Regulatory Aspects of Naming Pharmaceutical Drug Products: FDA's Review of Proprietary Names

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Presentation Overview

- Describe regulatory aspects related to naming pharmaceutical drug products.
- Provide an overview of the *draft* Guidance for Industry: *Best Practices in Developing Proprietary Names for Drugs*
- Describe FDA's current process for evaluating proposed proprietary names

FDA's Interest in Proprietary Names for Drugs

- Proprietary name is a critical element in use of drug products
- Proprietary names that are similar phonetically or in their spelling or orthographic appearance or are otherwise confusing or misleading, may lead to errors.
- Medication errors are a significant public health concern that account for an estimated 7,000 deaths annually in the United States
- Focus of draft guidance is to develop and communicate to sponsors a systematic, standardized, and transparent approach to proprietary name evaluation

FDA Guidance

- Two guidances related to proprietary names:
  1. Best practices for Developing Proprietary Names for Drugs- *draft*
  2. Contents of a Complete Submission (final)
- A "draft guidance," when finalized, represents the FDA's current thinking on a topic.
- It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.

Draft Guidance for Industry: **Best Practices for Developing Proprietary Names for Drugs**

- Issued May 28, 2014
  - Comment period closed in September
- Joint Guidance with CDER and CBER
- Applies to Rx and OTC products
- Intended to help sponsors of drugs and biological products develop proprietary names that do not cause or contribute to medication errors or the misbranding of the drug
- Focus in drafting the guidance was to communicate a systematic, standardized, and transparent approach to proprietary name evaluation

Contents of Best Practices for Developing Proprietary Names for Drugs

I. Prescreening considerations for proprietary name candidates

II. Consider attributes that may be misleading or error-prone

III. Misbranding review

- Avoid names that overstate efficacy, minimize risks, or make unsupported suggestions of unique effectiveness or composition

IV. Methods for Evaluating Safety of Proposed Proprietary Names

- Avoid names with orthographic, spelling, and phonetic similarity to other names that could result in errors

I. Prescreening proprietary name candidates

I. Prescreen the Proposed Name

Things to avoid:

- Obvious similarity to other names (see 21 CFR 201.10(c)(5))
- Inclusion of medical/coined abbreviations
- Inclusion or reference to inert or inactive ingredients (see 21 CFR 201.10(c)(4))
- For combination drug products: avoid suggesting the name of one or more, but not all active ingredients (see 21 CFR 201.6(b))
- Using the same root name for a product that does not share at least one common active ingredient
- Reusing a proprietary name of a different discontinued drug product
- Inclusion of USAN stem

I. Prescreening: Inclusion of USAN stem

- Proprietary names should not incorporate United States Adopted Name (USAN) stems in the position that USAN designates for the stem
- USAN stems are intended to indicate a pharmacological or chemical trait of a drug
- Use of these stems, even when such use is consistent with the USAN meaning, may lead to an increased risk of medication errors
  - Example: Retro**vir** (zidovudine) vs ritona**vir (**Norvir)
- Only allowed in rare circumstances when the proposed name includes a word that can only be spelled in the English language using a stem in the position designated by USAN

II. Misleading Nature or Error Potential of Other Nomenclature Attributes

II. Misleading Nature or Error Prone Attributes

- Inclusion of product-specific attributes
- Use of modifiers
- Brand name extension
- Dual proprietary name
- Drug names used outside the US
- Rx to OTC switch
- Avoid symbols; use words.
- Use of sponsor name in the proprietary name

III. Misbranding Review

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- Suggestions that a drug is safer or more effective than has been demonstrated by appropriate scientific evidence
- A fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not

IV. Look-alike Sound-alike (LASA) Safety Review

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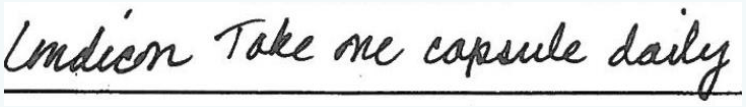
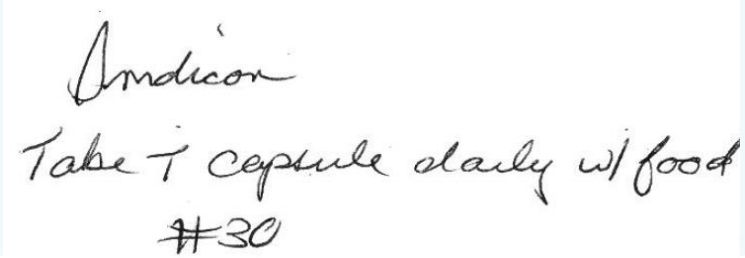
- Focus is to avoid similarity that would lead to errors
- Consider similarity in printing, writing, and speech
- Conduct name simulation studies (NSS)
- Search for similar names using FDA's Phonetic and Orthographic Computer Analysis (POCA) program
  - Determine similarity scores with other marketed names via POCA
  - Categorize as high, moderate, or low similarity based on match score
- Use checklists for the high, moderate, or low similarity to help determine whether the name is safe from a LASA perspective

