Introduction to Expanded Access Program

Sukhun Kang
London Business School
skang@London.edu
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What is “Expanded Access” Program? (FDA Website)

- Sometimes called “compassionate use”, expanded access is a potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

- Expanded access may be appropriate when all the following apply:
  - Patient has a serious disease or condition, or whose life is immediately threatened by their disease or condition.
  - There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
  - Patient enrollment in a clinical trial is not possible.
  - Potential patient benefit justifies the potential risks of treatment.
  - Providing the investigational medical product will not interfere with investigational trials that could support a medical product’s development or marketing approval for the treatment indication.

Also known as (and often confused with each other)

- Compassionate Use
- Early Access
- US vs. Europe

Table 1: Comparison of EAPs in the US to CUP and NPP in the EU

Criteria	EAP (US)	CUP (EU)	NPP (EU)
Legislation in place	• Expanded Access Programs (FDA, 1997)	• Article 83 (1) of Regulation (EC) No 726/2004	• Article 5 of Directive 2001/83/EC
Who initiates the Program?	• Manufacturer • Physician	• Manufacturer/Group of physicians (e.g. in Italy)	• Physician
Criteria to define/select target population is set by	• Manufacturer/FDA	• Manufacturer/CHMP	• Manufacturer/Physician
Who can benefit from Program? Limitation in Use?	• Group of patients (treatment INDs & treatment protocols) • Named patients (single patients INDs)	• Group of patients i.e. more than one (permission is granted to a clinic or hospital as opposed to a particular patient)	• Only named patients for whom physician has made a request
Liability	• Manufacturer	• Manufacturer	• Prescribing physician
Medicinal product should be undergoing clinical trials or awaiting marketing authorization?	✓	✓	×
Is off label use permitted?	×	×	×
Are Physicians paid for taking part in the program	✓	×	×
Are drugs in the program priced	×	×	✓

Source:[6] Yazdani Morteza, Boggio Francesca-initiating early access programs in Europe: Five things to consider: Executive insights. http://www.executiveinsight.ch/sites/default/files/publication_pdfs/Early%20Access%20programmes 5_things%20to%20consider.pdf. EAPs = Early access programs, NPP = Named patient program, CUP = Compassionate use program

EA Process and its stakeholders (FDA Report)

- FDA
- Patients
- Physicians
- Biopharma (Manufactures)
- IRBs
- Payers (Insurance)

Figure 7 – High-level view of the EA process

	Identification	Application	Treatment	Follow-up
Description	▪ Setting policy and learning about investigational products that could potentially be requested	▪ Submitting a completed EA request to the relevant parties	▪ Providing the therapy or treatment modality to the patient	▪ Monitoring the patient and providing required and requested information to relevant parties
Primary participants and activities	▪ Manufacturer **sets policy for EA,** either at a corporate or product level ▪ Patient and physician **search for information** on investigational products ▪ Manufacturer and FDA provide information about potential options, **either proactively or when contacted**	▪ If an appropriate product is found and physician recommends it, patient will decide whether or not to proceed ▪ If patient agrees, **physician works to get authorization from the manufacturers** and **works with the IRB** as required ▪ With manufacturer agreement and in parallel with IRB review, physician or manufacturer **submits a completed request to the FDA,** which will evaluate it	▪ If **FDA authorizes** and **IRB approves,** the physician contacts manufacturer and receives the product ▪ Physician obtains informed consent from the patient ▪ Physician administers the treatment to the patients and **monitor response per protocol**	▪ Patient continues to receive treatment per protocol **unless their condition changes or consent is withdrawn** ▪ Physician documents and sends **updates on treatment efficacy and adverse reactions** (as required)

Background (a little bit of history)

- Kefauver-Harris Drug Amendment Act of 1962
  - Thalidomide => Required stringent proof of drug efficacy in addition to safety
- Medical Cannabis by Robert Randall 1978 (Not at the federal level)
- AIDS 1987
  - Patients and caregivers urged pharma to provide investigational drugs
- Breast Cancer Patient Groups
- Abigail Burroughs – Her father sued FDA
- Social media 2000 - onwards
  - Patients without a treatment option put their stories online
    - Andrea Sloan
    - Josh Hardy
  - Patient advocates

Events (Formalization)

- 1987
  - EAP for Drugs and Biologics (Regulation)
- 1996
  - Device (Regulation)
- 1997
  - EAP Codified in law
- 2009
  - Revision
- 2016
  - Final Rule for Clinical Trials Registration and Results Information Submission
    - Must put EAP trials on ClinicalTrials.gov

Recent related events

- 21st Century Cure Act
  - Enacted by the US Congress in December 2016
  - Streamlines drug development process
  - Emphasis on Real-World Evidence (RWE)
  - Requires companies to disclose a company's EA policy (with contact information) for a product that enter phase 2

- 2017 GAO Reports
  - https://www.gao.gov/products/GAO-17-564

- 2018 Right-to-try Laws
  - Similar to EA but it bypasses FDA and IRB
  - Only limited to single patient use
  - No device

