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**Strategies for Filing NDI
Notifications with No FDA
Objections – Try and Try Again**

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Tweeting about this conference?

#ACIWandH



NDIs: Background

New dietary ingredients (NDIs) defined by DSHEA:

- 🌿 “...a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994.”

Premarket notification required*

- 🌿 “...information which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.”

Premarket approval NOT required



NDIs: Background

*Notification NOT required if the NDI is:

- 🌾 “...an article used for food in a form in which the food has not been chemically altered.”

Congressional Statement of Agreement:

- 🌾 “the term ‘chemically altered’ does not include the following physical modifications: minor loss of volatile components, dehydration, lyophilization [sic], milling, tincture or solution in water, slurry, powder, or solid in suspension.”



NDIs: Background

Five specific requirements (21 CFR 190.6):

- Name and address of the distributor or manufacturer (either of the NDI or the DS in which it will be used).
- The name of the ingredient, which must include the Latin binomial (including the author) if a botanical.
- A description of the supplement containing the NDI including the level of use and conditions of use.
- The evidence on which a reasonable expectation of safety is based; inc. English translations of references.
- A signature.

Unstated information requirements:

- A description of the NDI itself.
- Part of the plant if a botanical.



FDA Response options

- File without substantive comments.
- Specific objection, because FDA states:
 - The ingredient is NOT reasonably expected to be safe.
 - The NDI is not a “dietary ingredient” as defined (or the intended end product is not a “dietary supplement”).
 - The notification does not conform to 21 CFR 190.6.
- Other objection, where FDA states the notification does not provide sufficient information to make a safety determination.



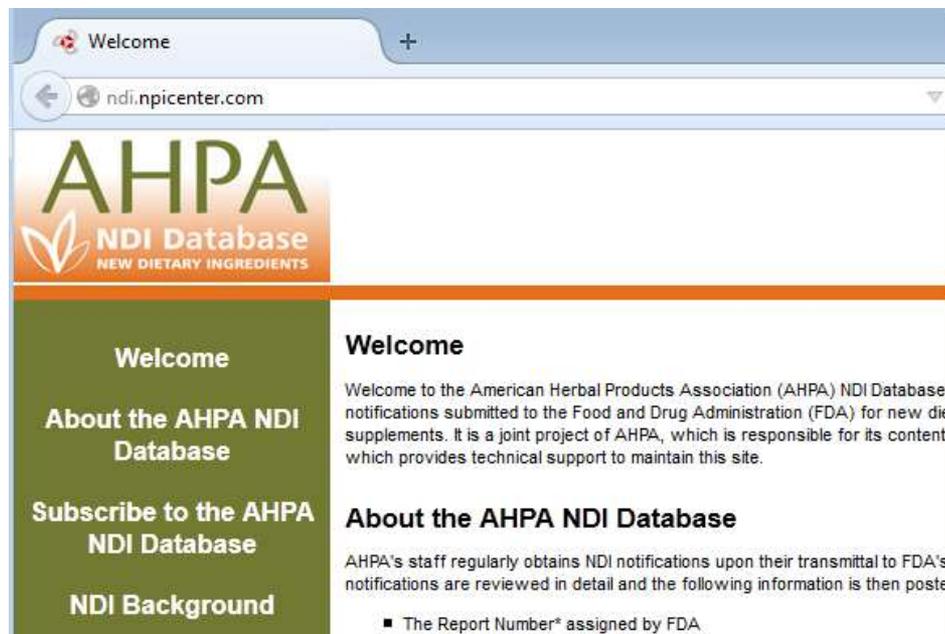
FDA Response options

- Other objection, where FDA states the notification does not provide sufficient information to make a safety determination:
 - Failure to fully characterize the NDI (*“FDA was unable to determine the identity of [the NDI].”*)
 - Disconnect between studies submitted as evidence of safety and the specific NDI (*“It is unclear how [the NDI] is qualitatively or quantitatively similar to the material [that is the subject of the safety information].”*)



The AHPA NDI Database

- Continually updated online access to NDI notifications.
- Includes actual documents (when provided by FDA), links to associated submissions, and an “outcome statement.”



