Investigational New Drug applications: a 1-year pilot study on rates and reasons for clinical hold

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Received 4 November 2015
Revised 3 December 2015
Accepted 16 December 2015

ABSTRACT

Background The Food and Drug Administration (FDA)'s Center for Drug Evaluation and Research (CDER) receives about 1500 initial Investigational New Drug applications (INDs) per year. In the first 30 days after initial IND submission, FDA conducts a review to determine whether the proposed investigation is safe to proceed, and if not, the IND may be placed on clinical hold.

Methods A retrospective study of rates and reasons for clinical hold for all initial INDs submitted to CDER in fiscal year (FY) 2013 was performed. INDs were assessed for reasons that led to clinical hold, included chemistry, manufacturing and controls (CMC), animal toxicology or clinical issues. INDs were further categorized by commercial versus research sponsorship, and rare versus common disease indications. All INDs placed on hold were reassessed by whether they remained on hold within the first year following hold imposition.

Results CDER received 1410 initial INDs in FY 2013, of which 125 (8.9%) were placed on hold during the first 30 days after initial submission. Of the INDs placed on hold, more than half became active within the first year after first imposition of hold. CMC reasons were most commonly cited, followed by clinical, then toxicology reasons. There were no substantive differences in rates and reasons for hold between INDs for rare or common disease indications, or between commercial or research INDs.

Conclusions The vast majority of initial INDs moved forward within 30 days after submission, and for those applications placed on hold, most became active within 1 year. The findings also suggest that many holds for new drug product programs can be avoided by following the available guidelines for investigational product development.

Significance of this Study

What is already known on this subject?

- There are no previous publications on the rates and reasons for clinical holds for investigational new drug applications (INDs) submitted to the Food and Drug Administration (FDA)'s Center for Drug Evaluation and Research (CDER).
- There is little published in the medical literature on the topic of clinical holds for INDs submitted to other FDA centers.
- Good practices for IND preparation and submission is an area that often lacks clarity for many clinical investigators.

What are the new findings?

- More than 90% of initial INDs submitted to CDER are able to move forward into clinical trials 30 days after submission, and for those INDs placed on clinical hold, more than half come off hold within 1 year after first imposition of hold.
- The most commonly cited reasons for clinical hold were for product quality issues, followed by clinical then toxicology issues.
- There were no substantive differences in rates and reasons for clinical hold between INDs for rare or common disease indications, or for commercial or research INDs.

How might it impact on clinical practice in the foreseeable future?

- The findings from this study suggest that many of the identified issues leading to clinical hold can be avoided by taking a proactive approach and by following guidelines and regulatory advice for investigational new drug product development.

INTRODUCTION

In the United States (US), conducting research on human participants with an investigational new drug or biological product[i] requires submission of an Investigational New Drug application (IND) to US Food and Drug Administration (FDA).[1] An investigational drug can be a novel drug that has not previously been administered to human subjects (ie, first-in-human use), or a drug whose active pharmaceutical ingredient (API) has previously been administered to human subjects, but is now being investigated for a different use or indication other than what it was approved for (repurposed) or a drug not approved in the US for this use. In all these cases, the drug is considered to be an investigational new drug, and is subject to regulation and oversight by the FDA.[2]

[i]Drugs and biological products will heretofore be referred to as "drugs" unless otherwise specified.

To cite: Lapteva L, Pariser AR. *J Investig Med* 2016;**64**:376–382.

The initial submission of an IND requires the study sponsor, drug manufacturer and research or principle investigator (collectively referred to as the 'sponsor') to wait 30 days after the application is submitted prior to proceeding with administration of the investigational new drug to human subjects.[3] During this time, FDA conducts a review of the application to determine whether the proposed investigation is safe to proceed. Generally, the IND will be evaluated by a multidisciplinary team of experts, including those with a background in product quality, animal toxicology, clinical and other disciplines.[4] If the proposed human clinical trial(s) under the IND is determined to be not safe to proceed, the IND may be placed on clinical hold (referred to as 'hold', and includes full hold and partial hold, see box 1).[5 6] While IND trials may be placed on hold at any time during clinical development, the first 30 days after the initial application submission is the first evaluation of the appropriateness and safety of use of an investigational new drug in human subjects, is the time when sponsors must wait for FDA review prior to proceeding, and is a common time for FDA-sponsor communications.

