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Developing A Successful Regulatory Strategy for Mobile Health Devices and Applications

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FDA Device Classifications

Class I	Class II	Class III
Low Risk	Moderate Risk	High Risk
General Controls	General & Special Controls	General Controls & demonstrate safety and effectiveness
Generally exempt from clearance/ approval	510(k) Clearance ("substantially equivalent" to a "predicate" device)	PMA Approval (must prove safety and effectiveness)

- Classification determines the regulatory pathway
- Novel products default into class III and, if low or moderate risk, can be reclassified into class I or II (De Novo pathway)

Device Regulatory Pathways

- Premarket Notification (510(k) Clearance)
  - Class I (most are exempt) and Class II devices
  - Gets its name from section 510(k) of the FDC Act
  - Goal: Demonstrate **substantial equivalence** to Class I or Class II legally marketed device
  - Clinical data support may be needed in 10% of approximately 4000 510(k)s filed annually, but this proportion is growing
  - The average time it takes to clear a 510(k) began declining in 2011, for the first time since 2005, and the trend is continuing

Device Regulatory Pathways

- Premarket Approval (PMA) – Class III Devices
  - Safety and Efficacy of device must be demonstrated
  - PMAs required for devices “Not Substantially Equivalent” to Class I or Class II devices
  - Clinical data is pivotal to assess Safety or Efficacy
  - Minimum review time of 180 days, but more typically takes > 1 year

Device Regulatory Pathways

- De Novo Review – Evaluation of Automatic Class III Designation
  - Pathway originally created in 1997, modified in 2012 to allow “direct” de novo
  - Intended for devices that are novel but low-to-moderate risk for which no predicate is available and where premarket approval (PMA) is not warranted
  - Approximately half of the instances in which FDA has granted *de novo* downclassification have involved *in vitro* diagnostic devices
  - Review times extremely variable

Premarket Clearance/Approval

PMA	De Novo	510(k)
Safety and effectiveness	General and special controls provide reasonable assurance of safety and effectiveness	Substantial equivalence
Must be “approved”	Request “granted”	Must be “cleared”
Valid scientific evidence	Requirements for Class I or II must be met	Comparison to existing (predicate) device
Almost always accompanied by clinical data	Most de novo requests contain clinical data	10-15% contain clinical data
Like a product license or regulatory patent	No exclusivity	No exclusivity
180 days	120 days	90 days
Longer total review (1-2 years)	Medium (9-12 months)	Shorter (6-9 months)

IDE Applications

- Investigational Device Exemption (IDE) needed to conduct most clinical evaluations of medical devices prior to clearance or approval
  - FDA review depends upon determination of Significant Risk (SR) or Non-significant Risk (NSR) Device (§ 812.3(m))
    - Determination made by sponsor, then IRB;
    - Significant Risk requires FDA approval before study initiation
- Additional regulations for informed consent and IRB oversight

Determining Product Classification

Possible Regulatory Pathways for Digital Health

- Several possible pathways:
  - Product is not a medical device (i.e., no FDA regulation)
  - Product is subject to enforcement discretion (i.e., no active FDA oversight)
  - Product is regulated as a medical device (class I, II or III)
  - In general, subject to same pre- and post-market regulations as any other medical device.
  - Certain types of software products may have particular additional requirements.
  - Product is regulated as a combination product (combination of drug, device, and/or biologic)

Determining Classification

- Begin with FDA precedent and guidance documents, consider by analogy
- Consider risk and similar products
- Make creative arguments

Options for Clarifying Status

- 513(g) Petition – Formal request for classification, non-binding on Agency
- Pre-Submission process
- Informal Discussions
- Marketing Submission
- Review Precedent

Pre-Submissions (Q-Subs)

Pre-Submissions Filings

- A formal submission for informal advice
- Nonbinding on company or agency
- Company must prepare submission with required information and include concrete proposals for discussion
- Typically 60-90 day review schedule (goal is 75 days)
- Appropriate topic areas:
  - Investigational plan – OUS and US
  - Complex testing
  - Novel device

FDA Pre-Submission Policy

- Increase early interaction between agency and sponsor to ensure timely review process
- Formal written request for feedback in written form, or at a meeting

Q-Sub Type	Meeting as Method of Feedback?	Timeframe for Meeting/Teleconference (from receipt of submission)
Pre-Submission*	Upon request	75-90 days**
Informational Meeting	Yes	90 days
Study Risk Determination	No	N/A
Agreement Meeting	Yes	30 days or within time frame agreed to with sponsor
Determination Meeting	Yes	Date for meeting agreed upon within 30 days of request
Submission Issue Meeting	Yes	21 days
Day 100 Meeting	Yes	100 days (from PMA filing date)

*As defined in MDUFA III Commitment Letter.
**21 days for urgent public health issues (see Section III.A.6.).

FDA Guidance e Available Here

Good Questions to Ask in a Pre-Sub

Biocompatibility

- In addition to the biocompatibility testing recommended for the type and duration of tissue contact defined by FDA's G95-1 Bluebook Guidance and ISO 10993-1, what other device-specific biocompatibility testing may be necessary to adequately evaluate the biocompatibility of my device?
- Is our justification for not conducting carcinogenicity studies adequate?

Bench and Animal Testing

- Does FDA concur it is appropriate to test only the smallest and largest sizes of my device in comparison to a predicate device when I plan to market at least ten (10) different sizes that differ in dimensions?
- Does FDA concur with our worst-case rationale for this device?
- Does the FDA concur with the use of the proposed alternative test method, which is different than the normally recognized standard?
- Is the animal model I propose appropriate for testing my device?