<http://ndi.npicenter.com/>

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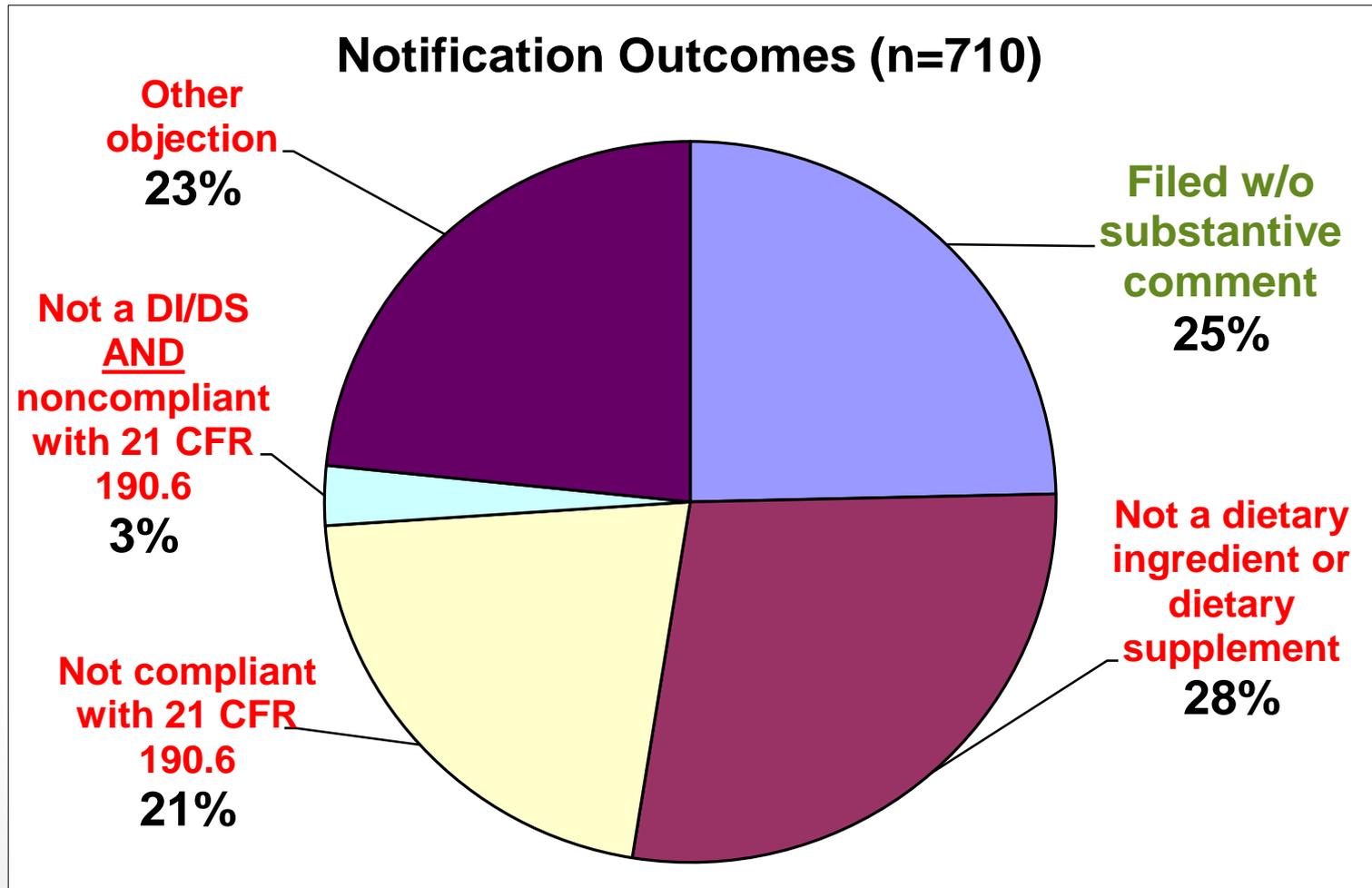


NDI notifications 1995-2014

- 710 NDI notifications filed
 - 175 filed w/o substantive comment
 - 369 specific FDA objections (identified as unsafe; not a dietary ingredient or dietary supplement; not in compliance with some detail in 21 CFR 190.6).
 - 166 other FDA objections (FDA: “information provided inadequate to support a reasonable expectation of safety for the ingredient;” “information provided inadequate to establish identity of the new dietary ingredient;” etc.).