Famous Examples of EAP

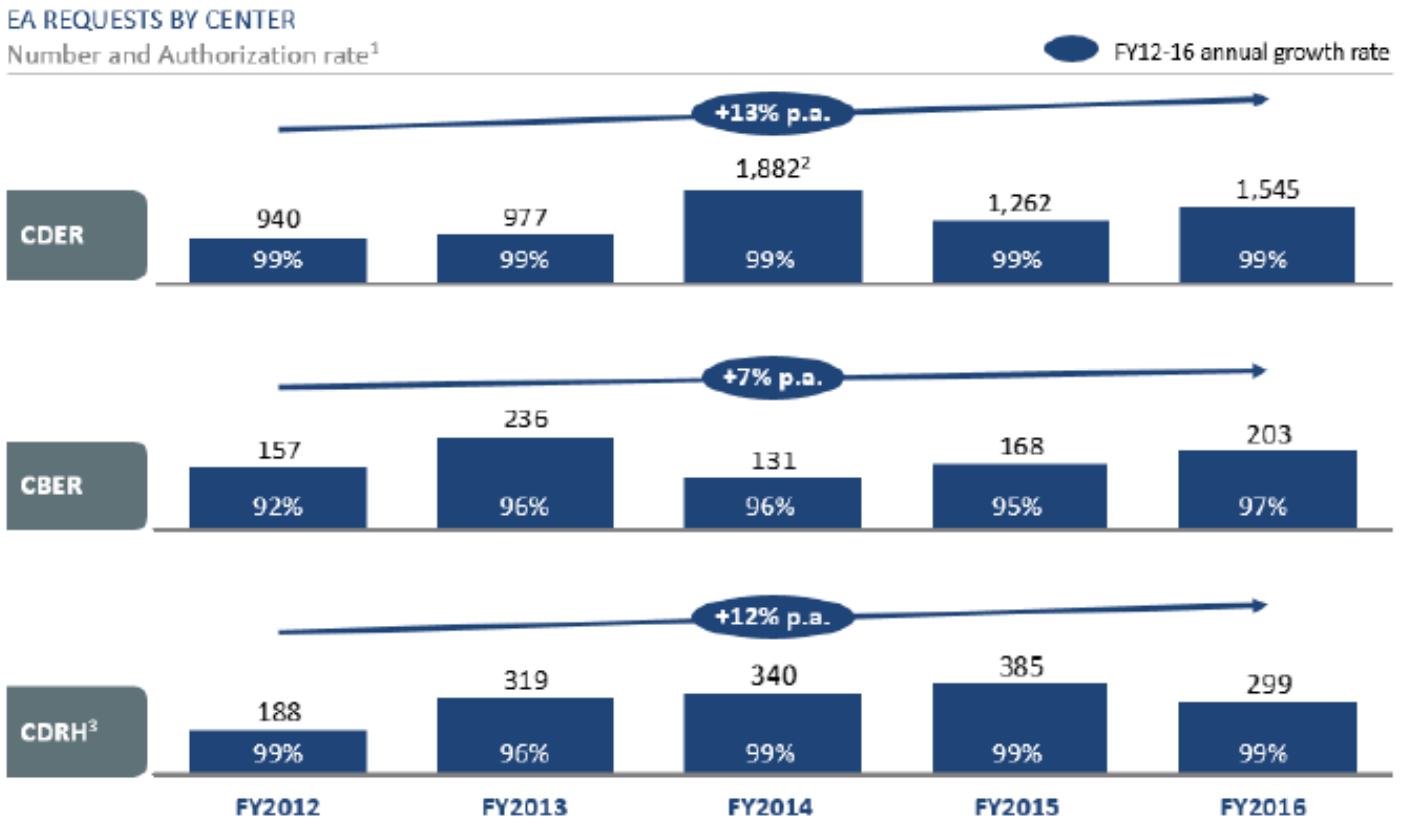
- Zmapp for Ebola
- Atazanavir / Ritonavir for AIDS
- Herceptin for Breast Cancer

- Most recently,
  - Remdesivir for Covid19

Why do we need EAP? (1)

Increasing # of requests

Figure 2 – EA requests for CDER, CBER and CDRH



1 For CDER and CBER, defined as authorized EA IND and protocol requests authorized divided by total requests received. For CDRH, defined as approved CU requests divided by evaluable submissions (excluding those withdrawn or converted to emergency use while under review)
2 Increase primarily due to two drugs (one of which was being taken off the market)
3 CDRH dataset based on calendar years and not fiscal years

Why do we need EAP? (2)

