U.S. FOOD & DRUG ADMINISTRATION

Access to Experimental Therapies / FDA Expanded Access Programs

Outline

- Overview of expanded access
- CDER/OHOP experience and data regarding expanded access
- Drug development considerations for expanded access
  - Single patient requests
  - Oncology case studies where expanded access facilitated drug approval
- Evidence pertaining to risks related to expanded access
- Conclusions

Criteria for Expanded Access

- Serious or immediately life threatening disease or condition
- No comparable or satisfactory alternative therapy
- Potential benefit justifies the risks
- Providing access will not interfere with clinical investigations that could support marketing approval

21 CFR 312.305

Types of expanded access

- Single patient (emergency or non-emergency)
- Intermediate size population
- Treatment IND
- EA protocols can also be submitted by commercial sponsors to an existing IND

Ultimately, approval represents the most optimal mechanism for patient access to new drugs

Expanded access requirements

- Patient, physician, and drug provider (sponsor) willing to participate (e.g., provide letter of authorization)
- Submission of an application (e.g., using Form FDA 3926 for single patient IND requests)
  - Emergency EA request can be granted via phone or email prior to submission of complete application
- IRB/consent (initial emergency EA treatment can begin prior to IRB notification)

Form 3926

- Simplified process for EA requests
- One and a half page form that contains required elements for single patient request (except LOA)
- Protocols (treatment plan) or additional information, if necessary, can be attached

CDER Experience (over 10 years)

- 10939 requests for EA
  - 8922 new EA IND applications
- 99.3% allowed to proceed
  - 24 SPIs (non-emergency requests) placed on hold (10 later allowed to proceed)
  - 38 eINDs denied
    - Most common reason was request not an emergency

Jarrow et al., TIRS, 2016 (online prior to publication)

Overview of SPIs in oncology

- FDA analysis of 1332 SPIs/eINDs from 2012 – 2014
  - Two placed on hold (one subsequently allowed to proceed)
  - Four withdrawn prior to FDA decision
  - Median review time for SPIs (2 days)
  - Median review time for eINDs (< 24 hours)
  - ~157 Unique drugs
  - Estimated 2/3 from major university hospital

Lemery et al., ASCO (poster presentation), 2016

Oncology Experience SPIs

- 61% of requests were for drugs subsequently approved
- Limited demographic data in submissions
- Age 62%; race/ethnicity 10%; sex 65%
  - (sex imputed for SPIs for patients with ovarian or prostate cancer)
  - 8% of requests (with data) were for pts age ≤ 17 yrs
- Annual reports received: ~ 15%

Data received in SPI withdrawal letters

- 100 SPI withdrawal letters reviewed
  - Most 83% contained *some* disease-related information
  - However, information generally not useful

    e.g., Patient stopped drug due to progression (without information such as prior response, listings of adverse events, or date of relapse)
- SPI information conclusion:
  - Without planning, unlikely to get useful/interpretable information from SPI EA requests

How could SPI EA information be used in an NDA/BLA?

- Could provide supplemental data, especially for rare diseases and drugs with high response rates (e.g., breakthrough drugs)
- Could provide data in patients who do not meet eligibility criteria of clinical trials (e.g., real-world experience)
- Single patient protocols under a sponsor's IND might facilitate this approach
  - e.g., collection of data (even if limited)

Assessing treatment effects in ultra-rare diseases

- Strategies to facilitate development
  - Broaden eligibility criteria
  - Increase number of sites
  - EA if cannot enroll into trial (may not be possible to have a trial site available in all localities)
    - Provide real world experience

Case Studies that have supported approval or labeling

- Glucarpidase
- Uridine triacetate
- Eculizumab
- Dinutuximab

Case Study #1: glucarpidase

- Approved for toxic plasma methotrexate concentrations in patients with impaired renal function
  - NCI EA study primary basis for approval
  - Efficacy assessed on pre- and post-treatment plasma samples measuring methotrexate

Case study #2: uridine triacetate

- Approved for 5FU or capecitabine overdose or severe toxicity
- Approved based on effects observed in two open-label access studies (n=60) (n=75)
- Survival assessed in these patients (97%) as were PD effects

Case study #3: eculizumab

- Retrospective EA data in 19 patients supported efficacy supplement
  - EA data supported extrapolation to pediatric patients with atypical hemolytic uremic syndrome
- Results consistent with results in adults in prospective studies – decrease in dialysis requirements and improvements in eGFR

Case study #4: dinutuximab

- Approved for pediatric patients with high-risk neuroblastoma
- Primary basis for approval was randomized trial (n = 226)
- Data from an EA study (n =793) provided safety information considered for approval
  - Safety data are described in labeling

What is the evidence regarding risks of EA?

- EA studied over *10* year period (1/2005 to 1/2014)
- Over 10,000 EA IND requests
  - Only 2 (of 1033) commercial programs with referenced INDs were placed on hold/partial hold due a serious adverse event in an EA IND.
    - One hold removed months later
    - Other was a partial hold limited to a specific population

Source: Jarow et al., TIRS, 2016.

What is the reality in oncology?

- FDA review staff are trained oncologists who understand context of adverse events in EA
  - Patients have late stage cancers
  - May have other co-morbidities
- While not related to EA, FDA's safety reporting guidance describes
  - Anticipated events
  - Events that cannot be interpreted in a single patient, e.g.,
    - an MI in a 80 year old person
    - a patient with colon cancer who develops GI obstruction or perforation

Data regarding non-approval decisions in oncology

- Review of all CR (or not-approvable) letters for NDA (NME) marketing applications reviewed from 3/2005 to 3/2015.
- Fifteen letters
  - Most Due to lack of efficacy (67%)
  - Others due to trial design flaws (33%)
  - None due to EA

Source: Khozin et al., Nature Reviews Drug Discovery, 2015

EA Takeaways

- Provide treatment options for patients with life-threating conditions and no available therapies
  - i.e., “compassionate use”
- Most requests are not primarily intended to support development/provide information about a drug

Takeaways (for development)

- EA may be a means to obtain important data, especially in rare diseases and in drugs with large treatment effects (e.g., breakthrough)
- *If* EA data may be useful
  - Try to recognize early
  - Be proactive to obtain useful data (e.g., through single patient protocols or treatment INDs later in development)
- Concerns regarding negative effects on drug development are not supported by available data

Takeaway

- While safety is assessed, it is exceedingly rare for a serious adverse event to result in a clinical hold to a commercial IND (0.2%).
  - Both holds were subsequently lifted
- In oncology, drugs not approved due to lack of efficacy or trial design issues (not EA)
  - Risk-benefit important but *highly unlikely* to be affected by a serious event in a single patient
  - Safety risks are accepted by patients/oncologists if a drug provides benefit