Box 1 Grounds for Imposition of Clinical Hold

Food and Drug Administration (FDA) may place a proposed or ongoing clinical investigation on clinical hold if it finds that:

Clinical Hold of a Phase 1 Study under Investigational New Drug application (IND).[6]

1. "Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;
2. The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;
3. The investigator brochure is misleading, erroneous, or materially incomplete; or
4. The IND does not contain sufficient information… to assess the risks to participants of the proposed studies.
5. The IND is for the study of an investigational drug intended to treat a life-threatening disease that affects both genders, and men or women with reproductive potential who have the disease are being excluded form eligibility because of a risk or potential risk of reproductive toxicity."[6]

Clinical Hold of a Phase 2 or 3 study under an IND.[6]

1. Any of the conditions listed above for Phase 1 studies; or
2. "The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives." [6]

Full (or complete) clinical hold and partial clinical hold are defined as.[5]

Full Clinical Hold: "A delay or suspension of all clinical work requested under IND."[5]

Partial Clinical Hold: "A delay or suspension of only part of the clinical work requested under the IND (eg, a specific protocol or part of a protocol is not allowed to proceed; however, other protocols or parts of the protocol are allowed to proceed under the IND)."[5]

To our knowledge, there have been no published assessments of reasons for clinical hold for initial IND applications to FDA's Center for Drug Evaluation and Research (CDER), nor an informative assessment of what happens to initial INDs after they are submitted to CDER. The Agency's review of INDs is under strict confidentiality rules that prohibit public disclosure of commercial confidential information,[7] and FDA cannot publically communicate knowledge about deficiencies associated with individual applications. While holds are frequently publically communicated for individual INDs by their sponsors (such as through a press release), these communications appear to be largely for the purpose of disclosing relevant information under Security and Exchange Commission rules, and are not usually intended for dissemination or discussion of the scientific issues underlying the hold.[8] Thus, in order to better understand the issues related to holds, we evaluated the initial INDs submitted to CDER in FY 2013 to assess how many were placed on hold during the first 30 days after initial IND submission, to explore the reasons for hold imposition (product quality, animal toxicology, or clinical), and to assess the fate of those applications placed on hold within 1 year following the hold imposition. Investigational new drugs were also assessed by whether they were novel or repurposed.

We additionally evaluated whether there were differences between drugs being investigated for rare and non-rare disease indications (a rare disease, also known as an orphan disease, is defined by the Orphan Drug Act (ODA) and includes a disease or condition affecting less than 200,000 persons in the US[9]).

The main purposes for conducting this 1 year pilot study were to identify frequent or potentially preventable reasons for hold and to assess any trends toward higher numbers of holds by selected IND application attributes. We presupposed that gaining a better understanding of the reasons for hold may enable IND applicants to avoid the future problems with IND submissions and to help facilitate pharmaceutical product development.

METHODS

FDA CDER's internal Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) database was searched for all original IND submissions with reported document activity ('INDs with activity') during FY 2013 (filtered for submissions received on October 1, 2012 through September 30, 2013). These submissions included those related to ongoing INDs and INDs submitted for the first time (total n=10,223 INDs). From this cohort, we identified all INDs submitted for the first time (referred to as initial INDs) and extracted them for further analyses.

The submissions were retrieved independent of the source and thus, included commercial and investigator-initiated ('research') INDs[ii]. INDs with investigational new drugs for rare diseases were identified according to the DARRTS submission property type 'rare disease'.

[ii]Both identified in DARRTS.

Table 1 FDA CDER FY2013, Initial INDs submitted and placed on hold

	All initial INDs	Initial INDs for rare diseases	Initial INDs for non-rare diseases
Number of initial INDs submitted, n	1410	211	1199
Initial INDs active after first 30 days, n (%)	1285 (91.1)	186 (88.2)	1099 (91.7)
Initial INDs placed on hold within first 30 days, n (%)	125 (8.9)	25 (11.8)	100 (8.3)
Sponsor type			
Commercial initial INDs submitted, n (%)	705 (50.0)	108 (51.2)	597 (49.8)
Research initial INDs submitted, n (%)	705 (50.0)	103 (48.8)	602 (50.2)
Commercial initial INDs on hold, n (%)	60 (4.3)	12 (5.7)	48 (4.0)
Research initial INDs on hold, n (%)	65 (4.6)	13 (6.2)	52 (4.3)

IND, Investigational New Drug application.