NDI notifications 1995-2014



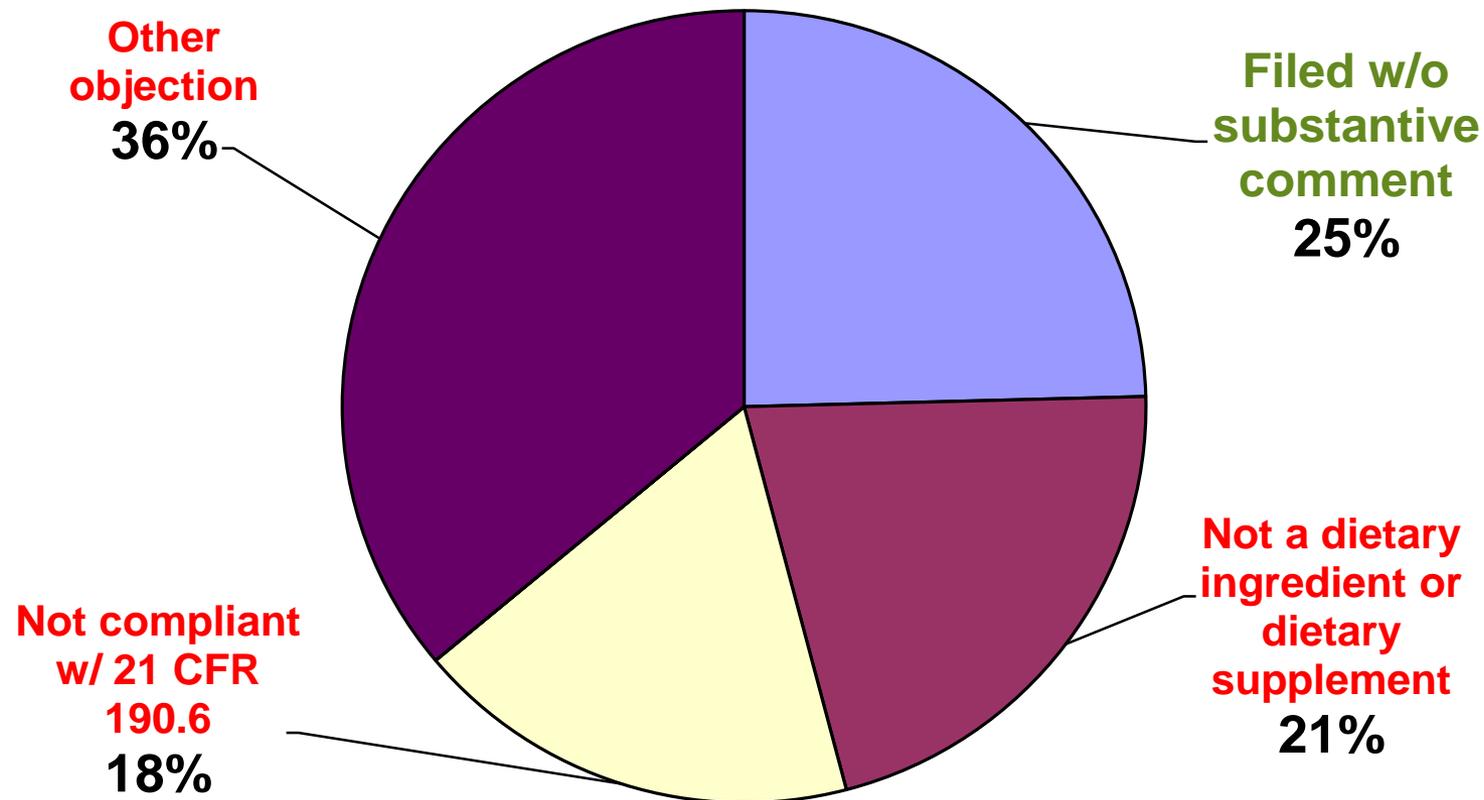
NDI notifications 2012-2013

- 61 NDI notifications filed
 - 15 filed w/o substantive comment
 - 24 specific FDA objections (not a dietary ingredient or dietary supplement; not in compliance with some detail in 21 CFR 190.6).
 - 22 other FDA objections (FDA: “information provided inadequate to support a reasonable expectation of safety for the ingredient;” “information provided inadequate to establish identity of the new dietary ingredient;” etc.).



NDI notifications 2012-2013

Notification outcomes (n=61)



NDI strategy = “Try...”

🌱 Examples of NDIs ≠ dietary ingredient

NDI	Reason
Enteric coated L-menthol derived from <i>Mentha arvensis</i>	“...intended to be used 'to restore the normal function of the GI tract ... due to Irritable Bowel Syndrome.”
Extract of trichosanthes root	Indicated to treat diabetes.
<i>Escherichia coli</i> strain Nissle 1917	“...not a dietary ingredient...”
Human placenta extract	“...human tissue is not 'food' or a 'dietary ingredient’”
N-Acetylcysteine (NAC) Ethyl Ester	“FDA first approved N-Acetylcysteine (NAC) as a new drug in 1985.”



NDI strategy = “Try...”

🌳 Examples of NDIs ≠ dietary ingredient

NDI	Reason
Pine tree phytosterols	“It is not clear how phytosterol esters that are synthetically derived from the extract of pine species...are a dietary ingredient.”
Calanus Oil extracted from a marine crustacean <i>Calanus finmarchicus</i>	“FDA [could] find no evidence...that [the source ingredient] has ever been used as human food [so] ...not a dietary substance for use by man to supplement the diet by increasing the total dietary intake.”
DS containing <i>trans</i> -resveratrol	“...first authorized <i>trans</i> -resveratrol to be an investigational new drug on January 30, 2001 [and] “does not have any information” on previous DS marketing.



NDI strategy = “Try...”

- 🌿 Examples of failure to comply with 21 CFR 190.6 (Most common: Level of the NDI; English translations; botanical author.)

Missing information

The “name of the new dietary ingredient that is the subject of the premarket notification, including the Latin binomial name (including the author) of any herb or botanical.”

“...the complete English translation of material submitted in a foreign language.”

“...the author of the botanical...[and] the level of NDI...and...conditions of use...[and]...reprints or copies of references cited.”

“...the signature of the person designated by the manufacturer of the dietary supplement...[and] the author of the botanical.”



NDI strategy = “Try...”

🌱 Examples of “other” objections.

FDA’s concerns:

FDA stated it was “unable to establish the identity of [the NDI], as the notification stated the extract would contain a minimum concentration of 1% huperzine A, but did not contain any information for the remaining 99%. Acceptance criteria did not provide an upper limit...for residual organic solvents...[and] an adequate description of the manufactur[ing process] was not provided.”

“...it was unclear whether the NDI was dried plant material or an extract.”

“The agency also stated that it was unclear whether the test substances used in the referenced studies were the same as the NDI.”

“The agency stated that the notification failed to... identify the manufacturing process used to produce the NDI.”



NDI strategy = “Try...”

🌿 Examples of “other” objections.

FDA’s concerns:

FDA noted “an acute toxicity study of [the NDI] administered to six rats which found ‘rapid, 100% mortality of the test animals at the highest dose’ appears ‘in the absence of further relevant information...to not provide a basis to support a determination that chronic consumption of [the NDI] will reasonably be expected to be safe.’”

The agency stated that it was “not evident that the test substances used in the referenced studies were qualitatively or quantitatively similar to [the NDI], or how the test studies were relevant to evaluating the safe use of [the NDI] under the recommended conditions of use.”

FDA stated the notification “lacked information regarding the testing for residual hexane and a specification for hexane removal from the final product.”



NDI strategy = “...try again.”

- FDA objections identify the specific issues viewed as incomplete.
- Review and revision, followed by resubmission, can address these issues.
- Resubmission can result in “success” (i.e., FDA files without substantive comment)



NDI strategy = “...try again.”

■ Case studies: A 67 percent “failure” rate?

248	Objection: noncompliance with 21 CFR 190.6
268	Other objection
300	Filed without comment
349	Other objection
369	Other objection
388	Filed without comment

NDI strategy = “...try again.”

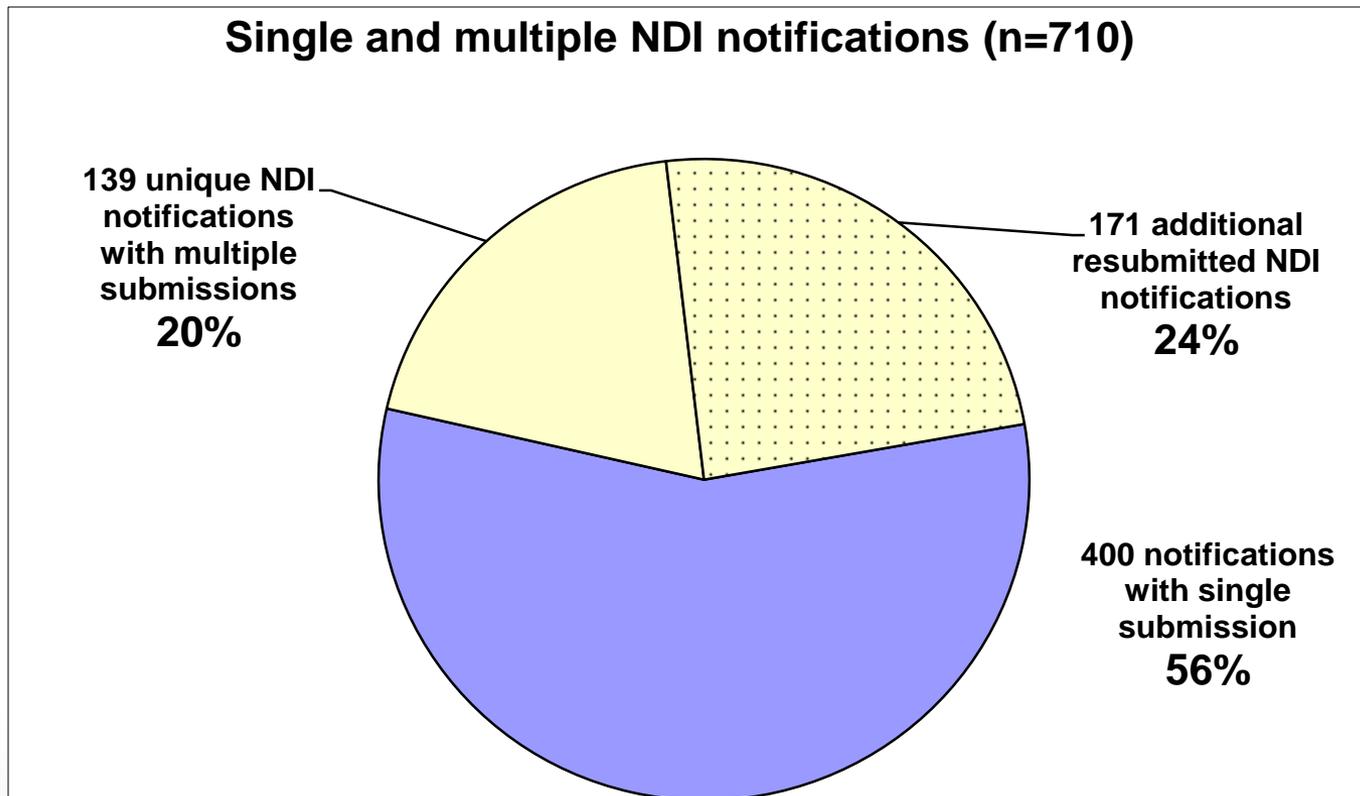
■ Case studies: In fact, 100 percent “success”

248	Access Business Group: Kakadu plum fruit extract (6/2004)	Objection: Not in 21 CFR 190.6 compliance
268	Access Business Group: Kakadu plum fruit extract (12/2004)	Other objection
300	Access Business Group: Kakadu plum fruit extract (9/2005)	Filed without comment
349	POM Wonderful: Pomegranate fruit polyphenol extract (4/2006)	Other objection
369	POM Wonderful: Pomegranate fruit polyphenol extract (8/2006)	Other objection
388	POM Wonderful: Pomegranate fruit polyphenol extract (12/2006)	Filed without comment



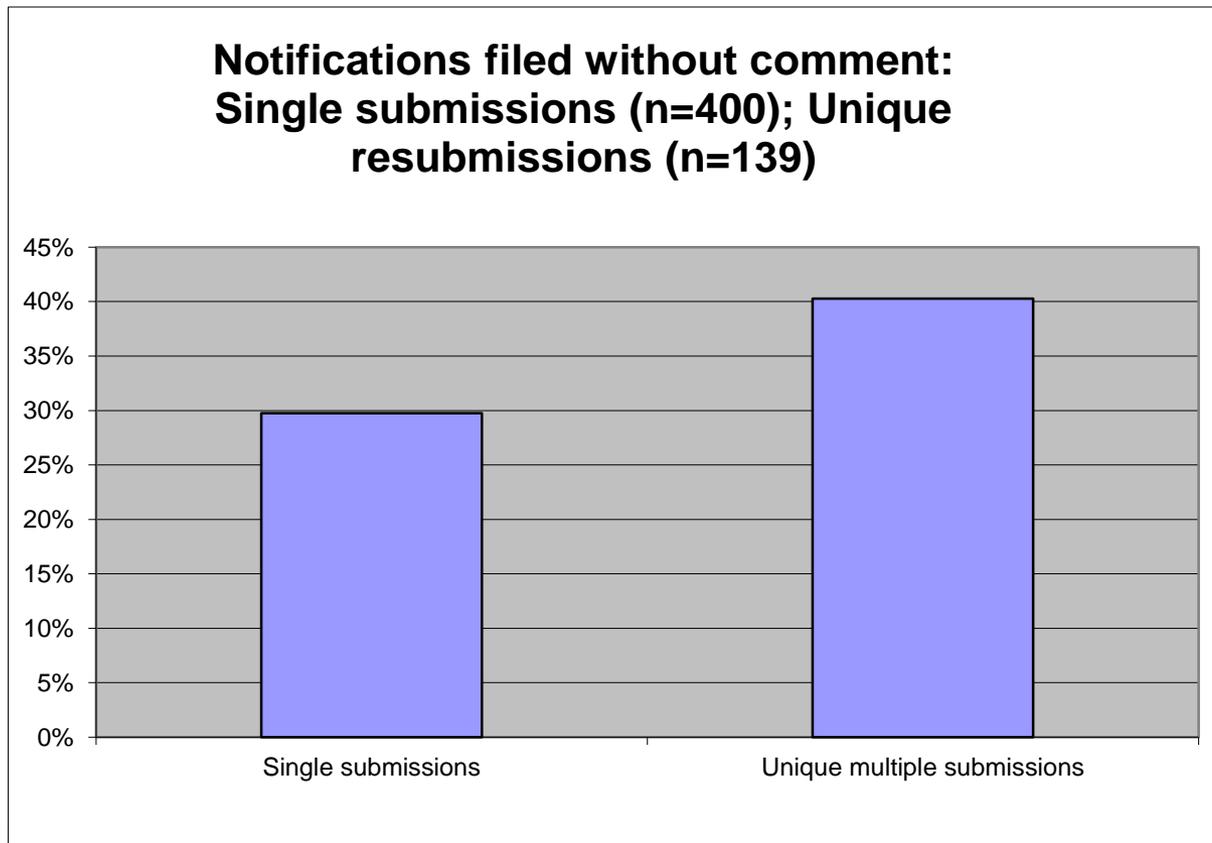
NDI strategy = “...try again.”

Multiple submissions = 44% of all NDINs (1995-2013)



NDI strategy = “...try again.”

- “Successful” outcome (i.e., filed by FDA w/o substantial comment) more frequent in NDIs with resubmissions.



Summary

- Accurately and completely describe the NDI.
- Create an informative narrative that clearly associates the NDI to the evidence submitted.
- Comply with all 21 CFR 190.6 details the first time.
- Don't make drug claims in notifications.
- Be prepared to document pre-IND marketing and conformity with 21 U.S.C. 321(ff)(1) definition.
- Get good advice (legal and scientific).
- Try, try again!



Good advice:

AHPA Members with NDI experience

Legal	Scientific/technical
Amin Talati (Ashish Talati)	AIBMR (Alex Schauss)
Bayne & Associates (Cassandra Soltis)	Burdock Group (George Burdock)
Greenberg Traurig (Jim Prochnow)	DBA Analytical (Jennifer Morr)
Kilpatrick Townsend (Emalee Murphy)	GRAS Associates (Richard Kraska)
Kleinfeld Kaplan & Becker (Tony Young)	Intertek/CANTOX (David Bechtel)
Patton Boggs (Stuart Pape)	PlantaPhile (Thomas Brendler)
Ropes & Gray (Paul Rubin)	Spherix Consulting (Claire Kruger)
Ryley Carlock (Susan Brienza)	
Ullman Shapiro & Ullman (Marc Ullman)	
Venable LLP (Claudia Lewis)	



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THANK YOU!

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American Herbal Products Association

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