Right to Try Laws vs. FDA Expanded Access: What You Need to Know and What You Need to Do

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Areas of Discussion

- Many states are passing laws allowing terminally ill patients access to experimental therapies that have not been approved by the Food and Drug Administration. But the FDA already allows access to such drugs through Expanded Access Programs. The Fed Right to Try Act of 2018 Created a model to try to standardize access (Has this Helped).
- Do you your doctors, IRB, pharmacists, compliance staff know the differences in these laws/regulations and the different processes for seeking permission to use unapproved therapies?
- Know which is best for your patient, which is best for your institution, and which is more likely to be approved Research

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Expanded Access Programs Are Considered Option of Last Resort

- Hierarchy of Access
  - Approved Drugs
    - Studied and characterized
    - Labeled
    - Broadest availability
    - Reimbursement by 3rd party
  - Clinical Trials
    - Provide Necessary Data & Effectiveness
    - Most Efficient Path to Market and Broad Availability
  - Expanded Access
    - Represent opportunity when other options exhausted
    - Goal is access for treatment

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What are Expanded Access Programs (EAP)?

- Regulations for Emergency Use were Amended by FDA to broaden access to investigational products while they're still undergoing clinical trials.
  - To improve access to investigational drugs for the treatment of patients with serious or immediately life-threatening disease or condition who do not have comparable or satisfactory alternative therapeutic options and who may benefit from access to such therapies
- Intent of EAP is to Treat **– it is not Research**
  - Differs from use of an investigational drug in a clinical trial where the primary purpose is research (i.e., the systematic collection of data)
- Method of obtaining access
  - FDA approval of an Expanded Access Submission, which is a type of an Investigational New Drug (IND) application (*i.e.*, a new IND or protocol amendment to existing IND)

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Negative Views toward FDA Expanded Access Program

- Tremendous discretion on the part of FDA
- Need Evidence of safety
- Can get different decisions from FDA
- Information on whether drug is being developed for population to be treated and if not, why/under what circumstances could it be
- EAP vs. open-label safety study
- Risk of interference with clinical investigations
- Fear on part of Sponsor that Adverse Event data will interfere with approval process

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Right to Try Efforts over Time (Access Beyond EAP?)

- Expanded access has existed since the 1970s. Cardiovascular - metoprolol, nifedipine – HIV - pentamadine, AZT – Oncology (Group C drugs)
- No official regulatory recognition until 1987 –New regulations for INDs
- Became more widely used during the 1980s (AIDS) & 1990s (breast cancer)
- In the 1990s, FDA revised the expanded access regulations
- But continued to be viewed as burdensome and restrictive.
  - Confusion: emergency use, compassionate use, emergent access
  - Difficult to process, Unbridled Authority of FDA, Liability
  - Only one use -must develop protocol if additional use is possible
- Since the 1990s, there have been failed legislative efforts to change the system [push to move government oversight out of access to investigational drugs for very sick/dying patients Right to Try Investigational Drugs
  - Abigail Alliance Litigation (Sued FDA in Federal Court for Right to access unapproved Drugs)

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Right to Try Act (RTT)

- 41 States have Right to Try Laws
- May 30,2018 “Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Federal Right to Try Act”
- Permits/allows eligible patients to have access to eligible investigational drugs
- Criteria:
  - Patient: Life threatening disease, exhausted approved treatments, unable to participate in a trial of the eligible drug, informed consent
  - Drug: Past Phase I, unapproved for any use, active IND, ongoing development (not on clinical hold)

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Expanded Access Program vs Right to Try

Issues	EAP	RTT
Patient eligibility	Immediately life-threatening or serious disease or condition	Life-threatening disease or condition
	No other treatment or research options (including eligibility for clinical trials)	No treatment options; not eligible for clinical trial of the investigational drug or biologic of interest
Required support	Treating physician	Treating physician
	Manufacturer or sponsor	Manufacturer or sponsor
	FDA	
	IRB	
Drug or biologic eligibility	No restrictions – Access to products at any stage	Completed a phase I trial and in current clinical development
Charging regulations	This pathway allows charging only for direct costs. Documentation must be submitted to the FDA.	This pathway allows charging only for direct costs; however, the requirements for documentation are unclear.
Liability	No Liability Protection	provides liability protection to companies and everyone else involved in therapeutic attempt;
Informed consent	Requirements in the Code of Federal Regulations must be met.	Written consent is required, but specific requirements are unclear.