Name Simulation Studies (NSS)

- Purpose is to test how subjects respond to a proposed proprietary name by asking them to use the name in simulated real-world use conditions.
- We recommend that name simulation study results should be analyzed carefully to identify potential errors

Name Simulation Studies (NSS)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order:  	**Imdicon** **Take one capsule daily with food** **Dispense #30**
Outpatient Prescription:  	

Total	21	17	24	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
AMDICON	2	0	0	2
ANDICON	1	0	0	1
DODICON	1	0	0	1
EMBICON	0	1	0	1
EMDICON	0	6	0	6
ENDICON	0	1	0	1
GNDICON	1	0	0	1
IMDACON	0	1	0	1
IMDECON	0	1	0	1
IMDICA	0	1	0	1
IMDICON	7	5	11	23
IMIDICON	0	0	1	1
INDICON	1	0	0	1
LINDICON	0	0	1	1
LINDICOR	0	0	1	1
LOMDICON	0	0	1	1
LONDICON	0	0	2	2
MDICON	0	1	0	1
OMDICON	5	0	0	5
SMDICON	1	0	0	1
SONDICON	1	0	0	1
SORDICON	1	0	0	1
UNDICON	0	0	6	6
UNDICOR	0	0	1	1

Integrate Results of NSS into Overall LASA Assessment

- We recommend that any findings suggesting names of concern should be analyzed further
  - Consider scoring the name pair using POCA
  - Then, use the appropriate checklists to determine the potential for error.

Identify Names with Orthographic, Spelling and Phonetic Similarity

Identify Names with Orthographic, Spelling and Phonetic Similarity

- FDA enters the proposed proprietary name into the FDA's Phonetic and Orthographic Computer Analysis (POCA)
  - analytic tool designed to help identify drug and biologic names and medical terminology that are phonetically and orthographically similar to one another.
- POCA queries the name against drug reference databases and other pending names

Rationale for Using POCA

- More scientific approach:
  - The POCA measures are objective
  - The COMBINED measure of similarity has been positively correlated to errors involving name confusion

- Publically available to download:

http://www.fda.gov/Drugs/ResourcesForYou/Industry/ucm400127.htm

- Automation of processes:
  - POCA search eliminates manual labor searching databases
  - Reproducible results: the measure of similarity for any given pair should be the same whether FDA or the Applicant performs the search* *(except for proposed names that are only available on FDA internal databases)*

Limitations of POCA

- Not designed to evaluate or consider influence of other known causes of name confusion that could lead to errors
    - For example, metathesis leading to confusion between Zocor and Cozaar is unlikely to be evaluated using POCA approach (similarity scores <50%)
    - To account for this limitation, evaluation of name simulation study findings are important
- Not designed to evaluate the influence of product characteristics
    - Product characteristics may increase or decrease the potential for confusion
    - Manual review of characteristics should be performed to fully asses the potential for name confusion
- However, additional processes (analysis of product characteristics and the name simulation studies) are recommended to uncover sources of error that might not be detected using POCA

Analyzing POCA Results

POCA Results: Analyze

1. Group the name pairs into one of the following three categories
   - Highly Similar Pair: combined match percentage score ≥70%.
   - Moderately Similar Pair: combined match percentage score ≥50% to ≤ 69%; and any names identified in the simulation studies that have combined scores ≤49%.
   - Low Similarity: combined match percentage score ≤49%.
2. Use checklists to determine if confusion and error would occur
   - Developed for each category using the principles of Failure Modes and Effects Analysis
   - Provided for each category in Appendices of Guidance

Role of Product Characteristics

- Product strength and dose is an important consideration
  - For similar names, the risk of medication error is potentiated when the strengths and doses overlap or are similar to one another.
  - However, if none of the strengths overlapped, the name similarity ***might*** not lead to errors.
- Other attributes such as indications, dosing frequencies and administration may contribute but with varying impact

