

JUNE 2, 2015



MEDICAL DEVICE INNOVATION CONSORTIUM

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MEDICAL DEVICE INNOVATION
CONSORTIUM (MDIC) CLINICAL TRIAL
INNOVATION AND REFORM PROJECT
REPORT

EARLY FEASIBILITY STUDIES IN THE U.S.

-A SURVEY OF THE MEDICAL DEVICE INDUSTRY

MEDICAL DEVICE INNOVATION CONSORTIUM (MDIC) CLINICAL TRIAL INNOVATION AND REFORM PROJECT REPORT

INTRODUCTION TO THE MDIC EARLY FEASIBILITY SURVEY FROM MDIC CEO BILL MURRAY

One of CDRH's strategic priorities is to facilitate U.S. patient access to safe, effective new technologies of significant health importance first-in-the-world. To support this priority in October 2013, the agency released final guidance titled Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies. MDIC stakeholders support this important initiative because developing an efficient, transparent and predictable device development ecosystem, including clear guidelines for the earliest phases of testing medical devices, will help encourage medical device innovation in the U.S.

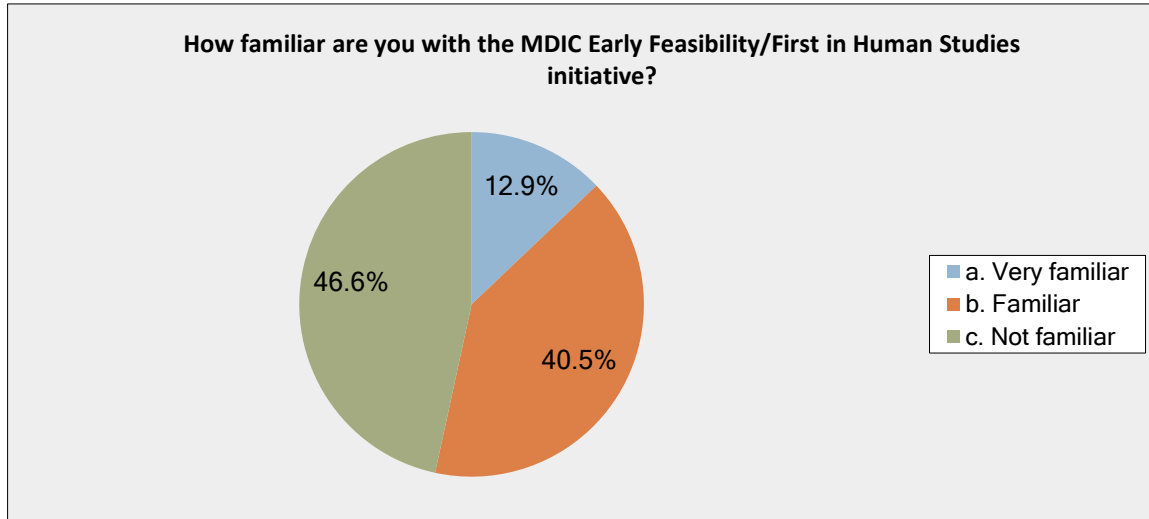
MDIC initiated an Early Feasibility project to facilitate the interpretation and use of this new CDRH guidance. We began the process by conducting in-depth interview with stakeholders in the medical device community to understand their perspective on U.S. early feasibility studies. Our second milestone was the completion of this survey of key stakeholders within the medical device ecosystem. The online 23 question survey was open for 8 weeks and was available to MDIC members and other relevant stakeholders in the medical device community. The survey received a total of 116 responses. While not a random sample, there was good representation of pre-revenue, small, medium and large companies. The results are illustrative of how medical device community view the barriers and opportunities with regards to U.S. early feasibility studies and potential solutions that may encourage companies to pursue such studies in the U.S.

A couple of notable takeaways from the survey. First, more than 57% of respondents indicated that they had not initiated an EFS study within the U.S. in the past two years. Second, almost 53% of companies initiated at least one EFS study exclusively outside the U.S. over the past two years; over half of those studies were conducted in Europe. Clearly, we must address this trend to achieve our patient access goal. Innovation and access are closely linked. Finally, while many respondents are not currently conducting EFS in the U.S., more than 60% indicated they are interested in trying EFS/FIH in the U.S. as a primary approach or as a parallel pathway.

The goal of MDIC's EFS project is to provide tools, methods and approaches that help sponsors understand and navigate this process. The next steps for this project will include educational outreach to MDIC members and other medical device stakeholders on US early feasibility studies, as well as the development of MDIC's planned "Blueprint for Early Feasibility Success," a best practices roadmap for navigating the challenges of early feasibility studies, including regulatory, ethical and legal considerations. We anticipate this Blueprint will be available in late 2015 on the MDIC web site: www.mdic.org/CTIR.

1. HOW FAMILIAR ARE YOU WITH THE MDIC EARLY FEASIBILITY/FIRST IN HUMAN STUDIES INITIATIVE?

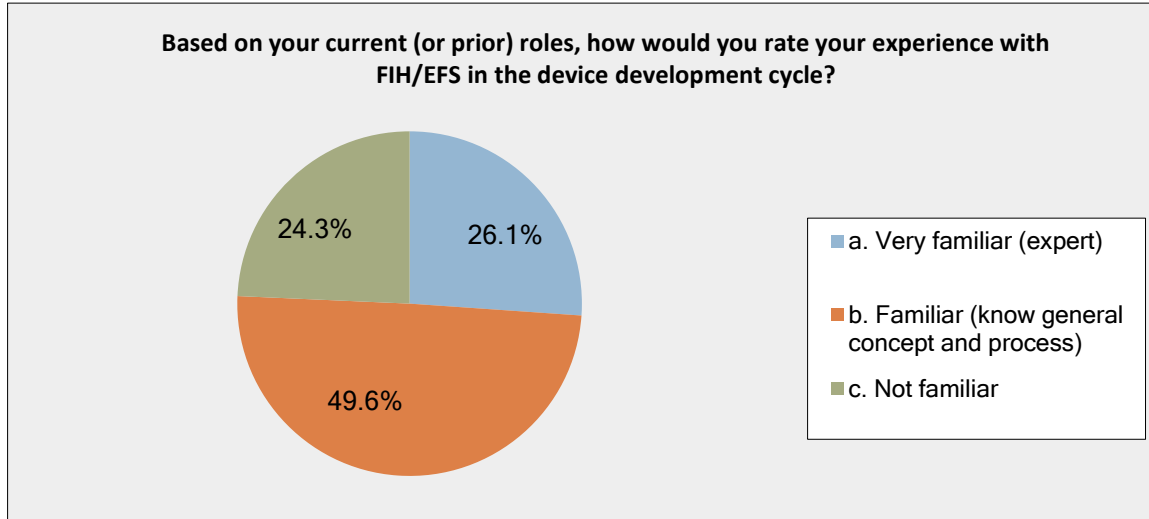
- A. VERY FAMILIAR
- B. FAMILIAR
- C. NOT FAMILIAR



N=116

2. BASED ON YOUR CURRENT (OR PRIOR) ROLES, HOW WOULD YOU RATE YOUR EXPERIENCE WITH FIH/EFS IN THE DEVICE DEVELOPMENT CYCLE?

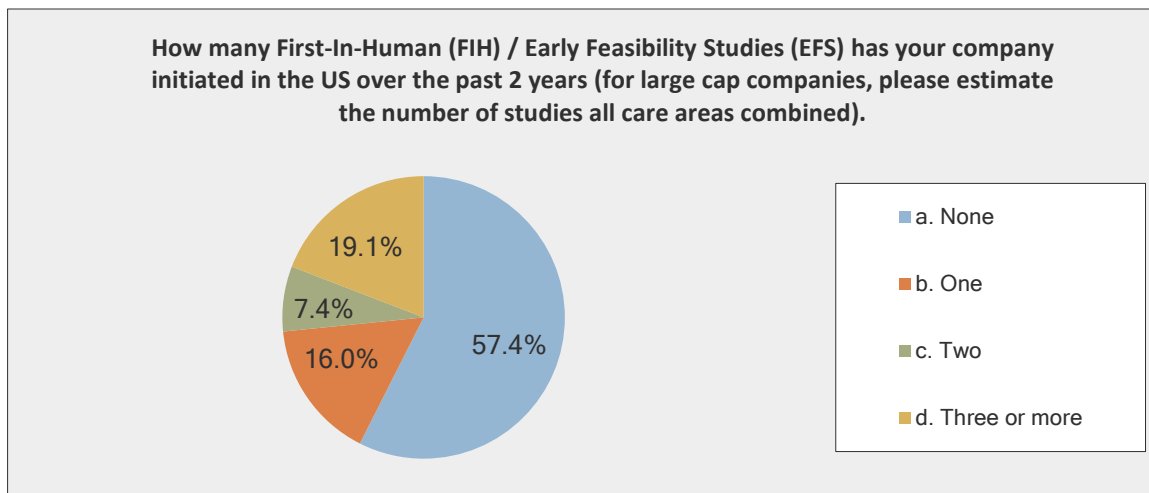
- A. VERY FAMILIAR (EXPERT)
- B. FAMILIAR (KNOW GENERAL CONCEPT AND PROCESS)
- C. NOT FAMILIAR



N=115

3. HOW MANY FIRST-IN-HUMAN (FIH)/EARLY FEASIBILITY STUDIES (EFS) HAS YOUR COMPANY INITIATED IN THE US OVER THE PAST 2 YEARS (FOR LARGE CAP COMPANIES, PLEASE ESTIMATE THE NUMBER OF STUDIES IN ALL CARE AREAS COMBINED).