Typical Drug Development Lifecycle

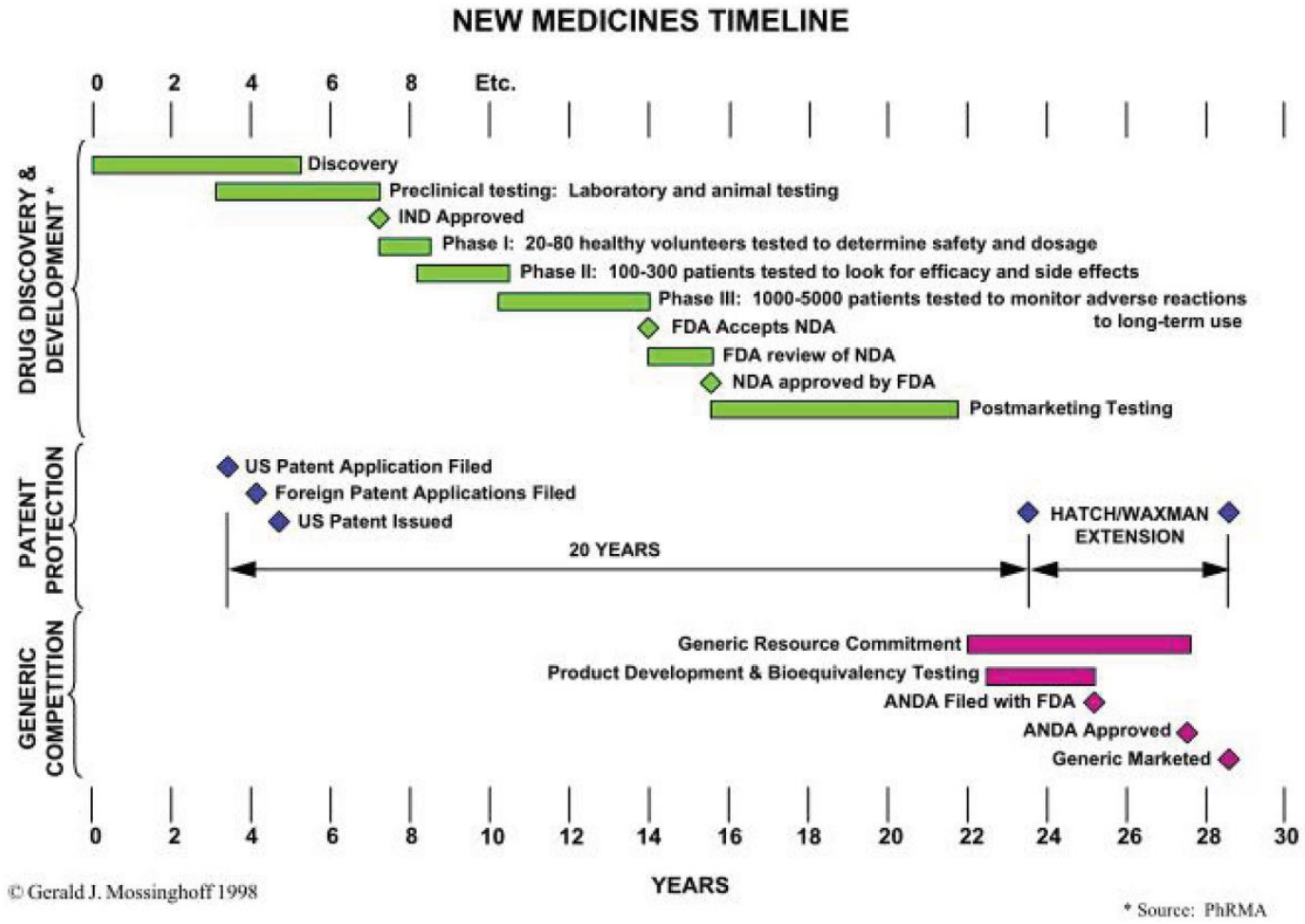


Figure 1. Schematic of Pharmaceutical Life Cycle

Once again, definition of EAP (FDA Website)

- Sometimes called “compassionate use”, expanded access is a potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

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Then, why does EAP generate so much controversy? (NYU CUPA)

- Access to investigational medicines is not a right, nor it is always fairly granted.
- Non-trial preapproval access may jeopardize the integrity of clinical trials.
- Available supply of investigational medicines may be scarce.
- Investigational medicines have unknown benefits and risks.

Characteristics of EAP (1) (Miller et al., 2017)

- Data: 398 EAPs on ClinicalTrials.gov (- July 2016)
  - Industry funded (61%), NIH funded (2.7%), Government funded (1.5%)
  - Drug (71%), Biologics (11%), Device (10%)
  - HIV (6.5%), Leukemia (5.5%), Multiple Myeloma (3.5%), Cholestasis (3%), Melanoma (2.7%), Diabetes (2.7%), Lymphoma (2.2%), Neuroblastoma (1.7%)
  - Adults / Seniors (54%), Child only (6.3%), Anyone (27.9%)
  - (Only Drugs) Approved (68%), Not approved (27%)

Characteristics of EAP (2) (McKee et al., 2017)