Why Consider Product Characteristics

- Root Cause Analysis shows that **shared strength or dose** contribute to confusion and has lead to errors between drugs with similar names.
- Conversely, evaluation of post-marketing errors leads us to conclude that **differences in strength** may help to mitigate the risk of confusion.
  - Consider: Intuniv and Invega 3 mg strengths **have** been confused
  - Intuniv 1 mg, 2 mg, and 4 mg and Invega 1.5 mg, 6 mg, and 9 mg product strengths **have not** been confused.
- Other attributes such as indications, dosing frequencies and administration may contribute but with varying impact

Limitations of Product Characteristics

- Different product characteristics may not prevent confusion between highly similar drugs names

- Confusion has occurred even when products have very different doses, therapeutic uses, dosage forms, route of administration, and setting of use. Consider these errors:
  - Cerebyx (an injectable anti-convulsant drug) and Celebrex (an oral NSAID) (combined POCA score of 74%).
  - Advair (an inhalation product) and Advicor (a tablet) (combined POCA score of 70%)
  - Durasal (a topical wart remover) and Durezol (an ophthalmic drop) (combined POCA score of 78%).

- **If two products have highly similar names, differences in the product profile may not reduce the risk of error.**

Checklists: Results

- If you find that the name is likely to result in error due to similarity and/or shared product characteristics, this is likely to be a concern identified in FDA's look and sound-alike safety assessment.

V. Final Determination on Name Acceptability: FDA evaluation

V FDA Determination

- The acceptability of a proposed proprietary name is based on FDA's review of all information and analyses described in the guidance (i.e. Sections I-IV)
- We also consider and evaluate any information submitted by the Applicant).
- FDA may reject a name if, based on the information provided or in its own review, it determines the name:
  - causes confusion with other products that can result in medication errors and preventable harm or
  - is misleading with respect to the therapeutic effectiveness, composition, or the safety of the product.

Overview of CDER Name Review Process for Prescription Drugs

Complete Submission Proposing Proprietary Name Received

- Review team notified
- Input sought from clinical and other discipline
- Misbranding review commences (Office of Prescription Drug Products)
- FDA Name Simulation Studies conducted
- DMEPA safety review commences