The initial INDs were categorized as those for rare and non-rare diseases and by commercial or research sponsor, and then analyzed for the rates and reasons that led to the regulatory action of hold. For the reasons resulting in hold, the hold notification letters issued to IND applicants were retrieved from the DARRTS database and examined for relevant information. The reasons for hold were further categorized into those related to clinical, animal toxicology, and product quality issues, and combinations of these issues. All INDs that had been placed on hold were also examined for evidence of drug repurposing. INDs for which the API had not previously been approved in the US for any indication were categorized as novel products, and those for which the API had been approved and was being investigated for a different indication or in a new formulation were categorized as repurposed.

In this study, we re-evaluated all initial INDs that were placed on hold within the first year following the hold imposition, and assessed whether they remained on hold, had been removed from hold by FDA (became 'active'), or were withdrawn by the sponsor. For those INDs that became active, we calculated the number of days from date of imposition of hold to active status.

This was a descriptive, retrospective, cross-sectional study and did not include a prespecified statistical hypothesis. Descriptive statistics analyses were prepared using Microsoft Excel 2010.

RESULTS

During FY 2013, there were a total of 1410 initial INDs submitted to CDER, including 211 (15%) rare disease INDs and 1199 (85%) non-rare disease INDs (table 1). All 6 Offices of Drug Evaluation (ODEs) and 17 of 18 Review Divisions within CDER's Office of New Drugs (OND) received and reviewed INDs for rare and non-rare diseases during the time period of the study.[iii] [10] [11] Approximately half of the applications submitted were from commercial sponsors and approximately half from research sponsors.

Overall, 8.9% (125/1410) of the INDs were placed on hold during the first 30 days after initial IND submission, including 11.8% (25/211) of rare disease INDs and 8.3% (100/1199) of non-rare diseases INDs (table 1). Of the 125 INDs placed on hold, 61.6% (77/125) were applications for novel products and 38.4% (48/125) were for repurposed drugs (table 2). Hold rates were similar for commercial 4.3% (60/125) and research 4.6% (65/125) IND sponsors (table 1).

Reasons for clinical hold

Table 3 shows the distribution of reasons for hold among 125 INDs placed on hold within the first 30 days of submission for rare and non-rare disease indications. As shown, rare disease INDs were placed on hold for clinical reasons in 28% (7/25), inadequate investigational product quality in 20% (5/25), and inadequate animal toxicology data in 16% (4/25) of initial INDs; the remaining 36% (9/25) were placed on hold for combinations of these reasons. The non-rare disease INDs were placed on hold for clinical reasons in 27% (27/100), inadequate investigational product quality in 30% (30/100), and inadequate animal toxicology data in 13% (13/100) of initial INDs; the remaining 30% (30/100) were placed on hold for combinations of these reasons. Of note, 6% (6/100) of non-rare disease INDs had substantial inadequacies, which included issues with product quality, and toxicology, and deficient clinical protocols (table 3). There were no discernable trends in rates and reasons for hold by discipline when considered by commercial versus research sponsor (data not shown).

Overall, issues related to product quality were commonly cited as reasons for hold in letters to drug sponsors in 48% (60/125) either alone or in combination with other issues.[12] Concerns with inadequate product quality were listed as leading to hold, at least in part, in 50% (50/100)

Table 2 Initial INDs placed on hold, product novelty

Investigational new drugs	All initial INDs on hold, n=125	Initial INDs for rare diseases on hold, n=25	Initial INDs for non-rare diseases on hold, n=100
Novel, n (%)	77 (61.6)	14 (56.0)	63 (63.0)
Repurposed, n (%)	48 (38.4)	11 (44.0)	37 (37.0)

IND, Investigational New Drug application.

[iii]Division of Nonprescription Regulation Development (DNRD) is not expected to receive INDs because the Division's primary responsibility is development of monographs as part of over-the-counter (OTC) drug review.

Table 3 Initial INDs on hold by reason

Discipline	Initial INDs on hold		
	All, n=125	Rare diseases, n=25	Non-rare diseases, n=100
Clinical, n (%)	34 (27.2)	7 (28.0)	27 (27.0)
Product quality, n (%)	35 (28)	5 (20.0)	30 (30.0)
Toxicology, n (%)	17 (13.6)	4 (16.0)	13 (13.0)
Clinical and product quality, n (%)	14 (11.2)	4 (16.0)	10 (10.0)
Clinical and toxicology, n (%)	10 (8)	2 (8.0)	8 (8.0)
Product quality and toxicology, n (%)	5 (4)	1 (4.0)	4 (4.0)
Clinical, product quality and toxicology, n (%)	6 (4.8)	0	6 (6.0)
Device, n (%)	1 (0.8)	1 (4.0)	0
Clinical and device, n (%)	2 (1.6)	1 (4.0)	1 (1.0)
Clinical, device and toxicology, n (%)	1 (0.8)	0	1 (1.0)

IND, Investigational New Drug application.

of INDs for non-rare diseases and 40% (10/25) of INDs for rare diseases (table 4), and the majority of these deficiencies concerned either drug product alone or in combination with issues related to drug substance[iv].