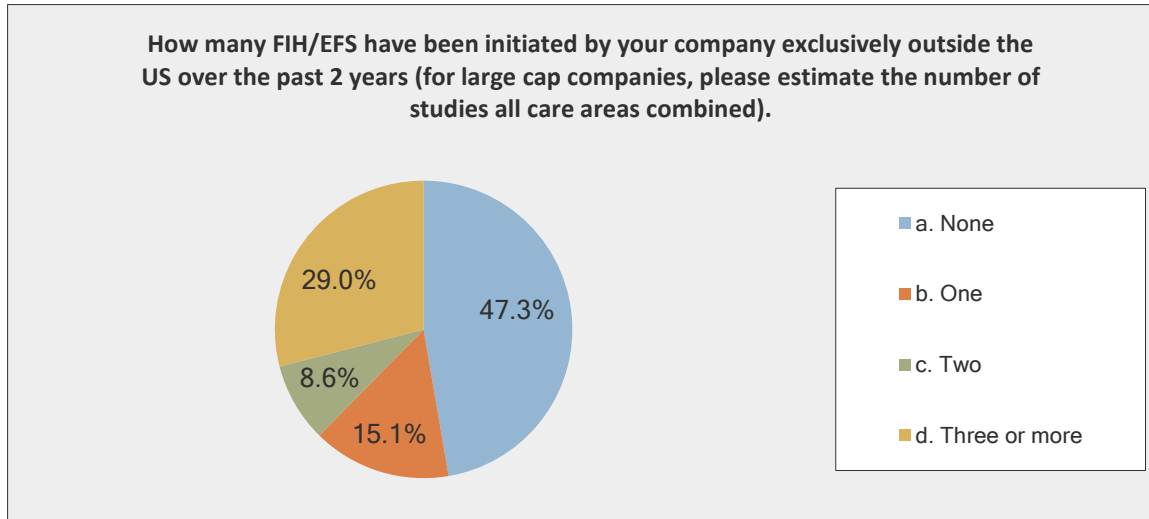
- A. NONE
- B. ONE
- C. TWO
- D. THREE OR MORE



N=115

4. HOW MANY FIH/EFS HAVE BEEN INITIATED BY YOUR COMPANY EXCLUSIVELY OUTSIDE THE US OVER THE PAST 2 YEARS (FOR LARGE CAP COMPANIES, PLEASE ESTIMATE THE NUMBER OF STUDIES IN ALL CARE AREAS COMBINED).

- A. NONE
- B. ONE
- C. TWO
- D. THREE OR MORE



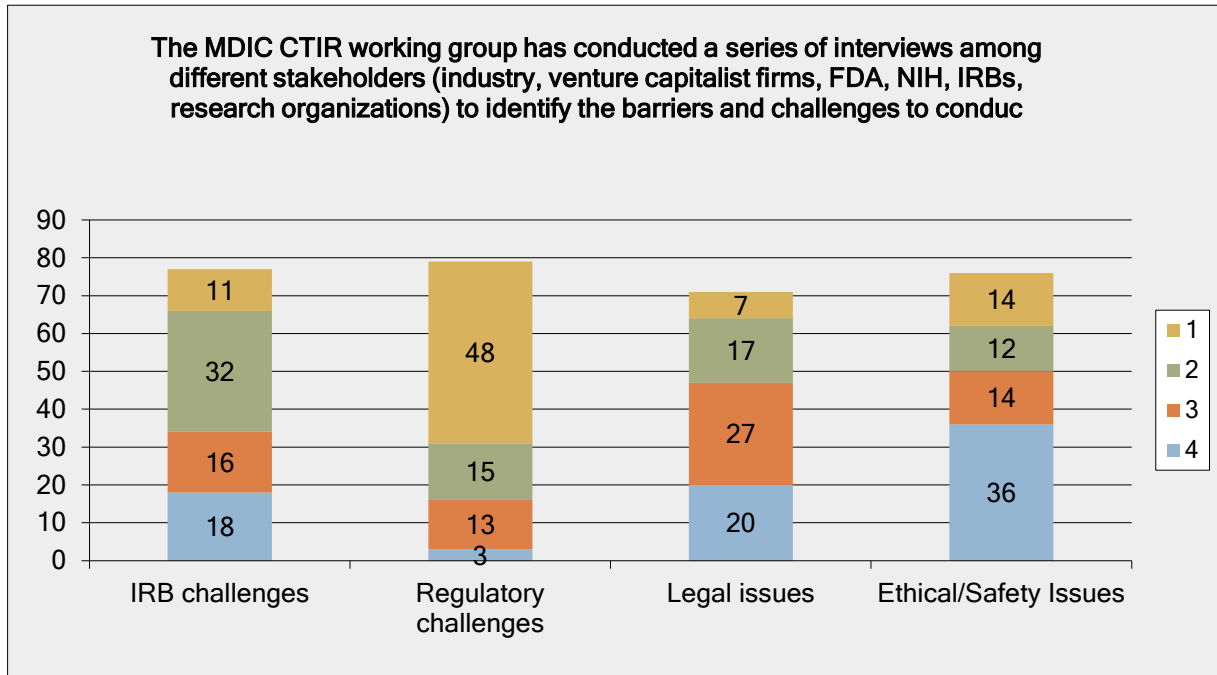
N=114

5. MY COMPANY HAS PERFORMED OUTSIDE US FIH/EFS PRIMARILY IN:

	Response Count
a. Canada	14
b. Europe	57
c. Asia & Asia-Pacific	21
d. Middle East	1
e. Mexico/Central & South America	9
f. Other	8

6. THE MDIC CTIR WORKING GROUP HAS CONDUCTED A SERIES OF INTERVIEWS AMONG DIFFERENT STAKEHOLDERS (INDUSTRY, VENTURE CAPITALIST FIRMS, FDA, NIH, IRBS, AND RESEARCH ORGANIZATIONS) TO IDENTIFY THE BARRIERS AND CHALLENGES TO CONDUCTING FIH/EFS IN THE US. SOME OF THESE CHALLENGES ARE LISTED BELOW. BASED ON YOUR COMPANY EXPERIENCE, HOW WOULD YOU RATE THE IMPACT OF THESE CHALLENGES ON THE EXECUTION OF FIH/EFS IN THE US [PLEASE RATE FROM THE MOST IMPORTANT (1) TO THE LEAST IMPORTANT (4)]:

- IRB CHALLENGES
- REGULATORY CHALLENGES
- LEGAL ISSUES
- ETHICAL/SAFETY ISSUES



N=85

Respondents were asked to rank the challenges from most to least important. 48/85 respondents indicated that regulatory challenges were most important. 14/85 indicated ethical and safety issues were most important. 32/85 indicated that IRB challenges were the second greatest challenge.

7. ARE THERE ANY OTHER IMPORTANT BARRIERS TO FIH/EFS IN THE US, IN YOUR EXPERIENCE, THAT ARE NOT LISTED ABOVE (QUESTION 6)? PLEASE LIST THEM ALONG WITH WHAT MDIC MIGHT DO TO OVERCOME THESE BARRIERS.

Important Barriers

- Cost
- Location of company R & D activities (if I am doing the research in Europe it is more likely I will do the study in Europe)
- Access to technology
- Physician access
- Access to patients

FDA reviewers are not usually prone to working with industry on facilitating new investigations. Management does not appear to be very engaged. Need to engage CBER as well for consistency

FIH & EFS are usually done once in a small company so the window may have been missed

Vendor personnel credentialing requirements - do they need to exist for Sponsor/CRO personnel involved in a clinical investigation?

The only other barrier I can think of is the financial barrier to the cost of doing these and ongoing studies. I think providing direction to smaller start-up companies on the options for early support for studies would be useful but may be in the scope of other groups.

Product Liability/Insurance in the U.S. is more difficult than EU countries for FIH studies. MDIC could work with Insurance companies to provide easier FIH application.