- Data: 5,394 EAP Requests during 2010-2014

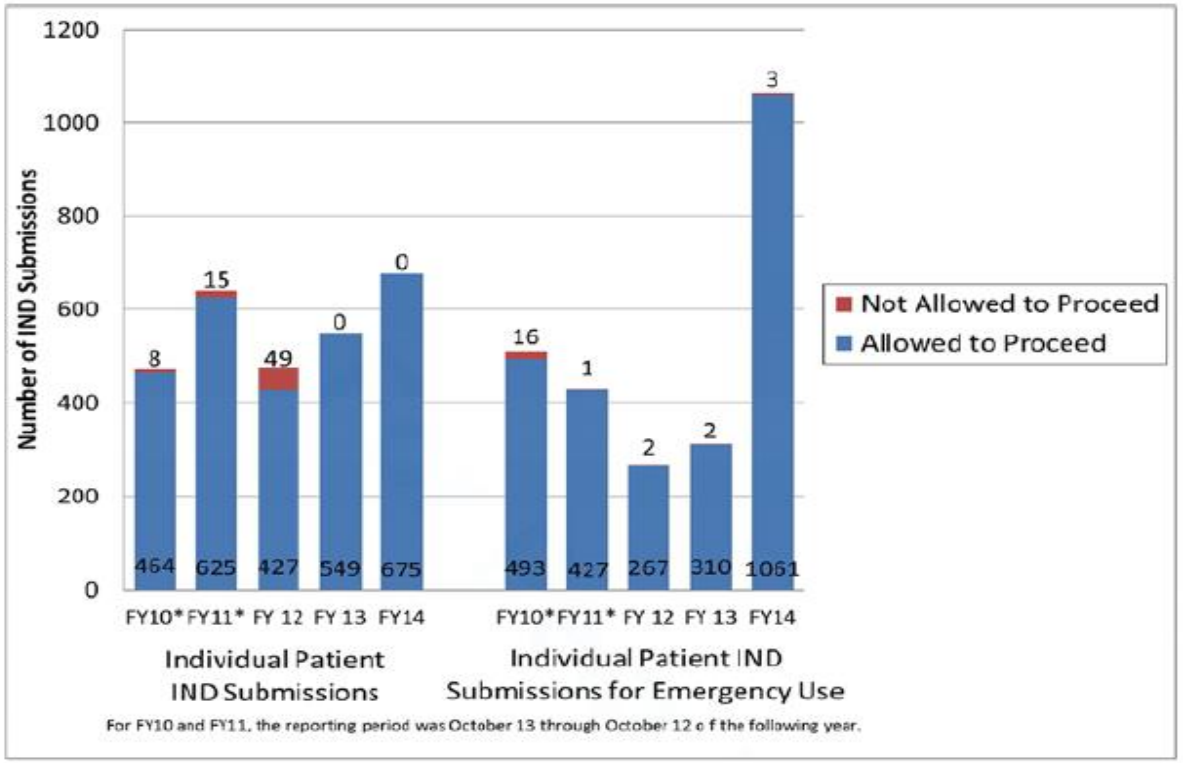


Figure 1. Individual patient expanded-access INDs, Fiscal Years 2010-2014. IND indicates investigational new drug.

Characteristics of EAP (2) (McKee et al., 2017)

Table 2. Ten Most Requested Drugs Under Individual Patient Expanded-Access INDs That Were Allowed to Proceed, Presented by Review Division and Their Approval Status as of September 30, 2015, FY 2010-2014*

Rank	Review Division (Number of INDs)[a]	Number of Requests	Percentage of Requests	Approved for Any Indication?
1	Anti-infective products (727) Special pathogen and transplant products (81) Transplant and ophthalmology products (54)	869	16.4	Yes
2	Antiviral products (573)	573	10.8	No
3	Hematology products (437)	442	8.3	Yes
4	Gastroenterology and inborn errors products (232) Gastroenterology products (71)	304	5.7	No
5	Antiviral products (235)	235	4.4	No
6	Gastroenterology and inborn errors products (119) Gastroenterology products (54)	173	3.3	Yes
7	Drug oncology products (98) Oncology products 1 (36) Oncology products 2 (14)	156	2.9	Yes
8	Hematology products (94) Oncology products (50)	153	2.8	Yes
9	Transplant and ophthalmology products (24) Anti-infective products (89) Special pathogen and transplant products (21)	134	2.5	No
10	Antiviral products (120)	120	2.3	Yes

IND indicates investigational new drug.
[a]Includes only divisions with more than 10 requests.