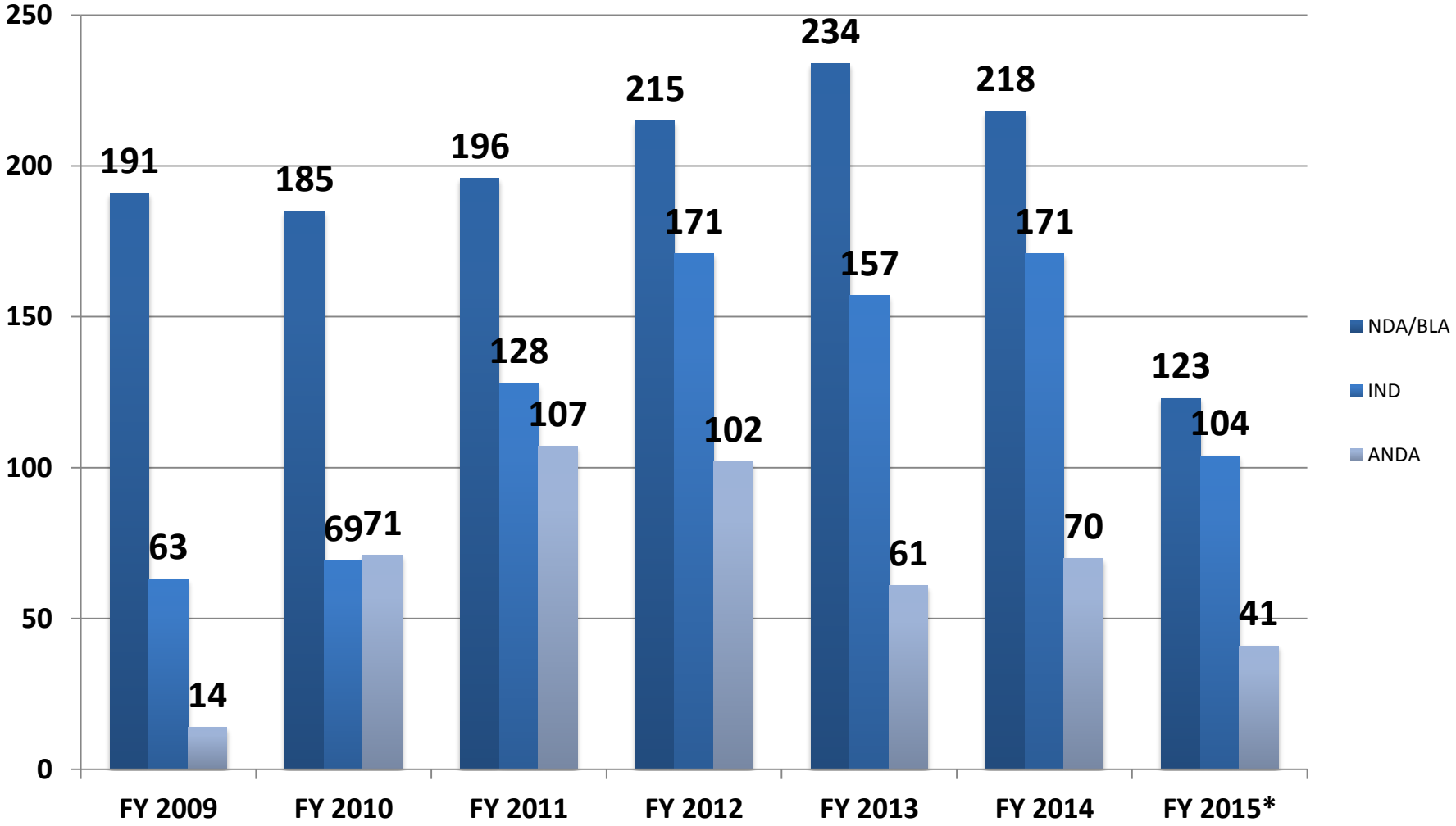
Mid-point

- Feedback given to DMEPA by OPDP, clinical and other discipline
- FDA prescription study results returned
- Internal discussions occur regarding any identified safety or misbranding concerns

Finalize

- Application review team notified of name conclusion
- Applicant notified that proposed name is conditional acceptable or unacceptable via a letter sent by DMEPA

CDER/CBER Proprietary Name Submissions (type, by FY)