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Oversight of Right-to-Try and Expanded Access Requests for Off-Trial Access to Investigational Drugs Carolyn Riley Chapman Ethics and Human Research 2-13 First Published: 22 January 2020

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FDA Improvements to EAP Due to RTT Movement

- Form FDA 1571 is intended for Commercial INDs and is very comprehensive
  - Has been viewed by many outside FDA to be confusing and overly burdensome for a physician seeking expanded access for an individual patient to complete
- In summer 2014, FDA started an effort to streamline the submission process for individual patient expanded access INDs
  - On June 2, 2016, FDA streamlined and simplified the application process for physicians.
    - Issued 3 final guidance rules about expanded access
    - Introduced a much simpler application form called the Form FDA 3926
    - Developed patient and physician fact sheets to further inform stakeholders about expanded access
    - Project Facilitate" Oncology Center of Excellence Project Facilitate call center
    - Revamped FDA's website to make it more user-friendly
      - New online tool: Expanded Access Navigator - Comprehensive online resource that collects in one location links to manufacturers' expanded access policies, procedures, and points of contact.
    - "

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Form 1571 v. Form 3926

	Form 1571	Form 3926
Purpose	Typically commercial IND applications	Individual IND expanded access application
Number of Pages	3	2
Number of Elements	26	11
Number of additional Documents	7 (+ Form 1572)	1 (and 1 voluntary)
Time to Complete	PRA estimate of 100 hours	45 Min.

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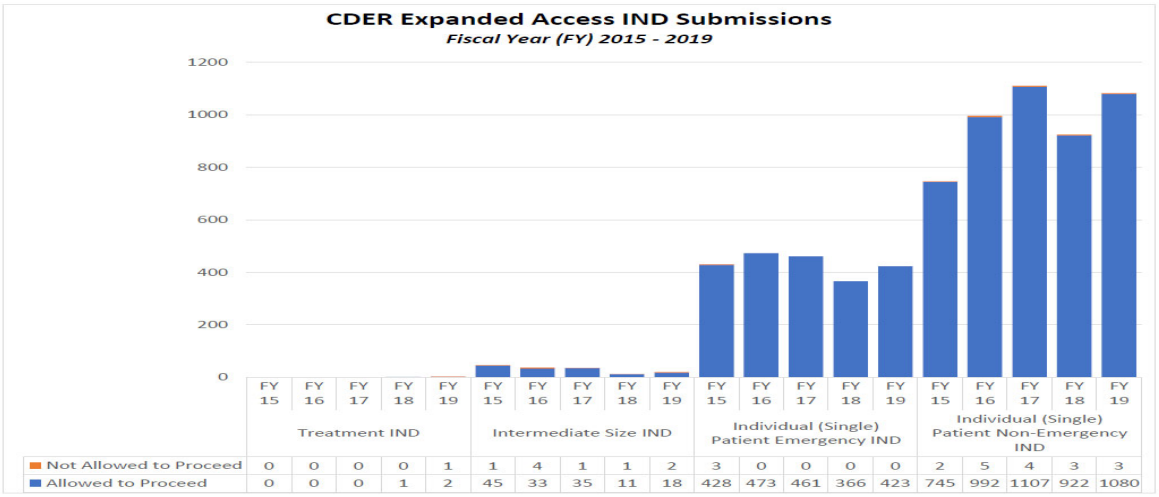
FDA EAP Track Record

Oct. 13, 2011 – Oct. 12, 2012: **Total received by CDER: 940. Total approved: 936**

Source: Presentation of Richard Klein, Office of Health and Constituent Affairs, FDA. CBI Expanded Access Conference, Philadelphia, PA, July 17 – 18, 2013.



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Expanded Access Drug Program

- FDA's Expanded Access Drug Program includes three categories:
  - •Individual patients, including emergency use 21 CFR 312.310
  - •Intermediate size patient populations 21 CFR 312.315
  - •Treatment IND or treatment protocol: widespread treatment use/ large patient populations 21 CFR 312.320
- Above Regulations describe general criteria, submission requirements, and oversight that apply to all categories and additional criteria, submission requirements, and safeguards that are unique to each category.
  - **Oversight Requirements:** Describes the safeguards applicable to Expanded Access Programs (EAP), such as informed consent, ethics review, and reporting requirements
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Individual Patients (21 CFR 312.310)