Characteristics of EAP (2) (McKee et al., 2017)

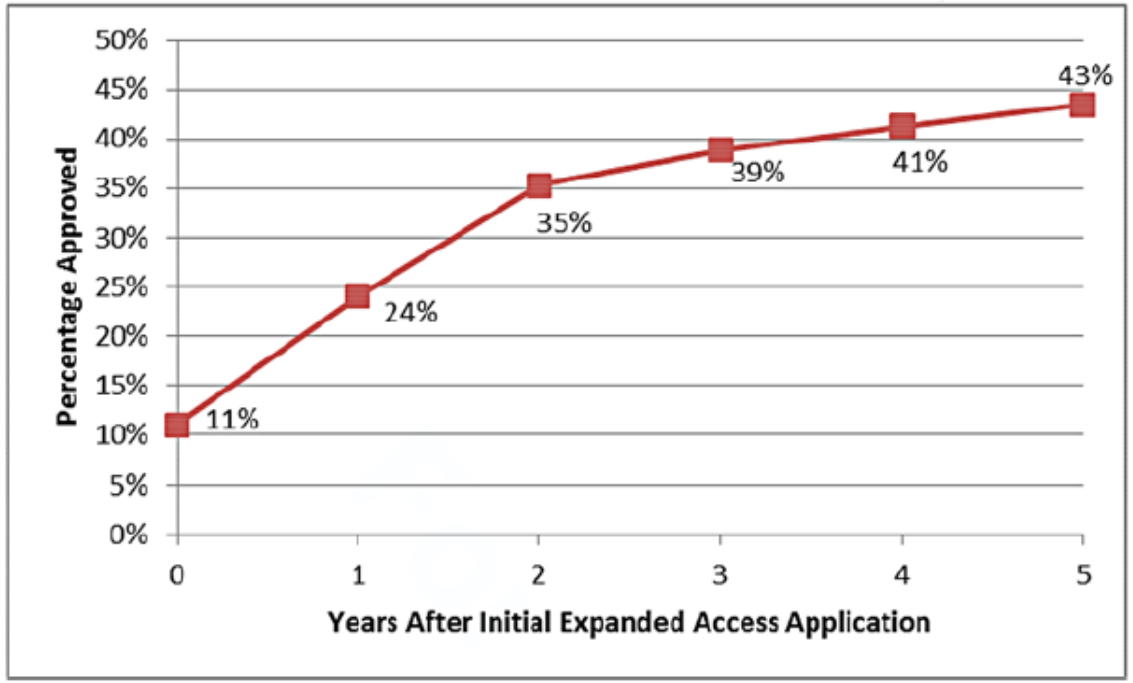


Figure 5. Percentage approval for any indication by September 30, 2015 for unique drugs for which expanded-access INDs were allowed to proceed, FY 2010-2014 (n = 471). FY indicates fiscal year; IND, investigational new drug.

Characteristics of EAP (3) (Jarow & Moscicki, 2017)

- Data: 321 Regulatory Decisions during 2010 – 2016

Types of Expanded Access INDs and Protocols Referencing Investigational Drugs for Submitted NDA and BLA.

Type of Protocol	Number
Intermediate size IND	40
Intermediate size protocol	3
Single patient, emergency IND	345
Single patient, nonemergency IND	549
Treatment IND	4
Treatment protocol	3

Abbreviations: BLA, biologic licensing application; IND, investigational new drug; NDA, new drug application.

Comparison of the Regulatory Actions for Applications That Did and Did Not Have Prior Expanded Access Experience.[a]

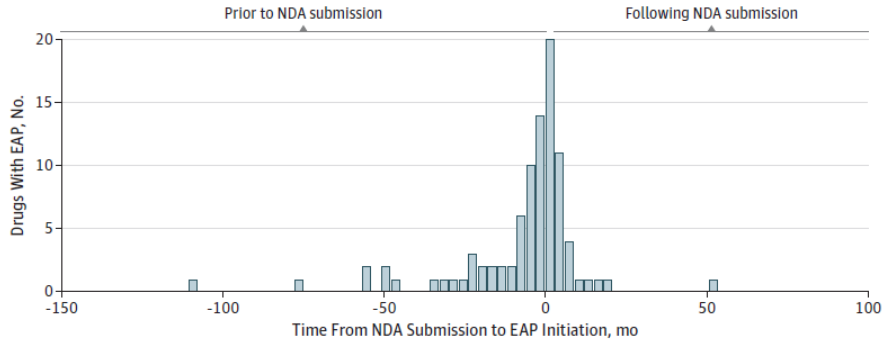
Regulatory Action	No Expanded Access, n (%)	Expanded Access, n (%)
Approved	175 (76)	76 (84)
Refuse to file	9 (4)	9 (10)
Complete response	47 (20)	6 (7)

[a]Nominal $P = .001$.

Characteristics of EAP (4) (Puthumana et al., 2018)