21 CFR 11 SOP development is challenging to a small company. Access to ICH-GCP compliant SOP templates would be very helpful

The most important is the exposure that comes the US and the risk associated with it. If you perform your first case in the US, all eyes are on it. That is risky for the very first human case. For case #10+, makes more sense.

Organizational training.

It would be helpful if CMS developed a guideline that would support coverage of standard of care procedures, even in the situation of a FIH/EFS.

Regulatory can be broken down into a number of specific areas. Consider evaluating US challenges related to biocompatibility testing.

IRB challenges are pretty broad. Many IRBs do not have sufficient members to adequately understand the risks as well as the risk/benefit profile of devices. There is not good training available for IRBs and members for how do some of these types of reviews so they are done inconsistently or incorrectly.

Access to funding to start and/or complete the trials

Important Barriers

We were not able to cross the regulatory barriers, so we abandoned efforts and moved them to Europe.

The new CMS process may have an impact on these types of studies, it would be good to have more information on how this will work.

FDA reviewers are reluctant to work with industry to approve studies regardless of having OUS experience. CBER is especially not consistent

General lack of understanding of FIH/EFS issues among non-clinical pharmacology professionals.

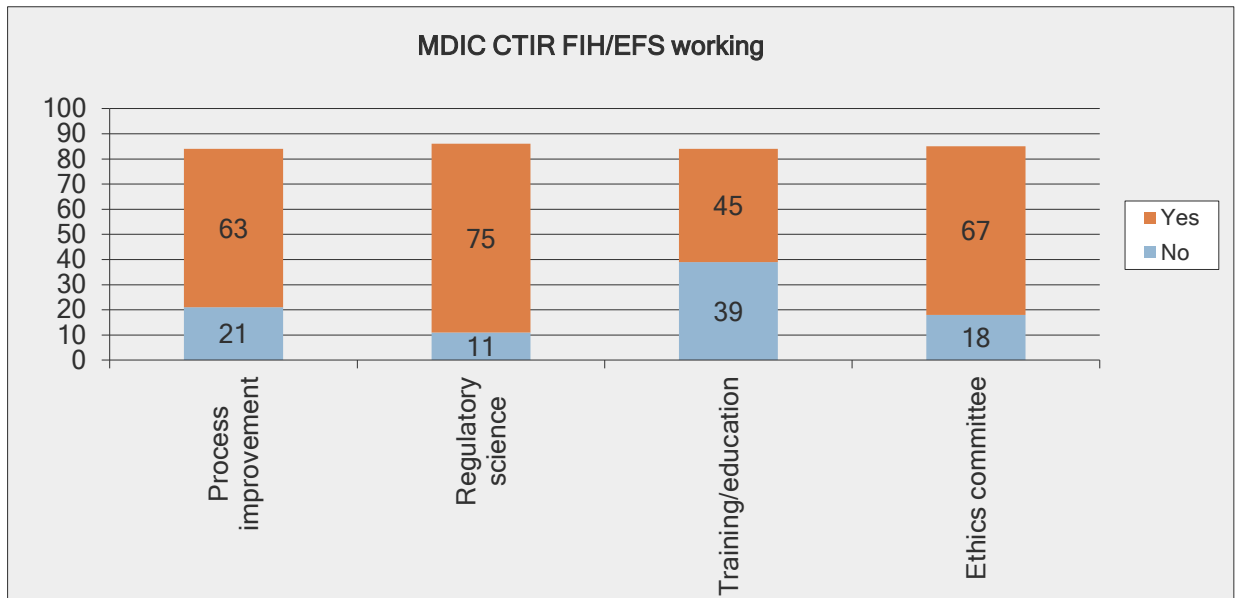
So much of what we are trying to do in FIH/EFS is to get feedback on a product effect and its design, and to be able to iterate quickly on the device to improve its safety and effectiveness. It is much easier to do that overseas where one may only need IRB approval to test changes to the device, whereas in the US you have to iterate through the FDA with each change.

Informed consent language requirements around risk for a device THIS early in the development process are likely to be a barrier to enrollments. In the US, the physician's "word" that it is okay is not what it used to be. Especially if companies are not going to pay for subject injury coverage. More trusting patient/doctor relationships + less litigious countries are more amenable to early research.

Regulations are a barrier, but I think the changes in the US IDE regulations are helping.

8. MDIC CTIR FIH/EFS WORKING GROUP IS COMMITTED TO EVALUATING ALL EXISTING OPPORTUNITIES AND WORKING WITH INDUSTRY, GOVERNMENT AGENCIES AND PATIENT ADVOCACY GROUPS TO HELP INCREASE THE NUMBER OF EFS/FIH IN THE US AS AN ULTIMATE GOAL. HOWEVER, BASED ON THE PRELIMINARY FEEDBACK RECEIVED, MDIC INTENDS TO FOCUS ITS FIRST INITIATIVE ON SPECIFIC TASKS/ACTIONS TO GAIN MOMENTUM AND SECURE SOME EARLY SUCCESSES. IN YOUR EXPERIENCE, WHICH OF THE FOLLOWING TASKS WOULD BE VALUABLE TO YOUR COMPANY AND LIKELY TO ENCOURAGE YOU TO CONDUCT FIH/EFS IN THE US.

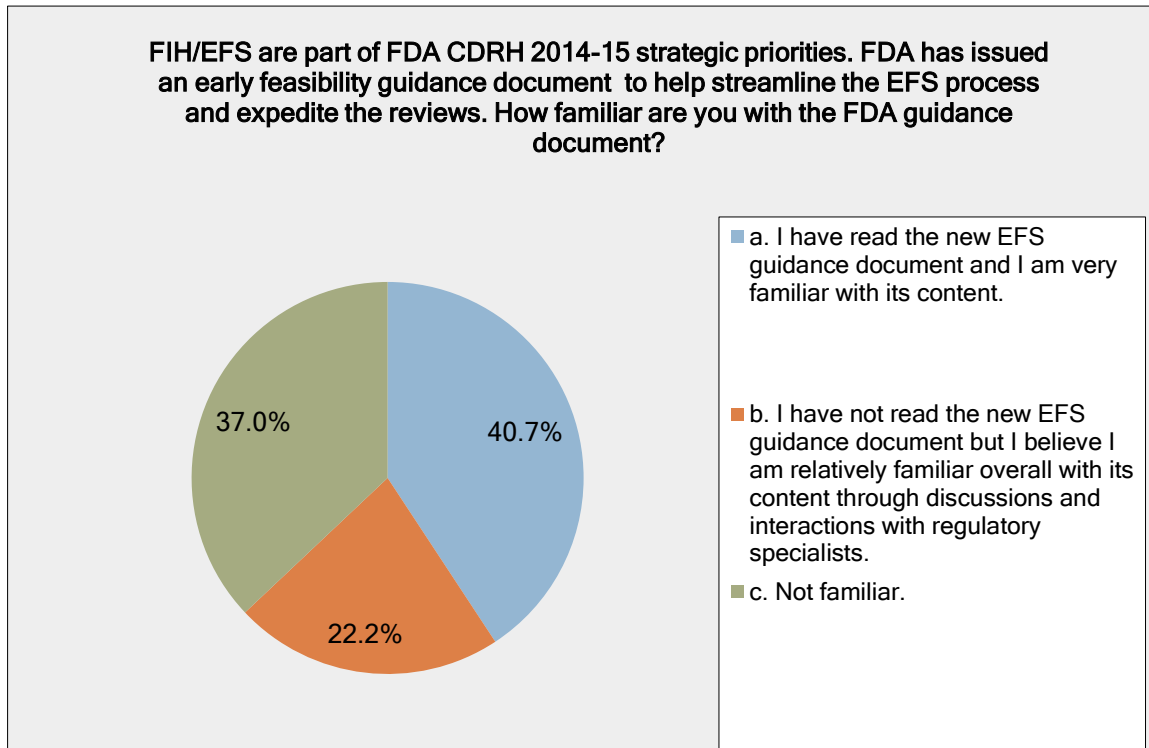
- **PROCESS IMPROVEMENT:** MDIC TO ISSUE A BLUE-PRINT BOOK ON “HOW TO CONDUCT FIH/EFS IN THE US”. THE BLUE PRINT BOOK WILL INCLUDE USEFUL INFORMATION ON THE REQUIREMENTS THAT NEED TO BE MET, CONTACT INFORMATION FOR KEY ORGANIZATION/PEOPLE, TEMPLATES, ETC.
- **REGULATORY SCIENCE:** MDIC TO WORK WITH FDA AND REGULATORY EXPERTS TO REDUCE THE BURDEN OF PRE-CLINICAL TESTING REQUIREMENTS FOR FIH/EFS (BIOCOMPATIBILITY, E/M TESTING, ETC.)
- **TRAINING/EDUCATION:** MDIC TO HELP ORGANIZE, PROMOTE “FDA-PUBLIC” FORUMS, WEBINARS ON EFS/FIH
- **ETHICS COMMITTEE:** MDIC TO WORK WITH (CENTRAL) IRBS TO STREAMLINE THE PROCESS OF SUBMISSION FOR EFS/FIH (A LIST OF PARTICIPATING IRBS WILL BE PROVIDED BY MDIC)



N=86

9. FIH/EFS ARE PART OF FDA CDRH 2014-15 STRATEGIC PRIORITIES. FDA HAS ISSUED AN EARLY FEASIBILITY GUIDANCE DOCUMENT¹ TO HELP STREAMLINE THE EFS PROCESS AND EXPEDITE THE REVIEWS. HOW FAMILIAR ARE YOU WITH THE FDA GUIDANCE DOCUMENT?