- **Physician** must determine that probable risk does not exceed that of the disease for the individual patient
- **FDA** must deem that patient cannot obtain access under another type of IND or protocol, and that **"potential risks are reasonable"**
- **Emergency use**
  - FDA may authorize without written submission, followed by written submission within 15 working days
- **Safeguards**
  - **Sponsor is often the physician who submits an IND for treatment use**, in roles of investigator and sponsor
  - Generally limited to single course of treatment
  - Submission of end-of-treatment report to FDA, including all adverse effects
  - Monitoring not generally required

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Intermediate-Size Populations (21 CFR 312.315)

- Generally up to 100 patients
- Demonstration of need for investigational drug
  - Drug being developed, but patient cannot participate in clinical trial
  - Drug not being developed (e.g., rare disease)
  - An approved or related drug is no longer marketed or not available (e.g., drug shortage with foreign version of drug)
- Sufficient evidence that drug is safe for proposed dose and duration relative to size of exposed population
- Preliminary clinical evidence of effectiveness or plausible pharmacologic effect
- Additional safeguards
  - Explanation of why drug cannot be developed or, if drug is being developed, why patients cannot be enrolled in a trial for the use
  - Monitoring, as well as annual report for review by FDA

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Large Populations: Treatment IND/Protocol (21 CFR 312.320)

- Drug is being investigated in clinical trial to support marketing, or all trials have been completed
- Company is actively pursuing marketing approval
- Sufficient evidence of safety and effectiveness for the use
  - **Serious Disease**: Evidence from phase 3 trial or compelling data from phase 2 clinical trials
  - **Immediately Life-threatening Disease**: Available evidence provides reasonable basis to conclude drug may be effective for the use and would "not expose patients to an unreasonable and significant risk of illness or injury" (could consist of evidence more preliminary than phase 2 or 3 trials)
- Additional safeguards
  - 30-day wait period for FDA review, or earlier notification of FDA approval
  - Monitoring, as well as annual report for review by FDA

Requirements for All Expanded Access Uses 21 CFR §312.305

Criteria

FDA must determine that:

1. Patient(s) has/have a serious or immediately life threatening disease or condition; and
2. No comparable or satisfactory alternative therapy;
3. Potential patient benefit justifies potential risk; potential risk not unreasonable in context of disease or condition; and
4. Provision of drug will not interfere with initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

Requirements for All Expanded Access Uses 21 CFR §312.305

Submission (cont'd)

•A licensed physician may not submit an expanded access protocol to an existing

IND for which he/she is not the sponsor.

•If an existing IND for a drug is in effect and the pharmaceutical company/manufacturer declines to be the sponsor, the licensed physician submitting the expanded access IND (i.e. e., the sponsor investigator) may satisfy some submission requirements by requesting the pharmaceutical company's/manufacturer's permission via a letter of authorization ("LOA") to reference the existing IND.

—If permission is obtained, physician files a copy of the LOA with the FDA.

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IRB/Human Subject Protections Apply to All EAPs

- Drugs used in FDA-approved Expanded Access Programs are investigational drugs, even though the drugs are being used for treatment, not research.
- Consent: The most important concept in expanded access programs is that the patient be aware of the risks he or she is undertaking, and that the company minimizes unnecessary risks to the extent possible.
  - " … patients who are candidates to receive investigational drugs under Expanded Access programs … should be afforded **a rigorous informed consent process** that effectively communicates the risks and potential benefits of any investigational therapy to be used for treatment use **in a way that does not raise false expectations about a positive outcome from treatment and makes clear what is unknown about the drug.**" *74 Fed. Reg. 40900, 40920 (Aug. 13, 2009)*
- All FDA human subject protections are applicable, including
  - Institutional Review Board (review and approval, including emergency use) – 21 CFR Part 56
  - Protection of Human Subjects (informed consent) – 21 CFR Part 50
  - FDA authority to issue Clinical Holds, based on safety and reporting requirements (adverse event reports, annual reports) – 21 CFR Part 312

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Submission Package

- An individual patient IND submitted using Form FDA 3926 may consist of only:
  - Completed form
  - Letter of Authorization (LOA) to reference existing IND, if applicable
  - A physician submitting an individual patient access IND can request that only one IRB member chair or another designated IRB member concur with the treatment use.
  - Sponsor-investigator's CV (if he/she elects to provide his/her qualifications in this way, rather than completing section 5 of the form) Form FDA 1572 is NOT required to be submitted with Form FDA 3926

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Charging – Individual Patient Expanded Access

- Sponsor of the expanded access IND must request and receive authorization to charge from FDA before charging may begin
- The sponsor may recover the direct cost of making the drug available to the patient (e.g., cost of the drug, cost of shipping & handling); indirect & administrative costs may not be recovered
- Unless FDA specifies a shorter period, charging may continue for 1 year. A sponsor may request that FDA reauthorize charging for additional periods.