Software

- Is a "moderate level of concern" the appropriate level of concern for my software?

Human Factors Evaluation

- Is my planned approach to human factors assessment appropriate for the intended use of my device?

Clinical Evaluation

- Is it advisable to conduct a clinical evaluation of my device or is the battery of bench and animal testing I propose likely to be adequate? (In some cases, FDA may not be able to assess whether bench and animal data are sufficient in lieu of clinical data until the agency has been able to complete a review of the nonclinical testing.)
- If clinical data are needed for my device, are the proposed trial design and selected control group appropriate or is the protocol from a previously conducted study appropriate?

Predicate Device

- Are there concerns with the predicate device proposed?

What NOT to ask in a Pre-Sub

- Will the information outlined in my Pre-Sub support a substantial equivalence determination?
- Are the results of my bench testing acceptable?
- Is the clinical data collected sufficient?

A Complete Submission Strategy

Regulatory Strategy Includes Path **AND** Data

- Key to successful strategy with FDA is appropriate proposal for supporting data
- Dependent on device type
  - Look to precedent (most recent new devices most relevant)
  - Consider design and claims you wish to make
  - Review any guidance documents applicable to device type
- Consider typical issues
  - Biocompatibility
  - Sterility/shelf life
  - Electrical Safety and EMC
  - Software Validation (and Level of Concern)
  - Cybersecurity and Wireless Communication considerations
  - Bench Performance Testing
  - Human Factors
  - Clinical Testing?

Regulatory Strategy Includes Path **AND** Data

- Propose and explain during pre-submission
  - Key goal of pre-submission is obtaining FDA feedback on testing
  - Remember that during marketing application process you will be required to disclose anything relevant to safety/effectiveness
- Discuss with advisors
  - Prior experience with FDA informs likelihood of success on certain strategies
- Organization and good writing count
  - Make any su

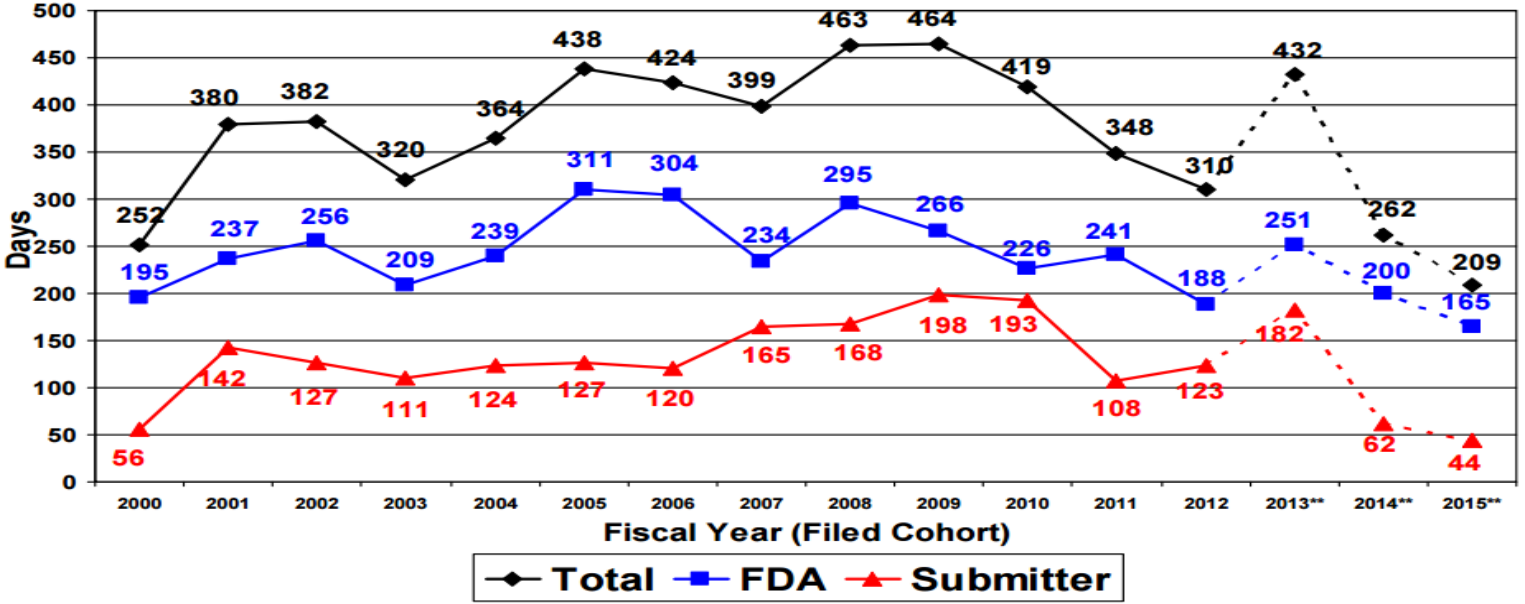
Regulatory Strategy Tips

- FDA responds best to a well thought out proposal with justification
  - Agency is not as helpful when asked to opine without a proposal
- Organization and good writing count
  - Make any submission clear, detailed and concise
  - Follow the eCopy guidance to avoid eCopy hold
- Think like your review team
  - If you were learning about the device for the first time – what would you want to know?
  - Try to anticipate potential questions and decide whether to proactively address them