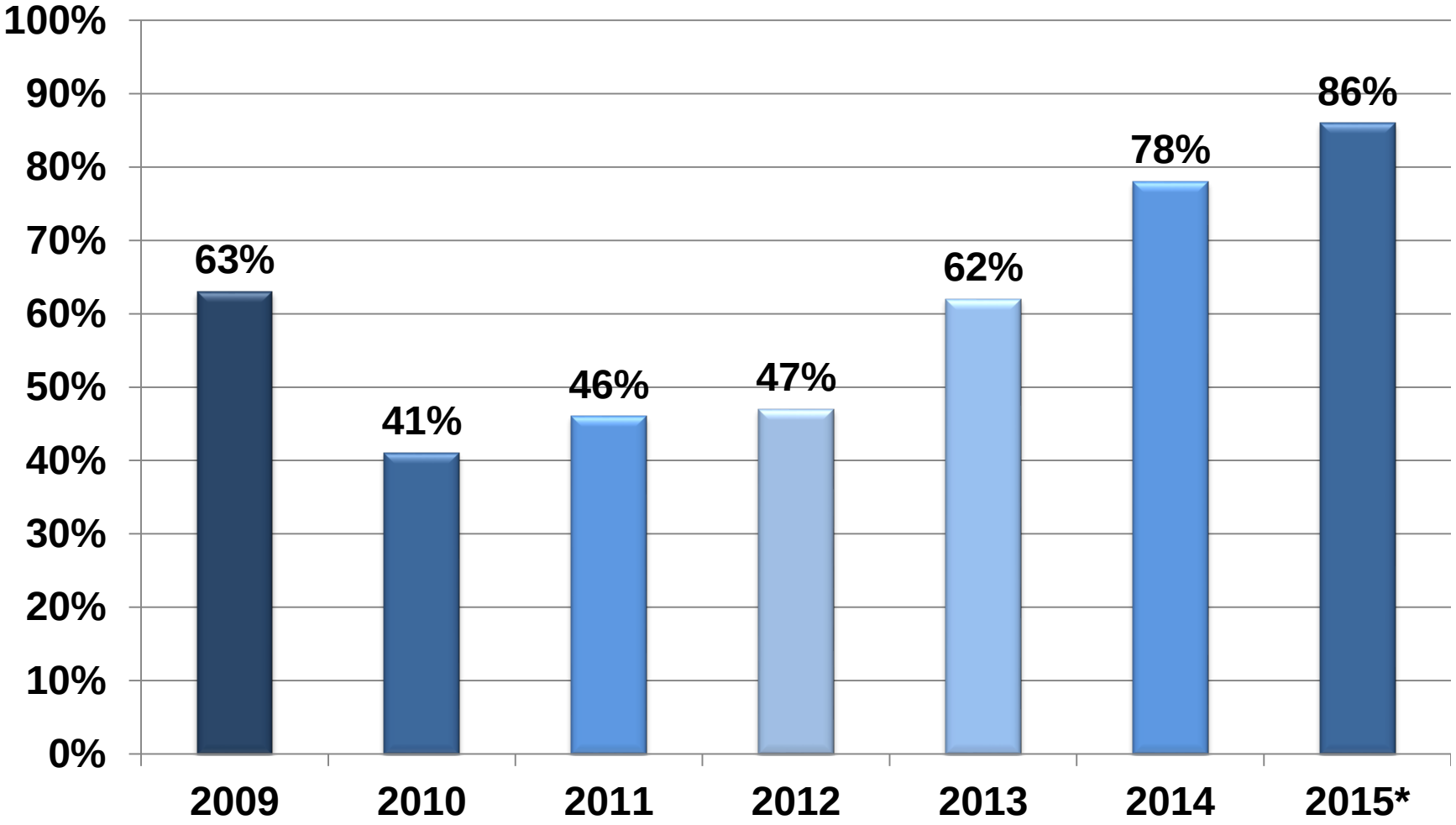


* CDER/CBER FY 2015 data from 1 Oct 2014 through 30 April 2015

PNR Submissions: Supporting Studies FY14/15 experience

- Submissions to CDER accompanied by an supporting evaluation of the proposed name
  - FY 14 = 58%; FY 15 YTD = 71%
- When our conclusion differs from the supporting study, we address the difference in the decisional letter
- Studies to support a proposed name following guidance in part
  - Mainly safety focused, some include misbranding assessments
  - Majority include name simulation studies, screen for USAN stems and other error-prone attributes using checklists

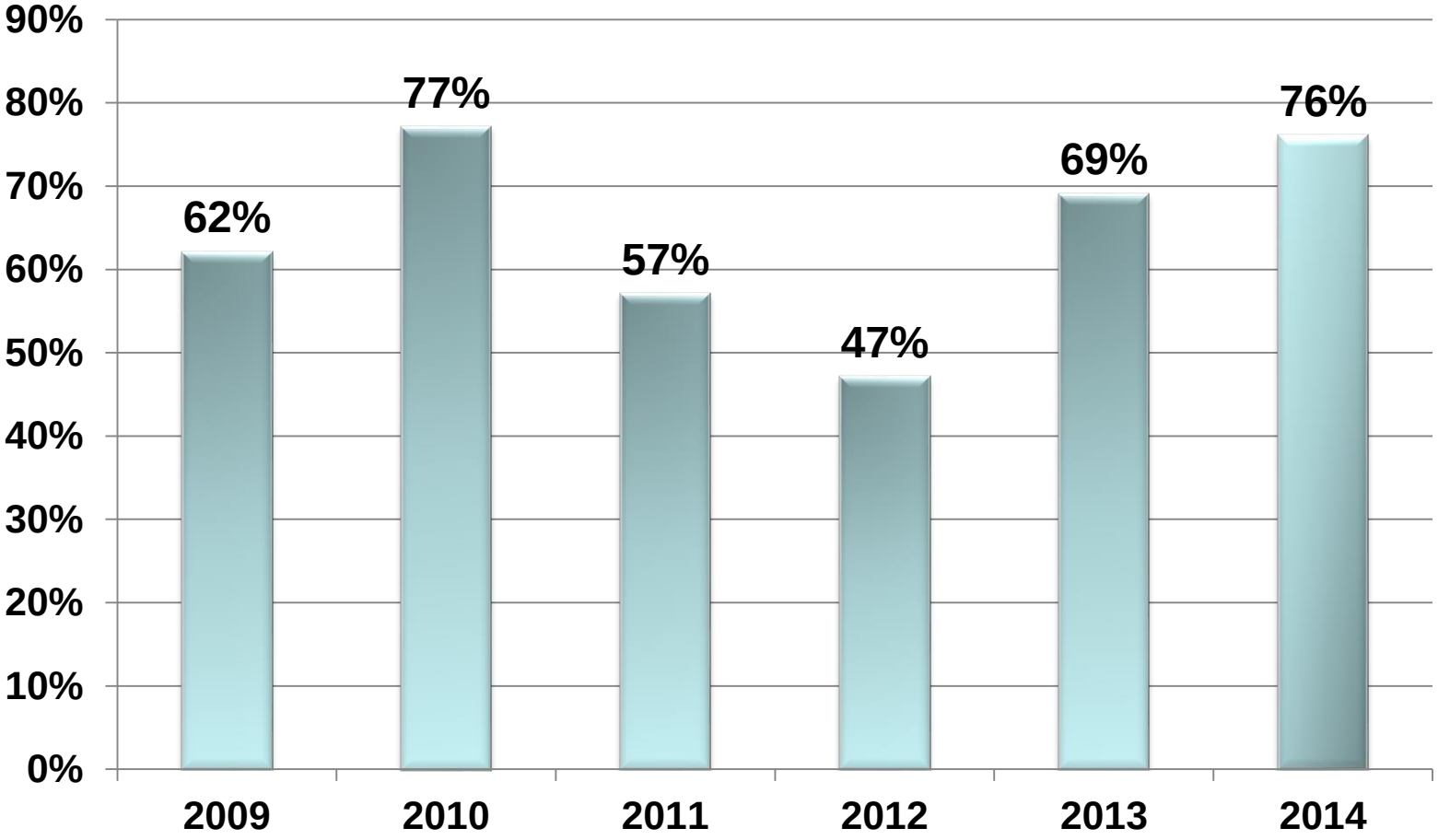
CDER Granted rates (% of names evaluated)**