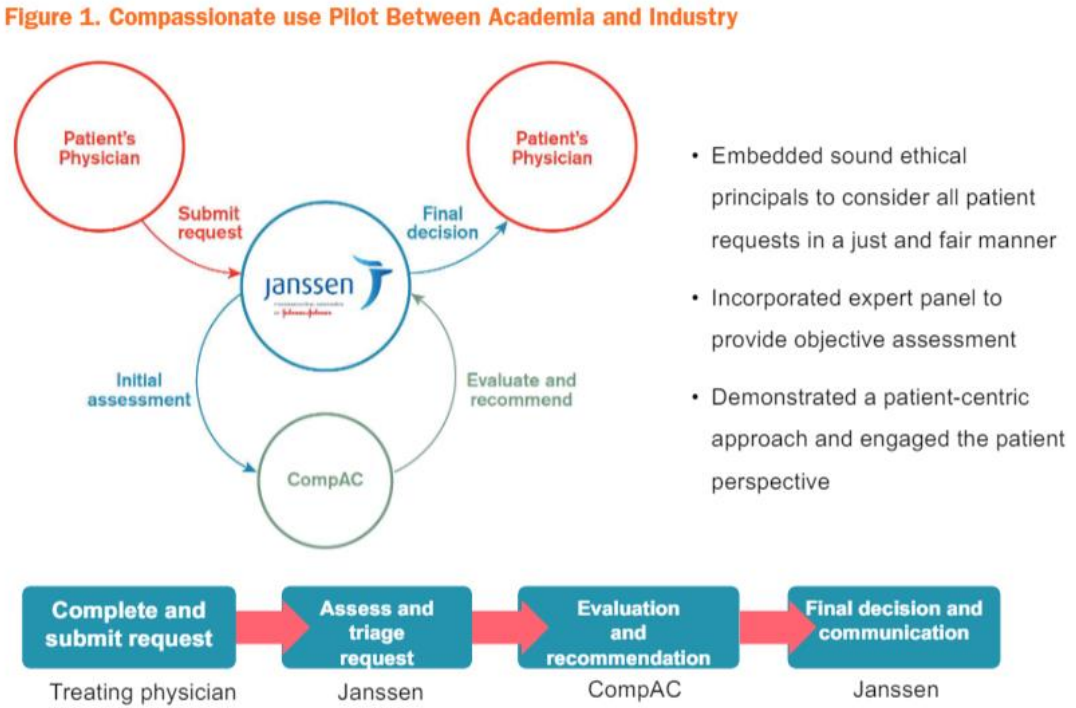
- Data: 92 FDA approved drugs and biologics had EAP (- Aug 2017)
  - Cancer (50%), Metabolic, endocrine, and genetic diseases (17.4%), Infectious disease (15.2%)
  - Median EAP availability: 10 months
  - 69.6% of EAP launched just before or after NDA submission

Figure. Distribution of Investigational Medicine by Time of New Drug Application (NDA) Submission to Expanded Access Program (EAP) Initiation



Case: Janssen's Daratumumab (Caplan & Ray, 2016)

- July – December 2015
  - 160 EAP Requests
    - 43 unfavorable profiles
    - 28 haven't exhausted all the options
    - 13 excluded by other reasons
    - 76 evaluated
      - 60 recommended
      - 62 final approved



Case: Memorial Sloan Kettering IRB

- Jan 2012 – Jan 2018: 208 EAP Approved
- Solid Cancer (57.9%), Blood Cancer (42.1%)
- 66 Unique Investigational Products
  - Drugs (28.8%), Biologics (12.5%), Cell therapy (12.0%)
  - Phase II (36.1%), Phase 3 (39.4%), Phase 1 (18.8%)
- Genomic data (38.0%)
- Median time to EAP treatment from request was 19 days.

- Of 159 evaluable patients, overall response rate was 20.1% with median OS of 11.4 months.

Physician's Perspective (Moerdler et al., 2018)

TABLE 2 Reported barriers to applying for compassionate use

I have not submitted an application for compassionate use because…	*n = 65 (%)*[a]
I am not familiar with compassionate use programs	12 (19)
I do not understand how to obtain pharmaceutical company approval	13 (20)
I do not understand how to obtain FDA authorization	16 (25)
I have not had a patient who needed access to an investigational drug outside of a clinical trial	36 (69)
I could not identify a drug that had the potential to help my patient	15 (29)
The process was too time consuming	9 (14)[b]
I found a clinical trial for the investigational drug in which to enroll my patient	7 (11)

[a]Multiple responses were allowed; therefore, total exceeds 100%.
[b]Five out of the 13 (38%) physicians who started but did not complete a compassionate use application stated that the process was too time consuming.

TABLE 3 Availability of institutional support and the need for assistance

	Availability of training/resources			Need for service to assist with application		
	Yes	No	Unsure	Yes	No	Unsure
Never applied	14 (11%)	24 (19%)	27 (22%)	54 (43%)	1 (1%)	10 (8%)
Applied	13 (11%)	36 (29%)	10 (8%)	49 (39%)	2 (2%)	8 (7%)
Total	27 (22%)	60 (48%)	37 (30%)	103 (82%)	3 (3%)	18 (15%)

IRB's Perspective (Chapman et al., 2019)

Table 4. Respondents' perspectives on IRB review of single-patient expanded access requests for investigational drugs, including biologics.