Premarket Application Review Timelines

Average Time to MDUFA Decision: PMAs*

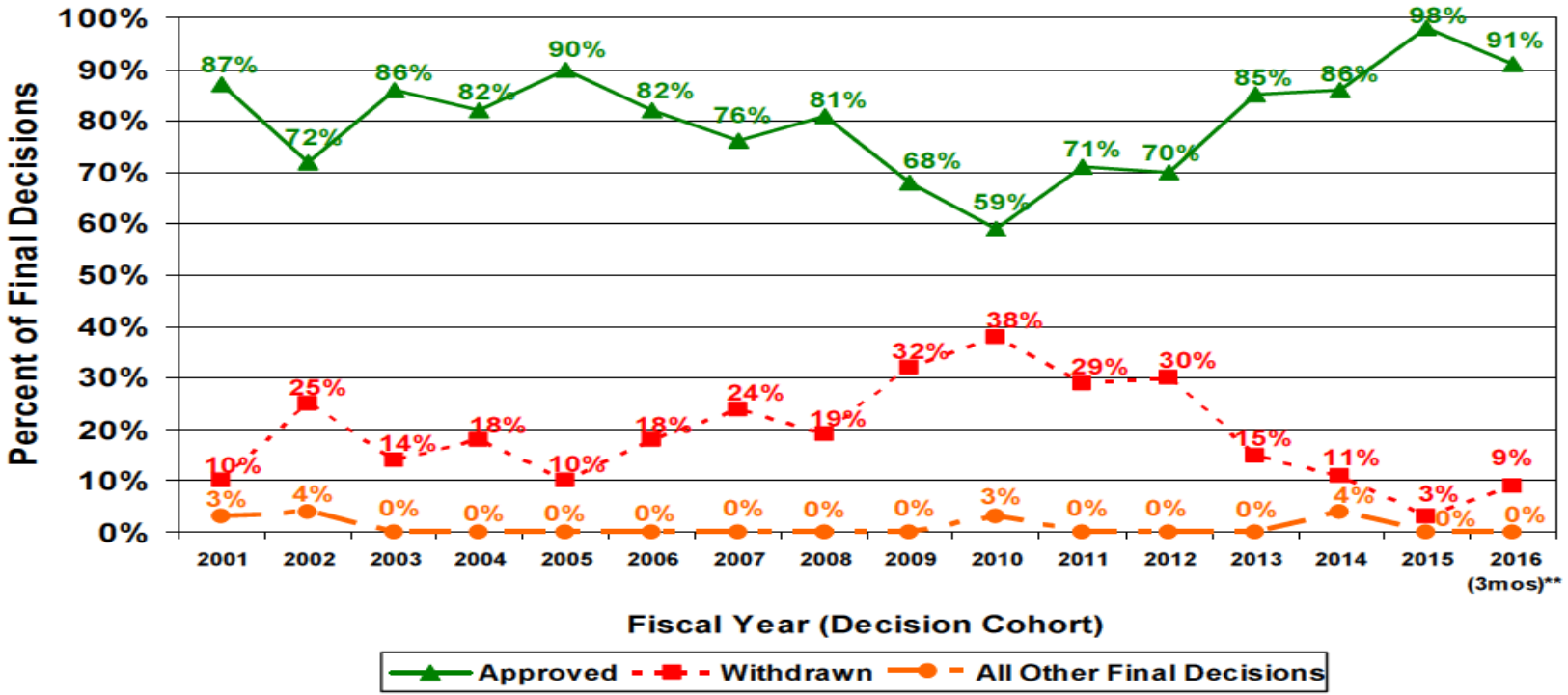
(As of December 31, 2015)



*Includes original PMAs only; FY13-FY14 are receipt cohorts including PMAs filed as of 12/31/2015, prior cohorts are filed cohorts; times may not add to total due to rounding

**Cohort still open, average times will increase; percent of cohort with MDUFA decision: FY13 = 97% (28/29); FY14 = 89% (25/28); FY15 = 45% (19/42)

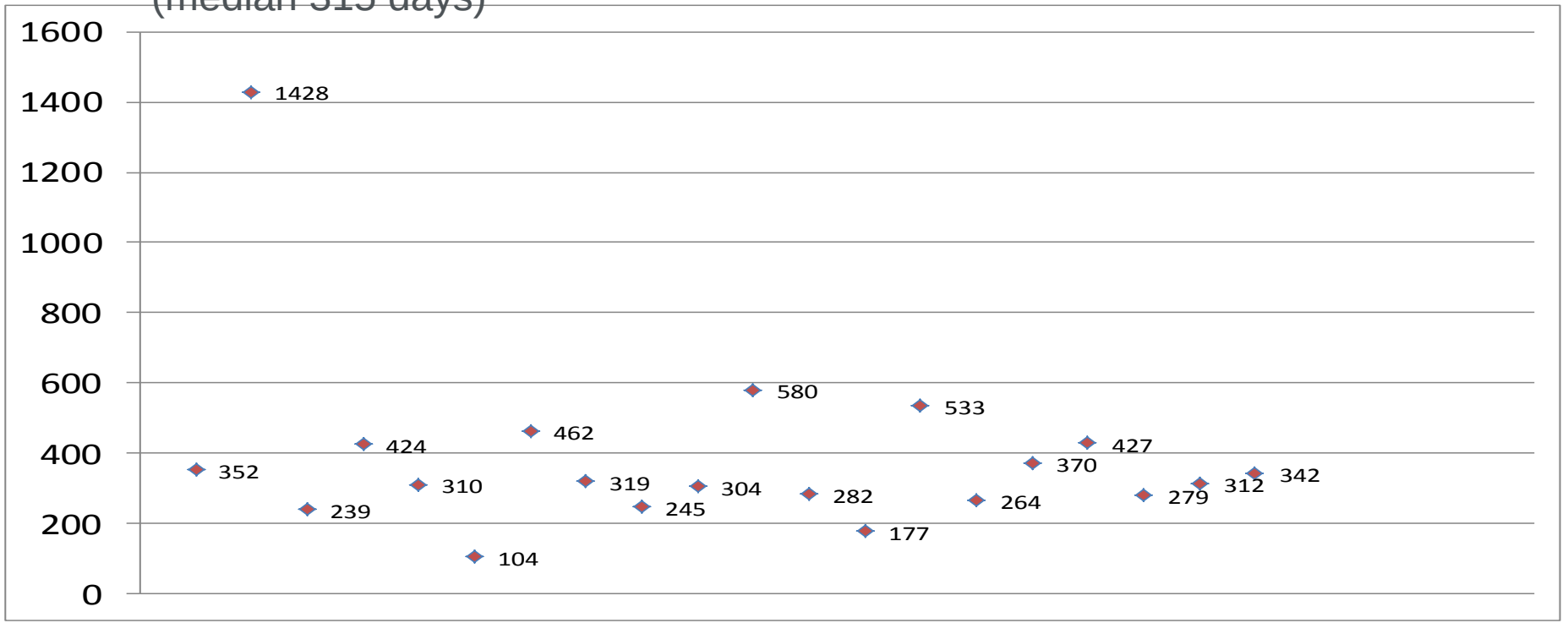
Percent of PMAs Approved*



*Based on original PMAs that were accepted for filing as of 12/31/2015; percentages may not add to 100% due to rounding

Variability in Length of Review:
Most Recent Original PMA Approvals

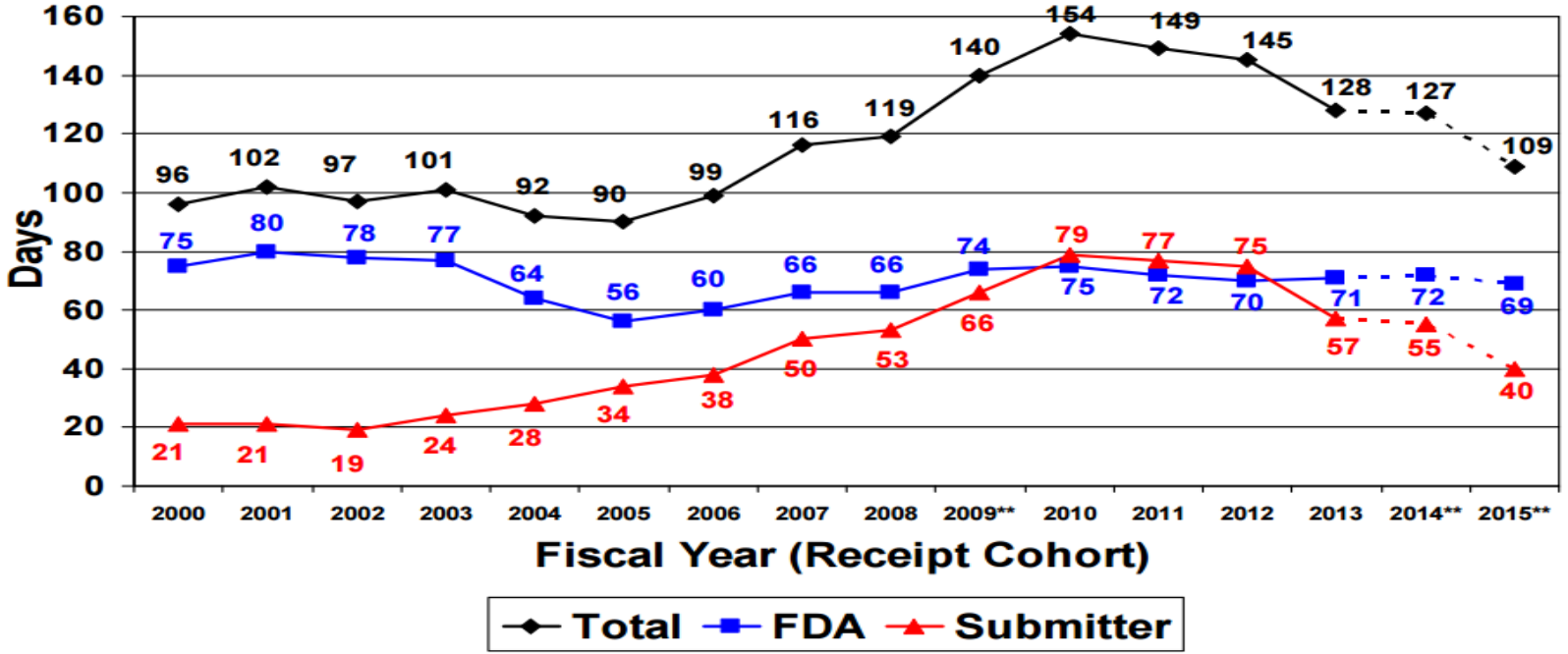
Review times for the most recent PMA submissions averaged 387 days (median 315 days)



Updated 11/20/2016

Average Time to Decision: 510(k)s*

(Receipt Cohorts as of December 31, 2015)

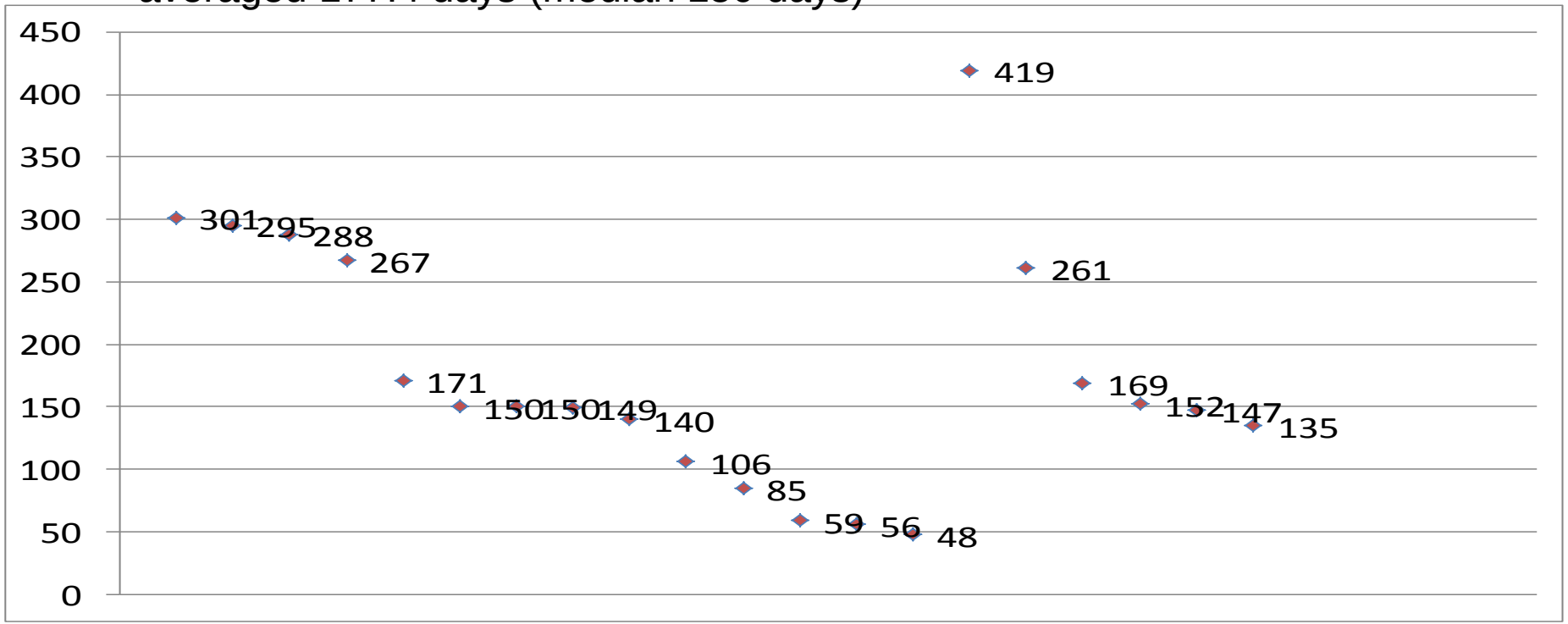


*SE and NSE decisions only; times may not add to total due to rounding

**Cohorts still open; percentage of cohort closed: FY 2009 = 99.9%, FY 2014 = 99.4%, and FY 2015 = 74.2% —average times for FY 2014 and FY 2015 will increase

Analysis of Review Time for last 20 available 510(k) Submissions Without Clinical Trials

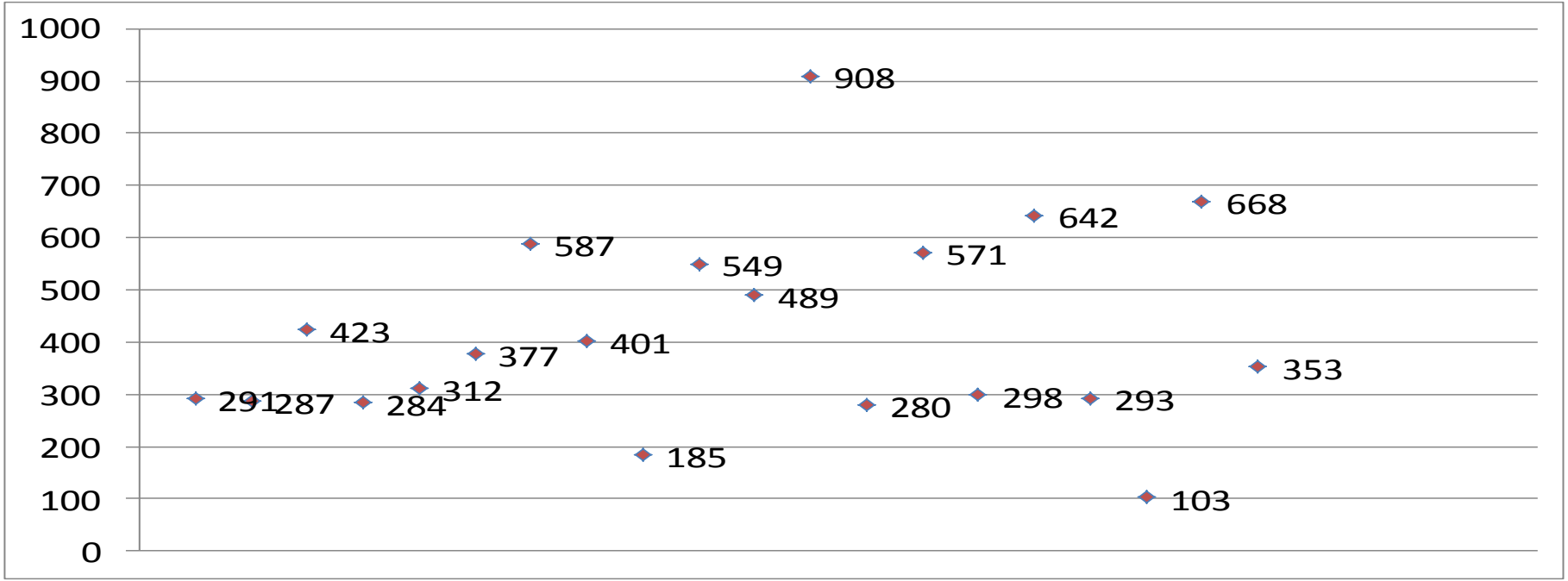
Review times for the most recent 510(k) submissions without clinical trials averaged 177.4 days (median 150 days)



Updated 11/20/2016

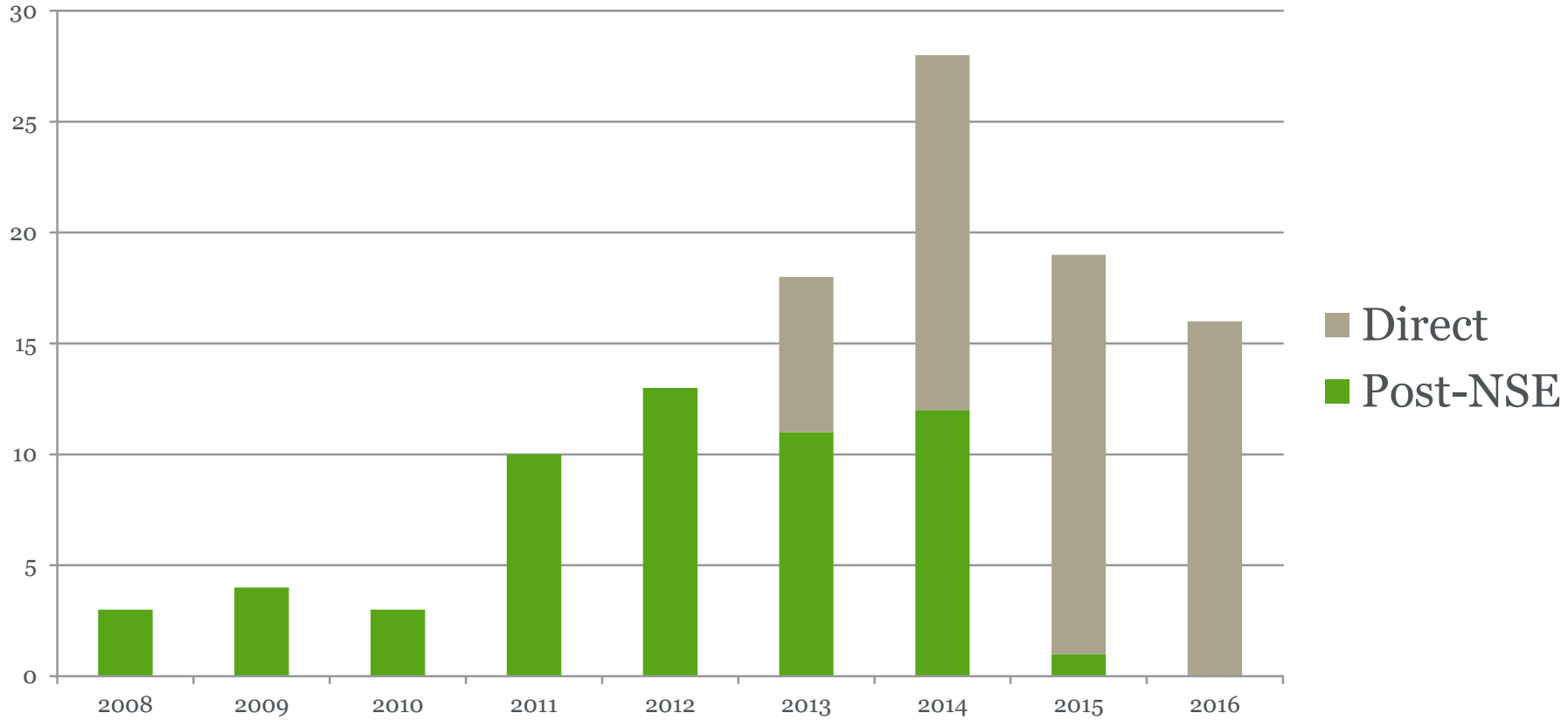
Analysis of Review Time for Recent Direct De Novo Petitions

A total of 20 Direct De Novo Petitions have been granted since the beginning of 2016. Average review time 415 days (median 365 days).