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GAO Recommendation on Adverse Events

GAO Report and Adverse Events • Clarification provided October 2017

- "FDA is not aware of instances in which adverse event information from expanded access has prevented FDA from approving a drug.
  - Very beneficial to learn of rare adverse events as early as possible – reporting is still of paramount importance
  - 0.02% (2 cases in 10,000 expanded access authorized requests) where adverse events have led to a clinical hold, and those were later resolved
  - Four key reasons added to FDA October 2017 Q&A Guidance A26 that describe why it is extremely difficult to draw a causal link between a reported AE and the expanded access treatment
  - FDA should clearly communicate how it uses adverse events data from expanded access use in the drug approval process. FDA agreed with the recommendation.

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21st Century Cures Act PL 114-255

- Requires sponsors to make their policy for evaluating and responding to expanded access requests publicly available
- The policy must include the following:
  - contact information for the manufacturer or distributor, – procedures for making requests,
  - the general criteria the manufacturer or distributor will use to evaluate and respond to EA requests,
  - the length of time the manufacturer or distributor anticipates will be necessary to acknowledge receipt of such requests, and
  - a hyperlink or other reference to the clinical trial record containing information that is required to be submitted to ClinicalTrials.gov about expanded access availability for the drug

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312.6 Labeling of an investigational new drug.

(b) The "label" or "labeling" of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

312.7 Promotion of investigational drugs.

(a) Promotion of an investigational new drug. A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.

- its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution

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Promotional Warnings (Applies to RTT and EAP)

- FDA increasingly cynical of corporate intent
  - Promotional role/involvement in creating demand through Implied claims
    - ChemGenex untitled letter for Omapro FDA warned that claims made in 2010 about the efficacy and safety of Omapro (omacetaxine mepesuccinate) were false or misleading
    - November 2019 On November 1, 2019, FDA Office of Prescription Drug Promotion (OPDP) Untitled Letter to sponsor of an investigational new drug studied for brain cancer - website presented new drug as safe and effective for the treatment of brain cancer, in violation of 21 C.F.R. Section 312.7(a).
    - **Hydroxy Chloroquine**
  - Patient access must be the intent not premarketing or off-label promotion

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What Your IRB Needs to Know and Address

- **In compliance with 21 CFR Part 50, how can the 8 Basic Elements of informed consent cited in 21 CFR 50.25(a) be incorporated?**
  - As example, element (1) requires a statement "*that the study requires research, an explanation of the purposes of the research*…"
  - FDA does not provided guidance or examples of informed consent templates appropriate for Expanded Access
  - To what depth should IRB review what is and isn't known about the investigational drug?
  - Is it best practice for IRB to have template for informed consent for Expanded Access Programs? Should templates differ for the 3 categories of Expanded Access?

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Emergency Use in Expanded Access: IRB Review

- Individual Patient Emergency use scenario – (e.g. COVID-19)
  - What does the IRB due to assess likelihood of additional need?
- FDA's answer *(See May 2013 FDA draft guidance):*
  - "There can be more than one expanded access emergency use of the same drug at the same institution.
  - FDA expects that, for expanded access uses authorized under the emergency procedures, there typically will not be time to obtain prior IRB approval of the use.
  - IRB is expected to make an assessment of likelihood of repeated use – needs a protocol for review.
  - In such cases, the emergency use must be reported to the responsible IRB within 5 working days of initiation of treatment (21 CFR 56.104(c)). Once an investigational drug is used in an emergency situation without prior IRB approval, any subsequent uses of the investigational drug at that same institution would ordinarily require prior IRB review and approval (21 CFR 56.104(c)).
  - **However, when prior IRB review and approval is not feasible for a subsequent expanded access emergency use at a particular institution, FDA does not intend to deny the subsequent request for emergency use due to lack of time to obtain prospective IRB review, as long as that use will be reported to the IRB within 5 working days of initiation of treatment." SIMPLIFIED - "Do not let the patient die"**

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Responsibilities of Manufacturer

- Decide whether to provide the investigational drug under an Expanded Access Program or an RTT – Not Required
- Decide whether to charge for the drug, pursuant to 21 CFR 312.8
- Expanded Access for Individual Patients
  - **In response to a physician's request for expanded access to an investigational drug as the sponsor-investigator**,
    - Company is <u>not</u> required to provide the drug
    - If company agrees to provide drug to a physician as sponsor-investigator, company provides physician with written authorization for FDA to reference the company's existing IND
    - If company decides to provide the EA submission to FDA for the single patient as the sponsor, company submits a *protocol amendment* to an existing IND that it holds.