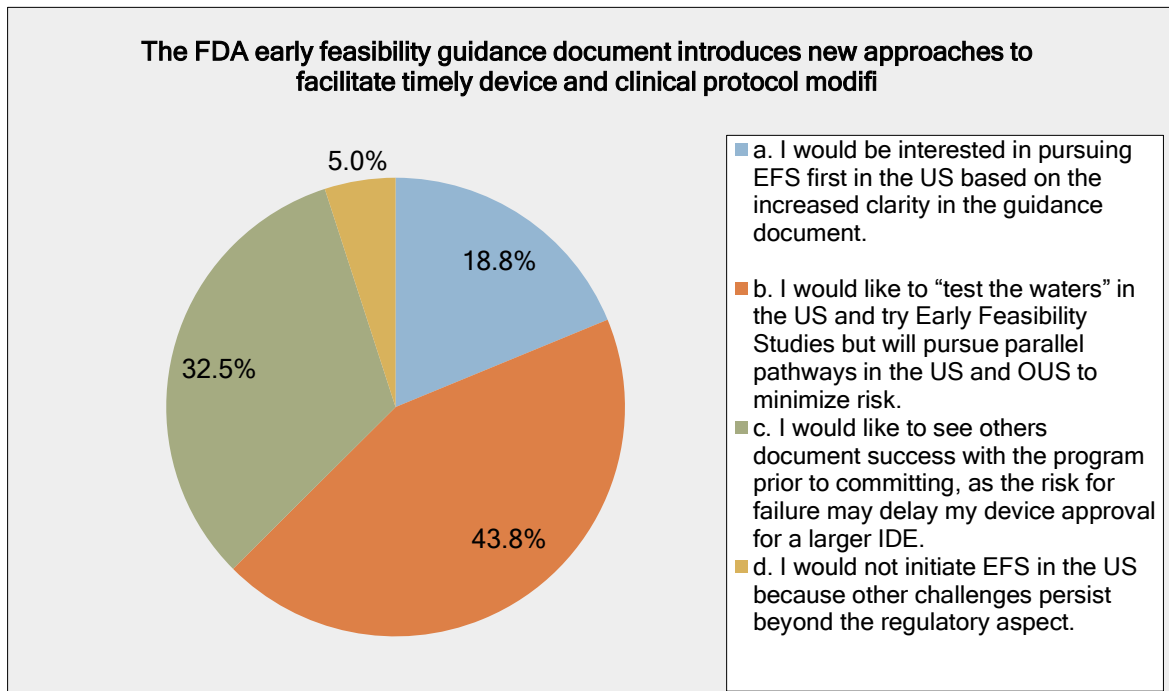
- A. I HAVE READ THE NEW EFS GUIDANCE DOCUMENT AND I AM VERY FAMILIAR WITH ITS CONTENT.
- B. I HAVE NOT READ THE NEW EFS GUIDANCE DOCUMENT BUT I BELIEVE I AM RELATIVELY FAMILIAR OVERALL WITH ITS CONTENT THROUGH DISCUSSIONS AND INTERACTIONS WITH REGULATORY SPECIALISTS.
- C. NOT FAMILIAR.



¹ <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>

10. THE FDA EARLY FEASIBILITY GUIDANCE DOCUMENT¹ INTRODUCES NEW APPROACHES TO FACILITATE TIMELY DEVICE AND CLINICAL PROTOCOL MODIFICATIONS DURING EFS INCLUDING 5-DAY NOTICE EXPANDED APPLICATION, CONTINGENT APPROVAL OPTION AND INTERACTIVE REVIEW. BASED ON YOUR EXPERIENCE WITH MEDICAL DEVICE DEVELOPMENT, WHAT IS YOUR FEELING ABOUT EFS IN THE US NOW THAT THE NEW GUIDANCE HAS BEEN ISSUED?

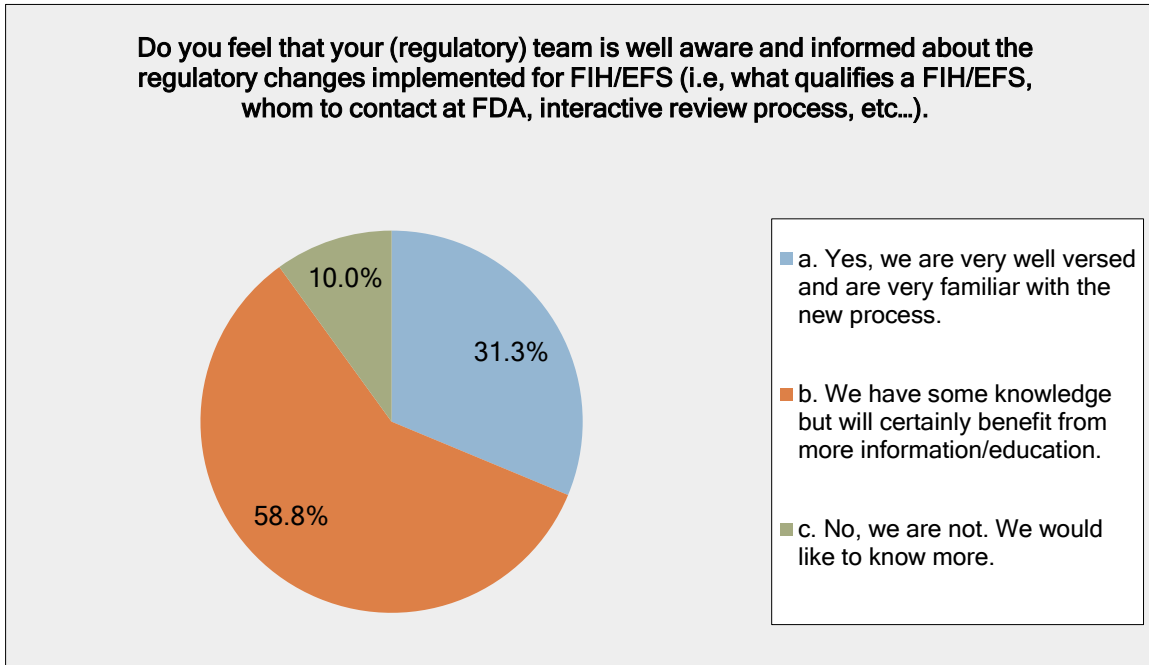
- A. I WOULD BE INTERESTED IN PURSUING EFS FIRST IN THE US BASED ON THE INCREASED CLARITY IN THE GUIDANCE DOCUMENT.
- B. I WOULD LIKE TO “TEST THE WATERS” IN THE US AND TRY EARLY FEASIBILITY STUDIES BUT WILL PURSUE PARALLEL PATHWAYS IN THE US AND OUS TO MINIMIZE RISK.
- C. I WOULD LIKE TO SEE OTHERS DOCUMENT SUCCESS WITH THE PROGRAM PRIOR TO COMMITTING, AS THE RISK FOR FAILURE MAY DELAY MY DEVICE APPROVAL FOR A LARGER IDE.
- D. I WOULD NOT INITIATE EFS IN THE US BECAUSE OTHER CHALLENGES PERSIST BEYOND THE REGULATORY ASPECT.



N=80

11. DO YOU FEEL THAT YOUR (REGULATORY) TEAM IS WELL AWARE AND INFORMED ABOUT THE REGULATORY CHANGES IMPLEMENTED FOR FIH/EFS (I.E., WHAT QUALIFIES A FIH/EFS, WHOM TO CONTACT AT FDA, INTERACTIVE REVIEW PROCESS, ETC...).