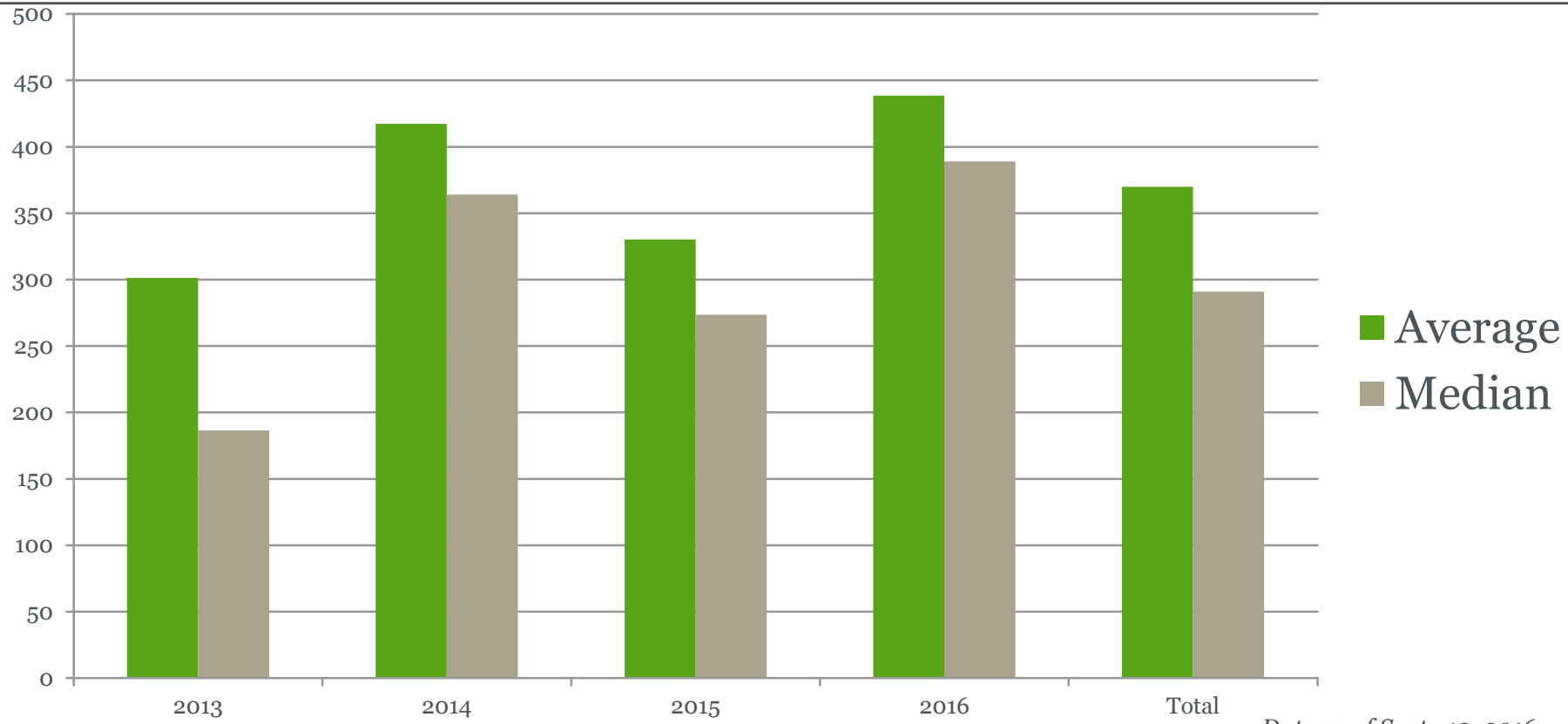


Updated 11/20/2016

Number of De Novo Petitions Granted (8/15)