	Strongly agree		Agree		Undecided		Disagree		Strongly disagree		Total # responses	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	n	%
When time allows, it is important for a designated member of an IRB to review single-patient expanded access requests before investigational drugs are used by patients.	43	51.8%	22	26.5%	4	4.8%	10	12.0%	4	4.8%	83	100.0
I believe that one IRB member (chairperson or designated member) is sufficient for review of single-patient expanded access requests for investigational drugs	28	33.7%	32	38.6%	15	18.1%	8	9.6%	0	0.0%	83	100.0
Review of single-patient expanded access requests for investigational drugs should be conducted by full (majority) IRB board.	1	1.2%	12	14.5%	16	19.3%	39	47.0%	15	18.1%	83	100.0
It is important to have local IRB review of single-patient expanded access requests for investigational drugs.	20	24.1%	33	39.8%	9	10.8%	17	20.5%	4	4.8%	83	100.0
IRB review of single-patient expanded access requests for investigational drugs would be sufficiently handled by a non-local IRB.	5	6.0%	19	22.9%	28	33.7%	24	28.9%	7	8.4%	83	100.0
IRB review of single-patient expanded access requests for investigational drugs is important to …												
… *protect the rights and welfare of the patient.*	41	50.0%	28	34.1%	4	4.9%	7	8.5%	2	2.4%	82	100.0
… *ensure adequate informed consent of the patient.*	43	52.4%	28	34.1%	4	4.9%	5	6.1%	2	2.4%	82	100.0
… *ensure proper qualifications of the treating physician.*	27	32.9%	27	32.9%	11	13.4%	15	18.3%	2	2.4%	82	100.0
… *confirm that the benefit/risk ratio of the experimental treatment is appropriate.*	30	37.0%	35	43.2%	4	4.9%	10	12.3%	2	2.5%	81	100.0
… *assess if there is conflict of interest on the part of the treating physician.*	30	37.0%	32	39.5%	9	11.1%	7	8.6%	3	3.7%	81	100.0

Patients' Perspective (Folkers & Caplan, 2019)