We performed a detailed examination of the hold letters to identify some of the most frequently cited reasons for hold for product quality issues, which are summarized in table 4. Lack of appropriate certificates of analyses (COAs) for either drug substance or drug product was the most frequently cited product quality deficiency leading, at least in part, to hold overall (36.7% (22/60) cited for product quality deficiencies) and reflected insufficient information needed to assess the risks to participants in the proposed studies. Additional reasons included inadequate or absent analyses for the product batches intended for use in clinical investigations, issues with product stability and sterility, and inadequate manufacturing processes; two applications lacked composition descriptions for the proposed placebo formulations. Notably, seven submissions were lacking major parts of or the entire product's chemistry, manufacturing and control (CMC) sections.

In addition to the reasons shown in table 4, other problems with product quality leading to hold for either rare or non-rare disease INDs included presence of chemical impurities higher than acceptable thresholds, lack of information about formulation excipients, issues with container closure and storage systems, concerns with drug master files, inadequate or absent analyses for the batches intended for use in the proposed investigations, inadequate cytotoxicity assays and other issues with individual parameters or assays specific to product's composition.

[iv]21CFR314.3: *Drug product* means a finished dosage form, for example, tablet, capsule, or solution that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

Drug substance means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use in the synthesis of such ingredient.

Next, we examined deficiencies identified from the animal toxicological programs in the analyzed pool of initial INDs placed on hold. Inadequacies in animal toxicology studies, alone or in combination with other deficiencies, were listed as issues leading to hold in almost 1/3 of applications for both rare 28% (7/25) and non-rare 32% (32/100) diseases.

Table 4 also shows the numbers of INDs on hold for the following attributed categories of toxicology issues: (1) inadequately performed or insufficient toxicology studies to support the proposed clinical investigations; (2) toxicity signals observed in animals that needed to be addressed before further studies in humans could be conducted; or (3) undefined No Observed Adverse Effects Level (NOAEL) and/or insufficient safety margin for human studies. Notably, the majority of INDs placed on hold for toxicology reasons were placed on hold for inadequately performed or insufficient toxicology studies which were not performed in one or more species in accordance with the internationally-accepted pharmacotoxicology regulatory guidance,[13] and for studies not conducted according to the good laboratory practices.[14] In about 1/3 of both rare and non-rare disease INDs that were placed on hold for toxicology issues, unacceptable toxicity signals preventing human dosing were observed in one or more animal species. There were a few applications that were sent to FDA with either undefined NOAEL or inadequate safety margins determined for clinical studies. The NOAEL dosing level is typically determined from animal toxicology studies conducted in the most appropriate animal species for the product and is used to define a safe dosing range and safety margin in humans. In guidance to industry, FDA has described a number of acceptable approaches to determine a safe human range of doses.[13] The absence of a NOAEL in this context means that all animals had adverse events with all doses tested in the non-clinical toxicology program.

We additionally examined all clinical deficiencies that were cited as reasons for hold. Clinical reasons, alone or in combination with non-clinical issues, were cited as reasons for hold in 56% (14/25) of INDs for rare diseases and 53% (53/100) of INDs for non-rare diseases. Table 4 shows commonly cited clinical deficiency reasons for hold. Given that the analyzed pool included only INDs submitted for the first time, the vast majority of clinical reasons—92.8% (13/14) for rare diseases and 92.5% (49/53) for non-rare diseases—were not related to an observed safety signal with the drug in humans, but rather consisted of inadequate safeguards incorporated into protocols for selection of patients for study, systematic approach to assessment, recording, reporting and treating expected and unexpected adverse drug reactions in future trial participants, as well as placement of decision criteria for dosing discontinuation in individual patients and studies on observation of adverse drug reactions. Other deficiencies noted in the hold letters included inadequate description of risks to human subjects in informed consent documents and issues with investigator's brochures. Notably, 7.1% (1/14) rare disease IND and 7.5% (4/53) non-rare disease INDs were placed on hold for known but unaddressed specific safety concerns previously observed with use of either the API of the investigational drug itself or a class of related drugs.