*FY 2015 data from 1 Oct 2014 through 30 April 2015

**Percentages calculated based on # of completed evaluations

CBER Granted rates (% of names evaluated)**



* CBER FY 2015 data currently not available

**Percentages calculated based on # of completed evaluations

CDER: FY10-FY15** Name Denial Reasons

CDER Denials by Fiscal Year (NDA/BLA and IND)						
Reasons Identified for Rejection (Misbranding or Safety)*	**2010 # Reasons**	**2011 # Reasons**	**2012 # Reasons**	**2013 # Reasons**	**2014 # Reasons**	**2015** # Reasons**
Misbranding	19 (8%)	21 (10%)	28 (11%)	31 (16%)	29 (25%)	2 (4%)
Safety (similar in spelling, writing, or pronunciation)	177 (77%)	170 (78%)	199 (75%)	120 (63%)	72 (63%)	31 (63%)
Other Attributes Within the Name That Posed Risk for Error or Found to be Misleading	35 (15%)	27 (12%)	41 (15%)	40 (21%)	14 (12%)	16 (33%)
Total # Denial Reasons per Fiscal Year	231	218	268	191	115	49

* Some of the proposed proprietary name denials may include n multiple reasons serving as the basis for denial. Thus, the total # of reasons cited in any given year will exceed the total number # of denial decisions issued.

**FY 2015 CDER data from 1 Oct 2014 through 30 April 2015

Resources

- *Guidance: Contents of a Complete Submission for the Evaluation of Proprietary Names*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf

- *Draft Guidance: Best Practices in Developing Proprietary Names for Drugs*

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf

  Docket comments: http://www.regulations.gov/#!documentDetail;D=FDA-2014-D-0622-0001

- *Public Docket: Exploring the Possibility of Proprietary Name Reservation for Drug Products*

https://www.federalregister.gov/articles/2014/07/28/2014-17691/exploring-the-possibility-of-proprietary-name-reservation-for-drug-products-establishment-of-a

Resources (continued)

- *Proprietary Name Review Concept paper (PILOT PROGRAM):*
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072229.pdf

- *FDA name differentiation project (TALL MAN lettering list):*
  http://www.fda.gov/Drugs/DrugSafety/MedicationErrors/ucm164587.htm

Resources (continued)

- Webinar hosted on 15 July 2014

- Overview of the *draft* Proprietary Name Review guidance that focuses on the safety aspects in the development and selection of proposed proprietary names for all prescription and nonprescription drug products and biological products.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm403376.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery