuster model (which determines whether it might be considered as an element in a new model alternative). An activity is considered to be indirectly incorporated into the model if it varies in direct proportion to submission volumes counted in the current model (i.e., submission counts serve as a good proxy for the workload of the activity). If an activity does not change in proportion to the submission volume, it is not considered to be incorporated into the current model.
[c] "Y" indicates that either: 1) two of the three data sources (interviews, time data, analysis of change relative to submission volume) indicate that the activity is a workload driver OR 2) one of the three data sources very strongly indicates a workload driver. "N" indicates that either: 1) no data source indicated that the activity is a workload driver OR 2) the data source indicating a workload driver only provided weak evidence. Expert judgment was used make a determination when data sources had conflicting results.
[d] Response only provided when activity identified as workload driver.
[e] Column only completed if driver is measurable.
[f] Column only completed if driver can feasibly be added to the model.
[g] Time data not available for this activity/process.
[h] Activity also falls under Center/Program Management activity listed above.
[i] Activity also falls under broader "Conduct Regulatory Science Activities" listed above.

Appendix B: Example PDUFA Process Diagram (NDA/BLA Review)



NDA/BLA Review Process (page 2)



Standard: Month 1.5-8 (ODE), 1.5-8.75 (DD)
Priority: Month 1-5 (ODE), 1-5.25 (DD)
Program Standard: Month 1.5-8
Program Priority: Month 1-5

Note: ODE = Office of Drug Evaluation. DD = Division Director.

NDA/BLA Review Process (page 3)