Table 4 Selected issues leading to hold*

Selected issues leading to hold	Initial INDs on hold	
	Rare diseases, n=25	Non-rare diseases, n=100
Product quality†		
Initial INDs on hold for product quality issues, n (%)	10 (40.0)	50 (50.0)
Product quality hold issues with	n=10	n=50
Drug product, n (%)	7 (70.0)	27 (54.0)
Drug substance, n (%)	0	4 (8.0)
Drug substance and drug product, n (%)	3 (30.0)	17 (34.0)
Placebo formulation, n (%)	0	2(4.0)
Selected product quality hold issues‡ with		
Lack of appropriate COAs for either drug substance or drug product, n (%)	4 (40.0)	18 (36.0)
Lack of assurance of drug product stability, n (%)	2 (20.0)	16 (32.0)
Lack of assurance of drug substance or drug product sterility, n (%)	1 (10.0)	7 (14.0)
Inadequate manufacturing process, n (%)	0	8 (16.0)
Lack of CMC information section in IND, n (%)	2 (20.0)	5 (10.0)
Toxicology†		
Initial INDs on hold for inadequate toxicology data, n (%)	7 (28.0)	32 (32.0)
Toxicology hold issues with	n=7	n=32
Inadequately performed or insufficient toxicology studies, n (%)	4 (57.1)	20 (62.5)
Unaddressed toxicity signal observed in animals, n (%)	2 (28.6)	10 (31.3)
Lack of NOAEL or insufficient safety margin, n (%)	1 (14.3)	2 (6.3)
Clinical†		
Initial INDs on hold for clinical reasons, n (%)	14 (56.0)	53 (53.0)
Clinical hold issues with	n=14	n=53
Inadequate safeguards incorporated in protocol(s), n (%)	13 (92.9)	49 (92.5)
Unaddressed known safety concern, n (%)	1 (7.1)	4 (7.5)

*Percentages in the table correspond to numbers of applications with deficiencies per each discipline.
†Includes all INDs for which the discipline was cited as a reason for hold, either alone or in combination with other disciplines.
‡Only selected issues are represented for product quality, therefore, the numerators do not add to the denominator.
CMC, chemistry, manufacturing and controls; COA, certificate of analysis; IND, Investigational New Drug application; NOAEL, no observed adverse effect level.

One year follow-up

The INDs that were placed on hold were followed up for 1 year after the first imposition of hold. Overall, 51.2% (64/125) INDs placed on hold came off hold and were active at some point within 1 year after a hold was first imposed (table 5). For the 25 rare disease INDs placed on hold, 76% (19/25) became active in the first year as did 45% (45/100) of the non-rare disease INDs. For these applications overall, the median time for removal of hold was 111 days (range 32–341 days).

Table 5 Status of initial INDs within one year after imposition of hold

	Initial INDs on hold	
	Rare diseases, n=25	Non-rare diseases, n=100
Remain on hold, n (%)	6 (24.0)	49 (49.0)
Withdrawn, n (%)	0	6 (6.0)
Hold removed, active, n (%)	19 (76.0)	45 (45.0)
Time to removal of hold (days)*	n=19	n=45
Mean	129	107
Median	151	126
Minimum, Maximum	52,301	32,341

*For active applications only.
IND, Investigational New Drug application.

DISCUSSION

This retrospective, cross-sectional 1 year pilot study of data obtained from CDER's internal database represents an assessment of rates and reasons for the regulatory action of IND hold issued by FDA after review of INDs submitted to CDER for the first time in FY 2013. The overall rate of hold among initial INDs was low and comprised 8.9% (125/1410) of all initial INDs. More than half of the initial INDs placed on hold (51.2% (64/125)) became active within the first year after first imposition of hold. Taken together, more than 95% of initial INDs became active within the first year after IND submission. This suggests that most drug development programs submitted are generally of good quality, drug sponsors are able to meet US- and internationally-recognized safety requirements for initiating investigational new drug testing and administration to human subjects, and that FDA review of initial INDs does not result in substantial delay to human testing for the majority of applications. A clinical hold action results in a detailed hold letter to the drug sponsor, in which a complete listing of the reasons for hold and the information needed to resolve hold are delineated. The action of hold may be perceived by some stakeholders as an adversarial

decision likely to prolong drug development time and delay product approval and marketing. However, we found that the deficiencies leading to a hold of clinical investigations in this cohort of INDs were often shown to be resolvable, either through submission of missing information or amendment of safeguards in clinical plans, and for most applications, this generally occurred within a relatively short amount of time relative to overall timelines for drug development.