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Responsibilities of the Sponsor Manufacturer (or Sponsor-Investigator) (21 CFR 312.305)

- As sponsor of an FDA-approved IND, obligations include
  - IND safety reports to FDA
  - Annual reports to FDA
  - Ensuring that the licensed physicians are qualified to administer the investigational drug for Expanded Access use
  - Monitoring the physicians as investigators (only for Expanded Access Programs for intermediate-size and broad populations)
  - Providing information to physicians to minimize risk and maximize potential benefits (including Investigator Brochure)
  - Maintaining an effective IND for the Expanded Access use
  - Records, including drug disposition/inventory
  - Other sponsor responsibilities under 21 CFR 312

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What Costs Are Covered in Expanded Access Programs?

- Medicare coverage policies do not specifically address when unapproved/investigational drugs are used for treatment purposes
- "Is it Safe and Effective" as well as "Reasonable and Necessary" (Sufficient data?)
- Are specific coverage decisions or requirements to be met under Clinical Trial Policy (NCD)
  - Possible Cancer trial exceptions or CED (but unlikely)
- Under either approach, the investigational drug itself is usually not covered, but other items and services associated with clinical care, safety assessments and/or treatment of the patient are likely covered
  - costs of infusion of an investigational drug and cost to monitor the patient during infusion
  - costs of hospital stay to monitor/treat complications resulting from use of the investigational drug
  - follow-up safety/monitoring visits with physician office to assess for potential side effects from investigational drug regimen
- Make Sure Investigator and Patient (consent) understand Who is Responsible for Paying Costs (including investigational drug cost)

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Conflicts in Right to Try Law Implementation

- What does this mean for the state "right to try" laws?
  - Which law takes precedent in a conflict (state vs. federal)?
  - Would parties proceeding under the FDA's Expanded Access Drug Program need to comply with specific requirements in the state "right to try" laws that go beyond FDA's requirements?
  - Specific Institutional Policies?
- How will the federal "right to try" law coexist with the FDA's Expanded Access Drug Program?
  - Many Sponsors prefer the comfort of FDA EAP approval. (Personal Experience)

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Right to Try Law Implementation

- Will the enactment of PL (115-176) influence stakeholders' behavior?
  - Liability Protection
  - Administrative burden – no FDA or IRB
- If a patient seeks an investigational drug under the state or federal "right to try" law, how will manufacturers, treating providers, institutions, and IRBs respond?
- Potential for **non-regulatory** protections/conditions to access products through "right to try."
  - Institutional policies requiring IRB or other review?
  - Manufacturers insisting on FDA pathway to make product available?
- Regardless of "right to try" –expanded access remains available.

Recommendation: Create an EAP SWAT Team

- Team Needs to Understand:
  - The Entire Submission and Reporting Process and Players (FDA (which Office), Sponsor, Investigator, IRB, Patient)
  - Checklist of Required Forms (3926, CV, HSP, License, Protocol, LOA,)
  - Consent Templates (Check if Sponsor has one)
  - Ability to Develop EAP Protocol as needed
  - Walk Physician Investigator through the Process
  - Is Consent always required (Emergency, LAR, Confirmation)
  - Reporting Requirements

Additional Tips

- Common issues of misunderstanding for patients, physicians and healthcare providers
  - EAP - Use of More than one Investigational drug is allowed – Just inform FDA
  - EAP - “Compassionate Use” – a potentially misleading term (device use not in RTT)
- EAP & RTT - Manufacturer is not required to provide investigational drug
- EAP & RTT Manufacturer is not required to provide drug free of charge
  - EAP - Physician always incurs regulatory obligations as investigator
    - Obligations as sponsor-investigator, if the physician is holder of the Individual Patient IND
  - EAO & RTTPotential medical costs may be incurred by the patient
    - Including costs of the drug and medical expenses for injury
  - Use of drug at stage of early and incomplete understanding of its safety risks: **Possible overestimation of benefit and underestimation of risk**

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QUESTIONS

THANK YOU

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