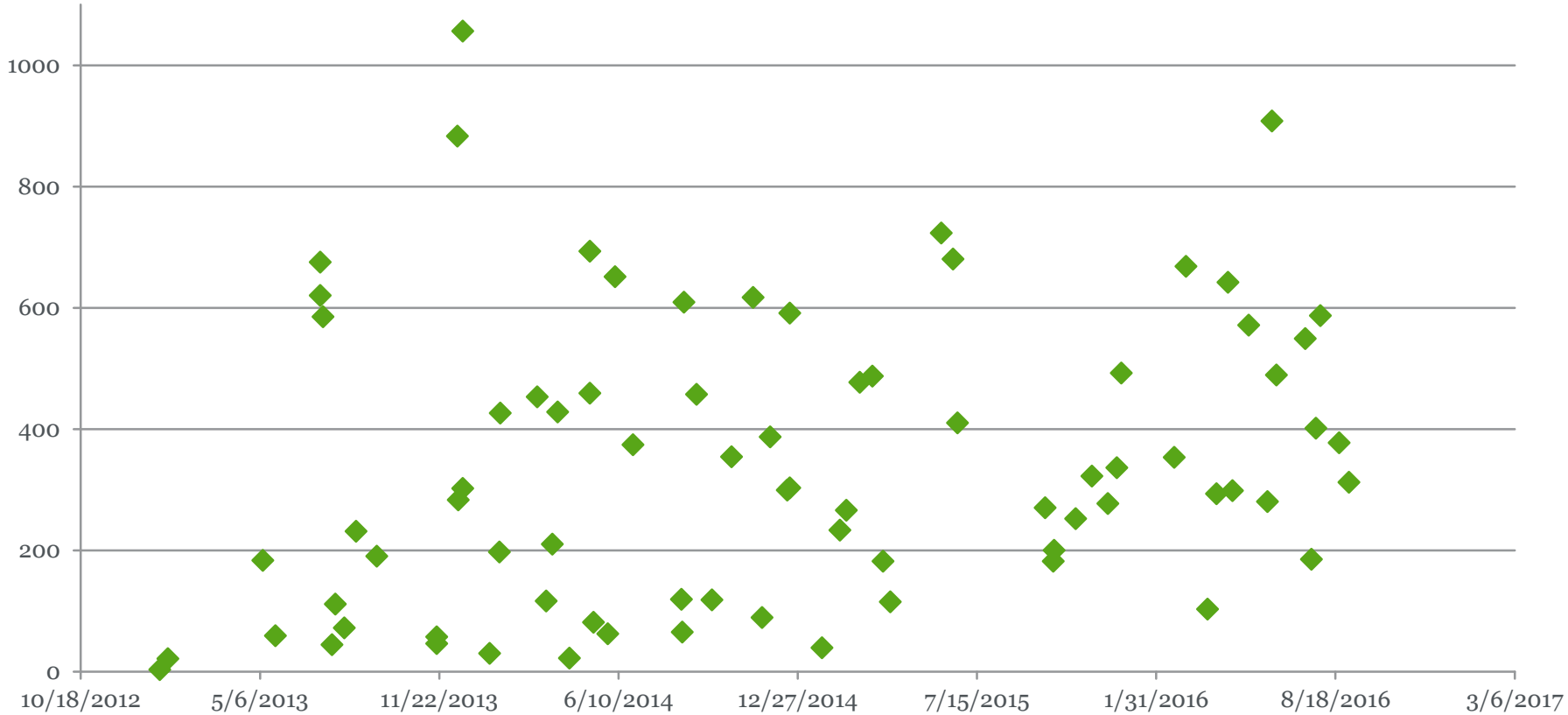


Review Time for All Direct De Novo Petitions

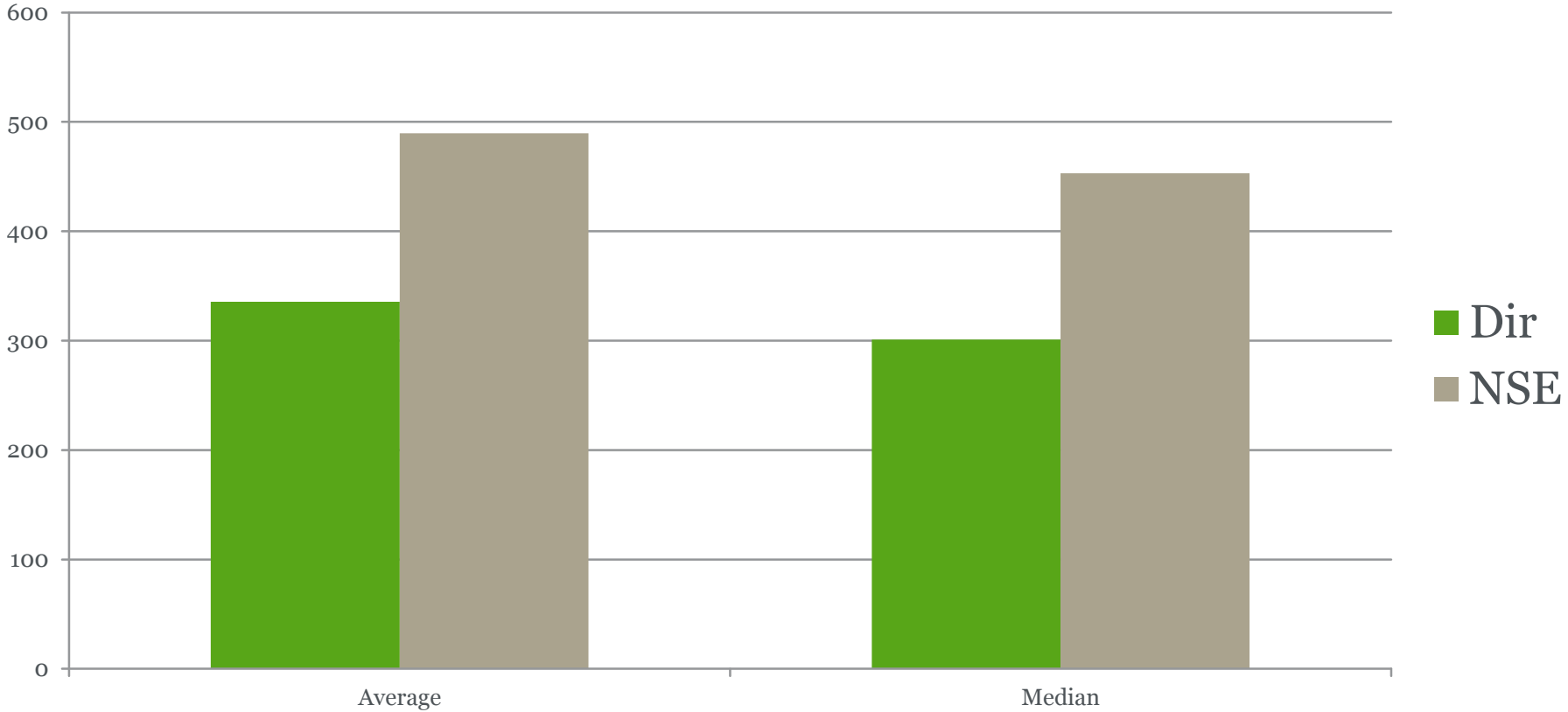


Data as of Sept., 12, 2016

Time to approval



Post-NSE vs. Direct De Novo



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