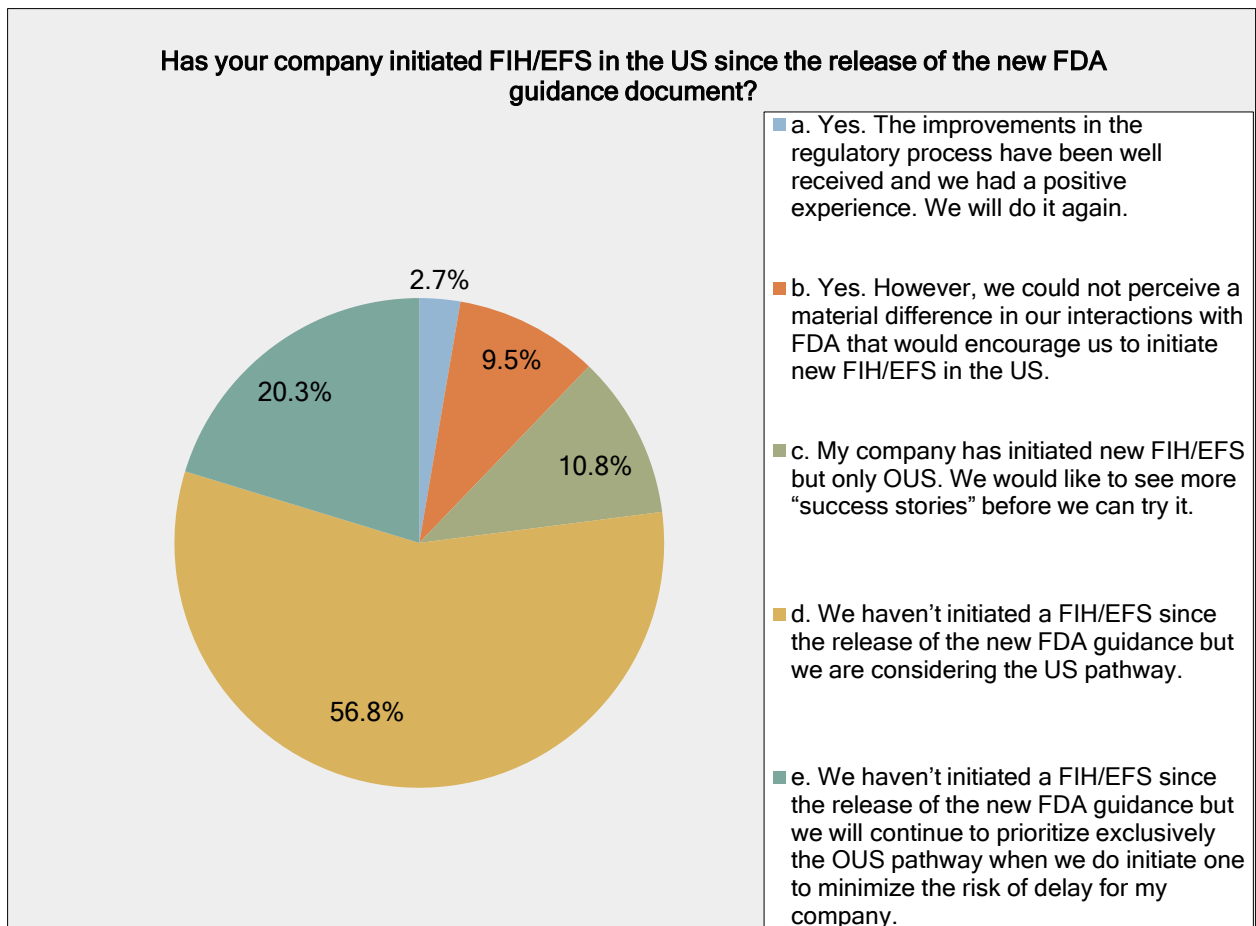
- A. YES, WE ARE VERY WELL VERSED AND ARE VERY FAMILIAR WITH THE NEW PROCESS.
- B. WE HAVE SOME KNOWLEDGE BUT WILL CERTAINLY BENEFIT FROM MORE INFORMATION/EDUCATION.
- C. NO, WE ARE NOT. WE WOULD LIKE TO KNOW MORE.



N=80

12. HAS YOUR COMPANY INITIATED FIH/EFS IN THE US SINCE THE RELEASE OF THE NEW FDA GUIDANCE DOCUMENT?

- A. YES. THE IMPROVEMENTS IN THE REGULATORY PROCESS HAVE BEEN WELL RECEIVED AND WE HAD A POSITIVE EXPERIENCE. WE WILL DO IT AGAIN.
- B. YES. HOWEVER, WE COULD NOT PERCEIVE A MATERIAL DIFFERENCE IN OUR INTERACTIONS WITH FDA THAT WOULD ENCOURAGE US TO INITIATE NEW FIH/EFS IN THE US.
- C. MY COMPANY HAS INITIATED NEW FIH/EFS BUT ONLY OUS. WE WOULD LIKE TO SEE MORE "SUCCESS STORIES" BEFORE WE CAN TRY IT.
- D. WE HAVEN'T INITIATED A FIH/EFS SINCE THE RELEASE OF THE NEW FDA GUIDANCE BUT WE ARE CONSIDERING THE US PATHWAY.
- E. WE HAVEN'T INITIATED A FIH/EFS SINCE THE RELEASE OF THE NEW FDA GUIDANCE BUT WE WILL CONTINUE TO PRIORITIZE EXCLUSIVELY THE OUS PATHWAY WHEN WE DO INITIATE ONE TO MINIMIZE THE RISK OF DELAY FOR MY COMPANY.



N=74

13. IN YOUR EXPERIENCE, WHAT ADDITIONAL REGULATORY CHANGES WOULD YOU LIKE TO HAVE INCORPORATED INTO THE EFS PROGRAM THAT YOU BELIEVE ARE LIKELY TO ENCOURAGE MORE FIH/EFS IN THE US? PLEASE LIST THEM.

The above list misses a key factor and that is cost. It is simply cheaper (today) in many cases to do the study OUS. MDIC is focusing on one issue - regulatory. There are other critical issues.

Involve CBER

Guidelines for use of FIH data in product marketing applications, e.g. 510(k) Premarket Notification.

Our organization looks at EFS in two phases - device release requirements (design review requirements, testing, labeling) and clinical trial design and execution (scaled deliverables, data collection requirements, risk-based operational practices) - an approach like this helps the business understand faster and safer design iterations.

I think the level of regulatory review in the US is still substantially higher and more time consuming than in other countries and until that is proven differently, it will be difficult for people to consider US first.

Perhaps a specific FDA review team or champion for FIH studies to help champion through the review teams. Our experience is that the regular review teams are not incentivized to aggressively work on improving the requirements for FIH.

Shorter time frames

21 CFR 11 compliance for data management.

The FDA acceptance of in-depth timely monitoring of each patient and reporting to FDA review team under pre-determined, pre-approved acceptance criteria in determining if next patient can be enrolled. This rolling enrollment approval (next patient) and/or stop criteria would be proposed in lieu of bench testing where appropriate. The physician is responsible to determine if each case met the pre-determined criteria to enroll next patient and that no new questions of patient safety were raised. This may be appropriate for low to moderate risk devices and to device function that is immediately observable in the field. This approach would be manageable as FIH/EFS trials as they are limited to a handful of sites and typically manufacturers already have manufacturing representation on site during FIH/EFS use for appropriate design control documentation.

FDA needs to maintain FIH/EFS feedback/review cycle. A final active negotiating FDA meeting prior to submission would increase understanding of FDA concerns.

Any approval to conduct a trial in any level 1 country in Europe should create strong but rebuttable presumption of approval by FDA and IRBs requiring affirmative disapproval with specified reasons within 30 days of FDA submission.

Let's not kid ourselves. The FDA putting out a press piece about FIH/EFS is not related in any meaningful way to actual changes taking place at FDA regarding IDE turnaround times. We are currently initiating another FIH study for our product OUS.

FDA should set reasonable minimal requirements for biocompatibility, animal testing to allow faster access to human testing. Many diseases or conditions do not have adequate animal models and the device must go to human feasibility testing to make an informed decision. In the past FDA would sometimes require human data from OUS before allowing FIH in US. This practice must be stopped, it's the whole purpose for doing the FIH in the US.

It would be nice if FDA knew what they wanted for pre-clinical testing before we made a submission. These are very complicated studies/devices and it may be helpful if there were FDA staff with more focused time to review these types of submissions as this may streamline the review process.

Simply to see clear cut examples of this working in the medical device world and across diff types of devices, especially class 3

The program still appears to have a lengthy process because of non-familiarity in the FDA. Would also like to see CBER involved and committed to the policy and procedure. It doesn't help to have the different centers that are so closely aligned operating differently

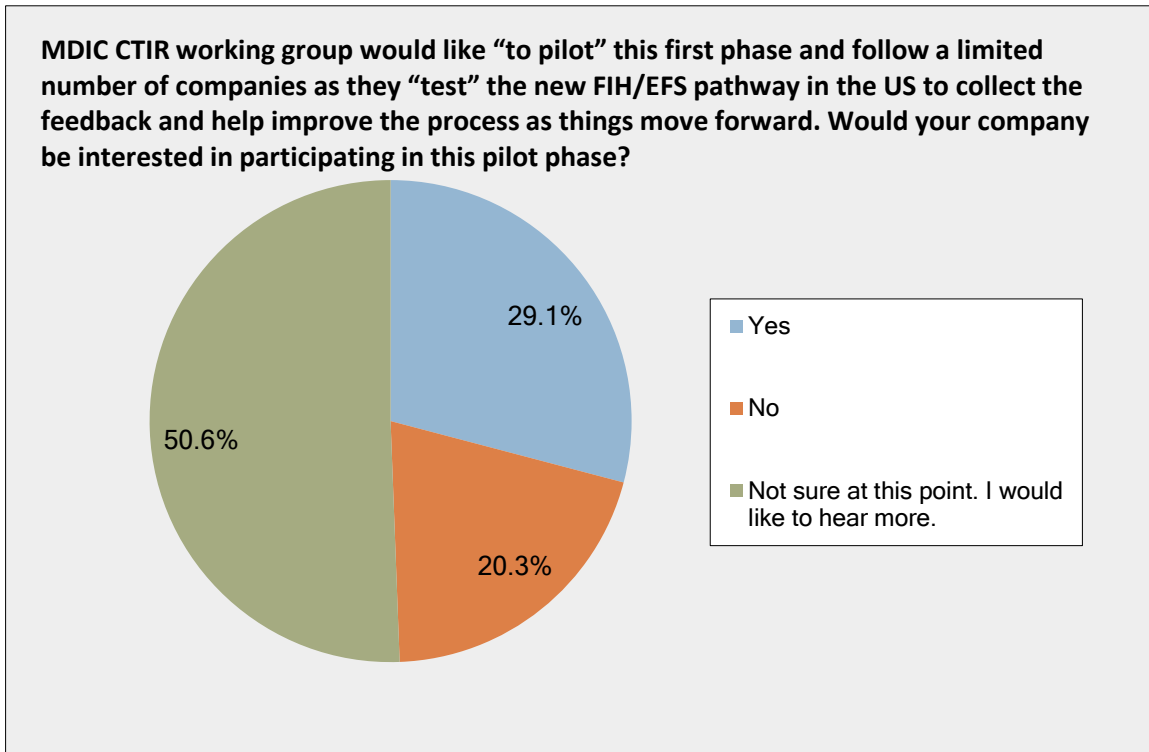
Difference in specific non-clinical testing for an EFS versus an FS need to be clearly defined. Moreover, as the much larger problem is the length to PMA, the primary driver for OUS studies is getting a quick CE mark.

Certain predictability in the process so business decisions can be made appropriately.

More direct interaction with FDA in advance.

14. MDIC CTIR WORKING GROUP WOULD LIKE “TO PILOT” THIS FIRST PHASE AND FOLLOW A LIMITED NUMBER OF COMPANIES AS THEY “TEST” THE NEW FIH/EFS PATHWAY IN THE US TO COLLECT THE FEEDBACK AND HELP IMPROVE THE PROCESS AS THINGS MOVE FORWARD. WOULD YOUR COMPANY BE INTERESTED IN PARTICIPATING IN THIS PILOT PHASE?

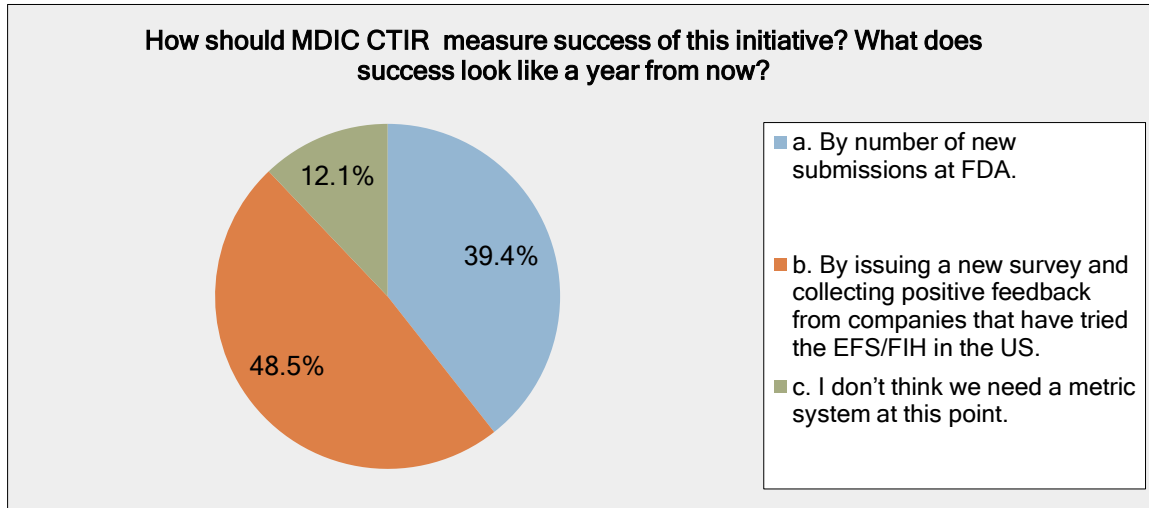
- YES
- NO
- NOT SURE AT THIS POINT. I WOULD LIKE TO HEAR MORE.



N=79

15. HOW SHOULD MDIC CTIR MEASURE SUCCESS OF THIS INITIATIVE? WHAT DOES SUCCESS LOOK LIKE A YEAR FROM NOW?

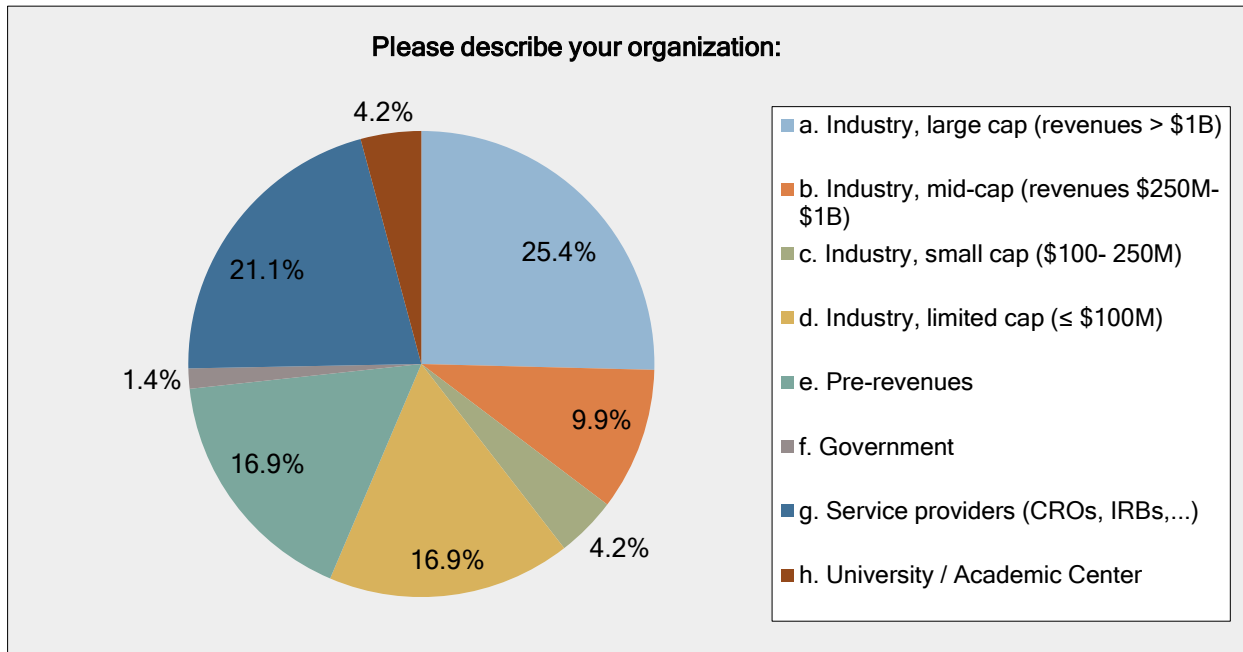
- A. BY NUMBER OF NEW SUBMISSIONS AT FDA.
- B. BY ISSUING A NEW SURVEY AND COLLECTING POSITIVE FEEDBACK FROM COMPANIES THAT HAVE TRIED THE EFS/FIH IN THE US.
- C. I DON'T THINK WE NEED A METRIC SYSTEM AT THIS POINT.



N=66

16. PLEASE DESCRIBE YOUR ORGANIZATION:

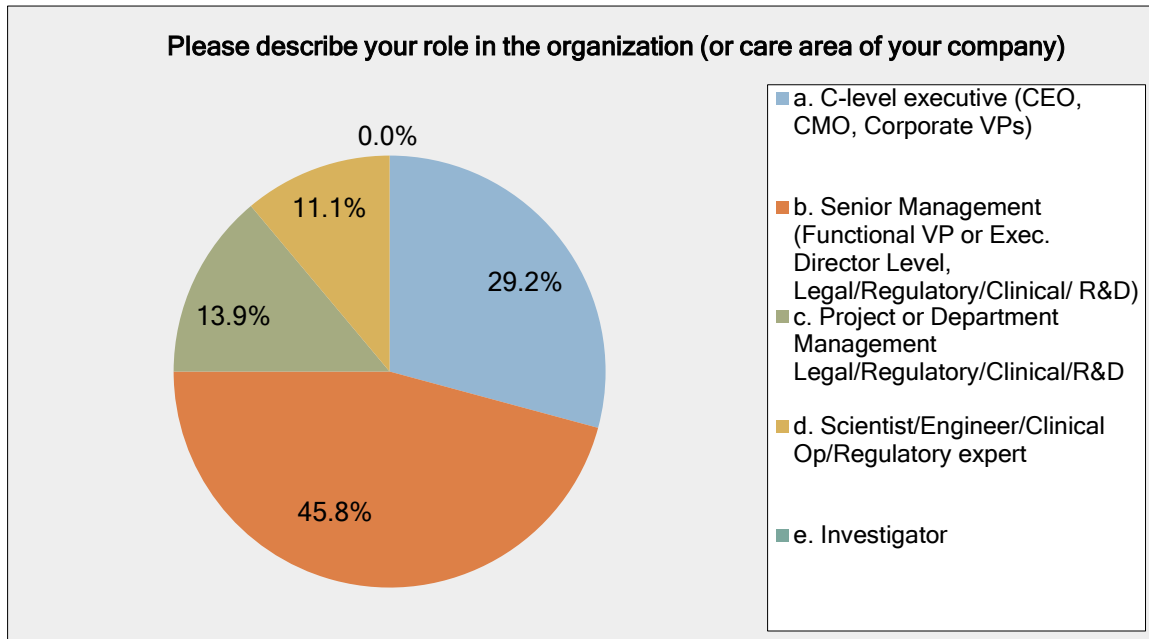
- A. INDUSTRY, LARGE CAP (REVENUES > \$1B)
- B. INDUSTRY, MID-CAP (REVENUES \$250M- \$1B)
- C. INDUSTRY, SMALL CAP (\$100- 250M)
- D. INDUSTRY, LIMITED CAP (≤ \$100M)
- E. PRE-REVENUES
- F. GOVERNMENT
- G. SERVICE PROVIDERS (CROS, IRBS...)
- H. UNIVERSITY / ACADEMIC CENTER



N=71

17. PLEASE DESCRIBE YOUR ROLE IN THE ORGANIZATION (OR CARE AREA OF YOUR COMPANY)

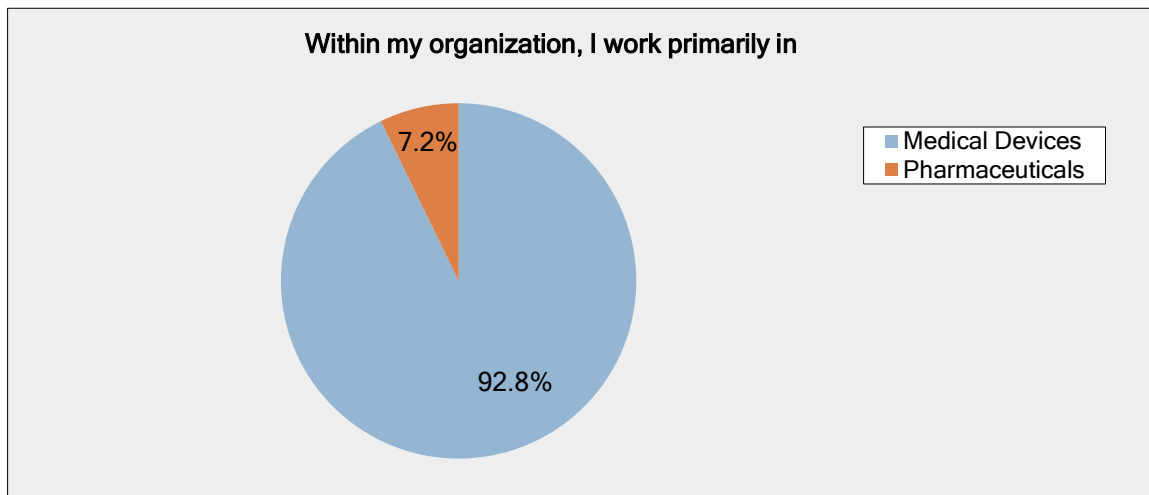
- A. C-LEVEL EXECUTIVE (CEO, CMO, CORPORATE VPS...)
- B. SENIOR MANAGEMENT (FUNCTIONAL VP OR EXEC. DIRECTOR LEVEL), LEGAL/REGULATORY/CLINICAL/ R&D
- C. PROJECT OR DEPARTMENT MANAGEMENT LEGAL/REGULATORY/CLINICAL/R&D
- D. SCIENTIST/ENGINEER/CLINICAL OP/REGULATORY EXPERT
- E. INVESTIGATOR



N=72

18. WITHIN MY ORGANIZATION, I WORK PRIMARILY IN:

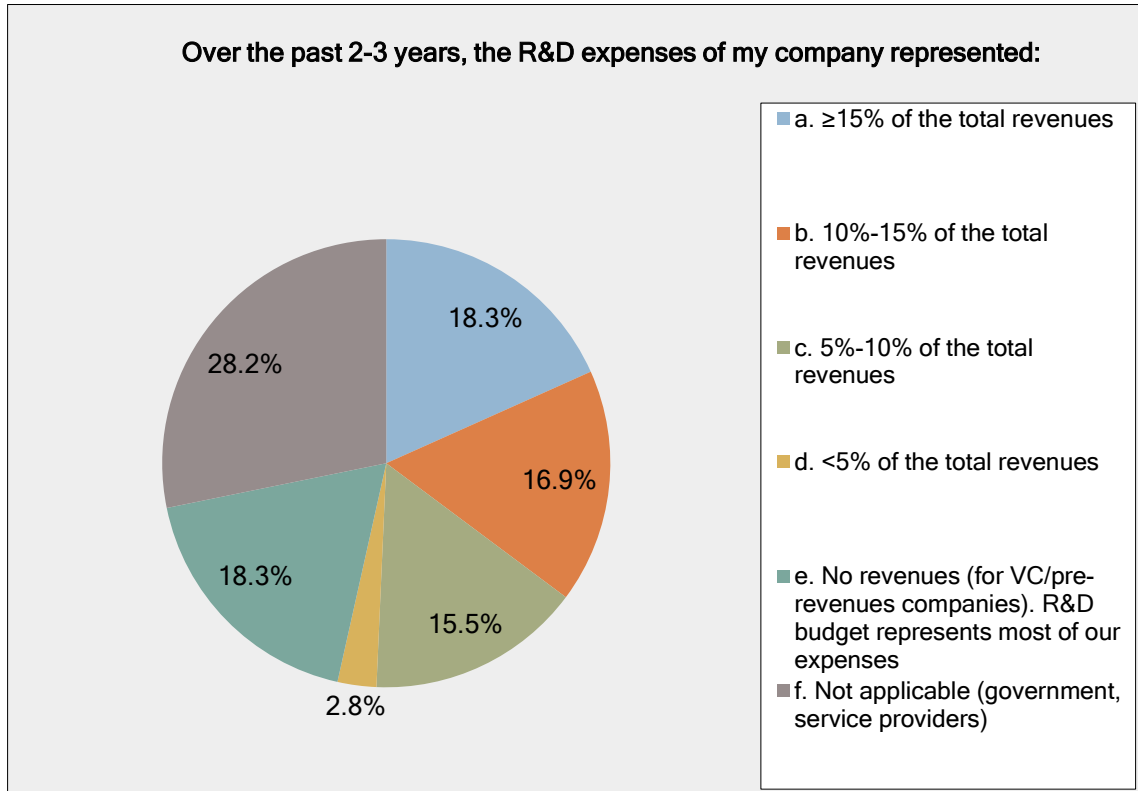
- A. MEDICAL DEVICES
- B. PHARMACEUTICALS