The most common reasons for hold were clinical and product quality issues. Poor quality investigational material constitutes an immediate and significant risk to the health of the trial participants and, given the central place of product quality in any development program, has the potential to place at risk the entire drug development program. There is extensive guidance available to sponsors on FDA's website for most circumstances relating to product quality and manufacturing, and sponsors are urged to consult these sources prior to IND submission. Product quality is also an appropriate topic of discussion at pre-IND meetings.[15 16] For clinical issues, failure to incorporate appropriate safeguards into clinical protocols was the most common clinical reason for hold, although five applications (table 4) included drugs with known safety concerns that were not addressed in the proposed protocols. Toxicology issues were less commonly cited as reasons for hold in our study. When toxicity signals are observed in animal toxicology studies, the hold decisions often depend on the origin and magnitude of the issue, applicability of the observed animal findings to the potential drug effects expected in humans, reversibility of the changes, and the ability to monitor the projected adverse effects in humans, among other factors. To this end, safety concerns that led to hold imposition based on observations of toxicity signals in animal studies may or may not be resolvable. If deemed resolvable, such issues can be resolved in a variety of ways, which include, for example, conducting additional animal toxicology studies, incorporating safety modifications in clinical protocols, and providing data-driven scientific rationales to support absence of relatedness of the observed signal to the effects of the drug. Because occurrence of toxicity signals with novel products is often difficult to predict and their identification may preclude safe use of investigational drugs in human subjects, appropriate conduct of animal toxicology studies is expected for all investigational drugs.

This study did not reveal substantial differences in rates and reasons for hold between INDs for investigational new drugs for rare and non-rare disease indications (table 3). While the initial hold rate was slightly higher for rare disease INDs, more rare disease INDs came off hold within the first year after imposition of hold than did non-rare disease INDs, and the percent of INDs becoming active within the first year of submission was generally similar between the two. The study also showed that commercial- and research-sponsored INDs had hold rates that were generally similar.

Not unexpectedly, more applications with novel drugs were placed on hold compared to repurposed drugs in rare and non-rare disease categories. This is likely due to the existing knowledge with repurposed drugs, and hence, less uncertainty associated with their use.

Limitations of this study relate to the retrospective nature of this analysis which included only a subset of INDs submitted to FDA during one fiscal year (FY). Active INDs for which a hold was imposed during the ongoing investigations after the initial IND was allowed to proceed were not included in this study; they will be a topic for additional analysis. Also, this study only encompassed initial INDs received by FDA in a 1-year time period; however, based on the number of IND applications received, hold rates observed in FY2013, and the absence of any recent policy changes related to IND regulations, we do not have any reason to believe that the findings for FY2013 would be markedly different from other recent years. While this study represents the first qualitative assessment of reasons for hold imposition with initial IND submissions to CDER, we were able to locate two other studies[17 18] examining applications submitted to CBER, which noted similar patterns of deficiencies resulting in hold and rates of hold in other years, which support the generalizability of the results. We additionally note that since this was the first assessment of initial IND holds at CDER, the information may be useful for further developing CDER's IND IT tracking system through the identification of critical scientific and regulatory attributes that may be used to enhance data capture from ongoing drug development programs over longer time periods.

In conclusion, this retrospective cross-sectional view was undertaken to evaluate the rates and the reasons for regulatory hold of initial IND applications submitted to CDER. The analysis showed that in this 1 year time period, the vast majority of initial IND submissions are allowed to proceed following FDA review, and for those applications placed on hold, most of the issues are resolvable. Our findings demonstrate that issues with product quality, inadequate conduct of toxicological programs and deficient clinical protocols constitute concerns only in a small percentage of drug development programs. The findings also suggest that many of the identified issues leading to hold can be avoided by taking a proactive approach and by following guidelines and regulatory advice for investigational new drug product development. This study further helped to identify IND application attributes critical for the quantification of rates and reasons for hold that could be captured over a longer time period with the intended purpose of informing regulatory advice or policy that may improve drug development efficiency.

Acknowledgements The authors of this article would like to thank Nader Qassim and Sallamar Worrell for their help with DARRTS IND applications search and identification, and Drs Todd Bourcier, Ramesh Raghavachari, and Robert O'Neill for their comments and review of this article.

Disclaimer The opinions represented in this article are those of the authors and do not necessarily represent the views or policies of the FDA.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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