N=69

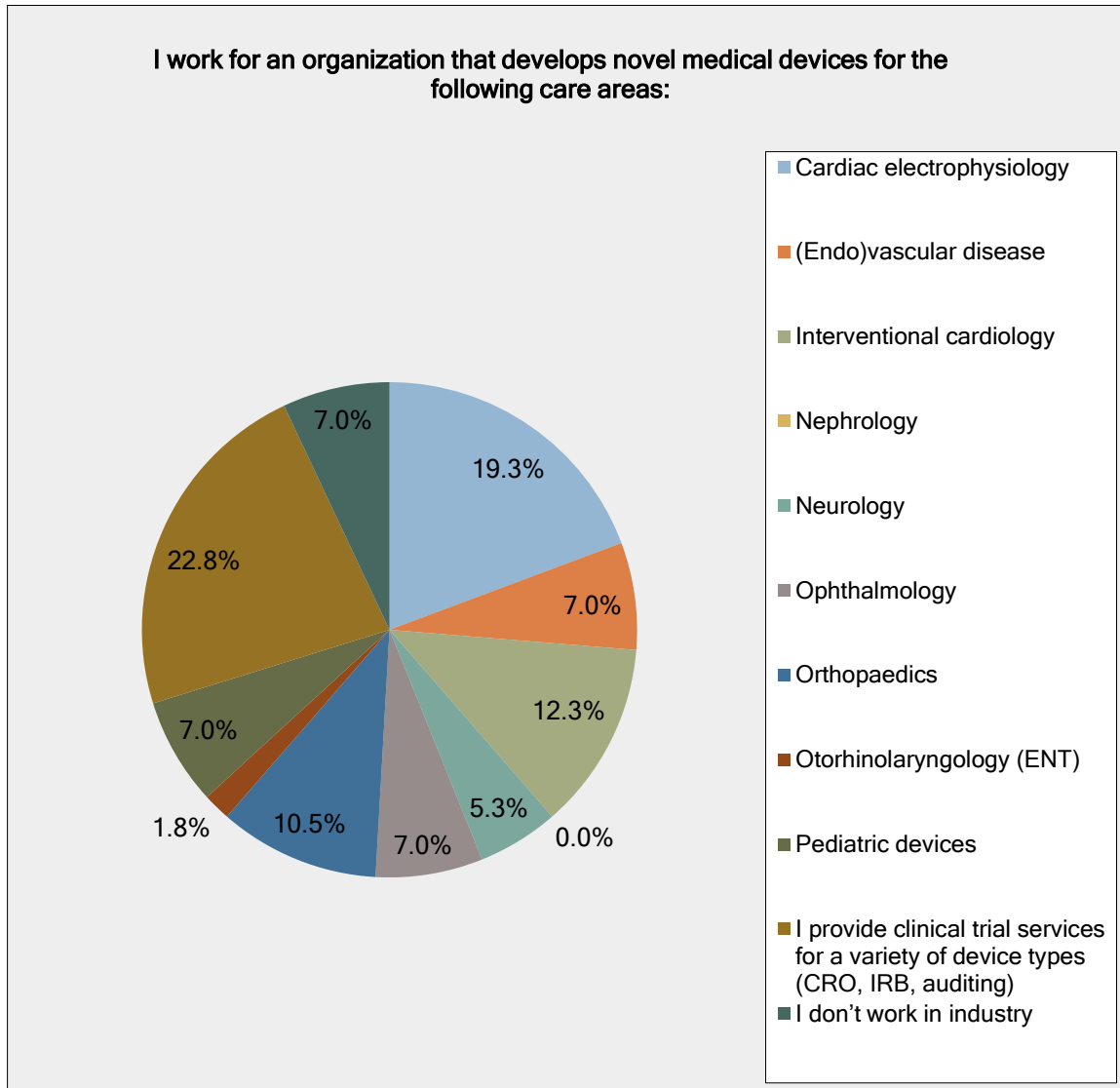
19. OVER THE PAST 2-3 YEARS, THE R&D EXPENSES OF MY COMPANY REPRESENTED:

- A. ≥15% OF THE TOTAL REVENUES
- B. 10%-15% OF THE TOTAL REVENUES
- C. 5%-10% OF THE TOTAL REVENUES
- D. <5% OF THE TOTAL REVENUES
- E. NO REVENUES (FOR VC/PRE-REVENUES COMPANIES). R&D BUDGET REPRESENTS MOST OF OUR EXPENSES
- F. NOT APPLICABLE (GOVERNMENT, SERVICE PROVIDERS)



N=71

20. I WORK FOR AN ORGANIZATION THAT DEVELOPS NOVEL MEDICAL DEVICES FOR THE FOLLOWING CARE AREAS:



N= 57

	Response Percent	Response Count
Cardiac electrophysiology	19.3%	11
(Endo)vascular disease	7.0%	4
Interventional cardiology	12.3%	7
Nephrology	0.0%	0
Neurology	5.3%	3
Ophthalmology	7.0%	4
Orthopedics	10.5%	6

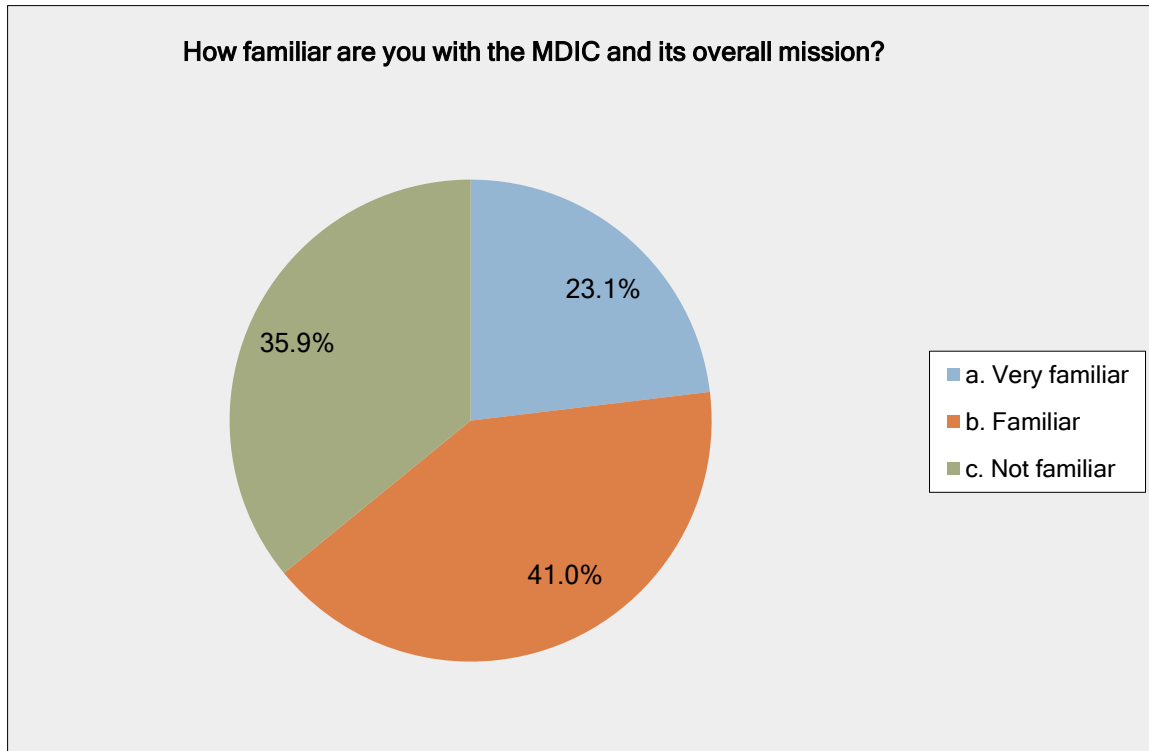
	Response Percent	Response Count
Otorhinolaryngology (ENT)	1.8%	1
Pediatric devices	7.0%	4
I provide clinical trial services for a variety of device types (CRO, IRB, auditing)	22.8%	13
I don't work in industry	7.0%	4
Other (please specify)		28

21. WHICH CDRH DIVISION REGULATES YOUR WORK? (IF MORE THAN ONE, SELECT THE DIVISION YOU MOST OFTEN SUBMIT TO).

	Response Percent	Response Count
Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices	3.0%	2
Division of Cardiovascular Devices	48.5%	32
Division of Ophthalmic and Ear, Nose and Throat Devices	10.6%	7
Division of Neurological and Physical Medicine	6.1%	4
Division of Orthopedic Devices	9.1%	6
Division of Surgical Devices	7.6%	5
Division of Reproductive, Gastro-Renal and Urological Devices	4.5%	3
Division of Chemistry and Toxicological Devices	0.0%	0
Division of Immunology and Hematology Devices	4.5%	3
Division of Microbiology Devices	0.0%	0
Division of Radiological Health	6.1%	4
Division of Mammography Quality Standards	0.0%	0

22. HOW FAMILIAR ARE YOU WITH MDIC AND ITS OVERALL MISSION?

- A. VERY FAMILIAR
- B. FAMILIAR
- C. NOT FAMILIAR



N=78