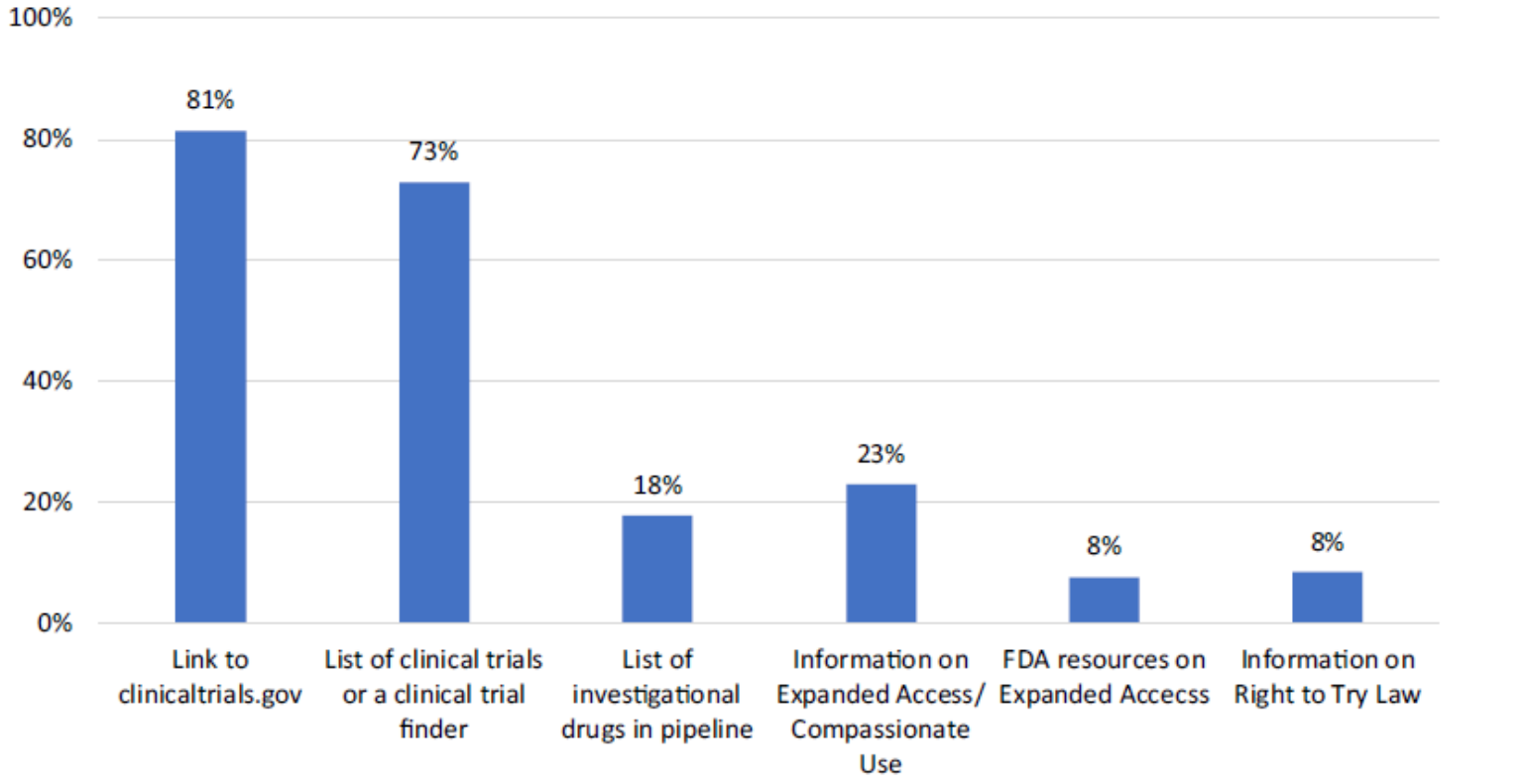


Fig. 1 Analysis of patient advocacy organization (PAOs) and the extent to which they provide information and resources on clinical trials, the U.S. Food and Drug Administration's expanded access program, and the Right to Try Act. Bars represent the percentage of PAOs that provided information on 7 different criteria presented in the "Methods" section

Pharma’s Perspective - Benefits

- Saving lives
  - In a compliant manner.
- Education / Marketing
  - Physicians
  - Patients
- Real-World Evidence
  - May help marketing approval
- Developing relationships with government
- Pre-launch revenue (Andree, 2008)

Pharma’s Perspective - Costs

- Efficacy / Safety Events that may affect marketing approval
- Requires significant HR
- Mostly provided without profit

Useful Links

- FDA
  - https://navigator.reaganudall.org/
  - https://www.fda.gov/news-events/public-health-focus/expanded-access
- myTomorrows
  - https://mytomorrows.com/en/industry-services/#expanded-access-programs
- NYU Working Group on Compassionate Use & Preapproval Access (CUPA)
  - https://med.nyu.edu/departments-institutes/population-health/divisions-sections-centers/medical-ethics/research/working-group-compassionate-use-preapproval-access

References

- FDA (2018) Expanded Access Report https://www.fda.gov/media/119971/download
- Feit NZ, Goldman DA, Smith E, et al. Use, Safety, and Efficacy of Single-Patient Use of the US Food and Drug Administration Expanded Access Program. *JAMA Oncol.* 2019;5(4):570–572. doi:10.1001/jamaoncol.2018.7002
- Elena Fountzilas, Rabih Said, Apostolia M. Tsimberidou. (2018) Expanded access to investigational drugs: balancing patient safety with potential therapeutic benefits. *Expert Opinion on Investigational Drugs* 27:2, pages 155-162.
- Carolyn Riley Chapman, Jenni A. Shearston, Kelly McBride Folkers, Barbara K. Redman, Arthur Caplan, Alison Bateman-House. (2019) Single-Patient Expanded Access Requests: IRB Professionals' Experiences and Perspectives. *AJOB Empirical Bioethics* 10:2, pages 88-99.
- Moerdler, S, Zhang, L, Gerasimov, E, et al. Physician perspectives on compassionate use in pediatric oncology. *Pediatr Blood Cancer*. 2019; 66:e27545. https://doi.org/10.1002/pbc.27545
- Miller, J.E., Ross, J.S., Moch, K.I. *et al.* Characterizing expanded access and compassionate use programs for experimental drugs. *BMC Res Notes* 10, 350 (2017). https://doi.org/10.1186/s13104-017-2687-5
- Jeremy Puthumana, Jennifer E. Miller, Jeanie Kim and Joseph S. Ross Journal: JAMA Network Open, 2018, Volume 1, Number 2, Page e180283 DOI: 10.1001/jamanetworkopen.2018.0283
- Jarow, J.P., Moscicki, R. Impact of Expanded Access on FDA Regulatory Action and Product Labeling. *Ther Innov Regul Sci* **51,** 787–789 (2017). https://doi.org/10.1177/2168479017707800
- McKee, A.E., Markon, A.O., Chan-Tack, K.M. and Lurie, P. (2017), How Often Are Drugs Made Available Under the Food and Drug Administration's Expanded Access Process Approved?. The Journal of Clinical Pharmacology, 57: S136-S142. doi:10.1002/jcph.960
- Folkers *et al. BMC Res Notes (2019) 12:706* https://doi.org/10.1186/s13104-019-4745-7

Further Readings

- Chapman, C.R., Moch, K.I., McFadyen, A. *et al.* What compassionate use means for gene therapies. *Nat Biotechnol* **37,** 352–355 (2019). https://doi.org/10.1038/s41587-019-0081-7
- https://pink.pharmaintelligence.informa.com/PS124296/Expanded-Access-Data-Can-Support-Approval-Decisions-US-FDA-Says
- Gail A. Van Norman, Expanding Patient Access to Investigational New Drugs: Overview of Intermediate and Widespread Treatment Investigational New Drugs, and Emergency Authorization in Public Health Emergencies, JACC: Basic to Translational Science, Volume , Issue 3,2018, Pages 403-414, ISSN 2452-302X, https://doi.org/10.1016/j.jacbts.2018.02.001.
- https://www.kidsvcancer.org/expanded-access-programs-making-compassion-work/
- Caplan AL, Ray A. The Ethical Challenges of Compassionate Use. *JAMA.* 2016;315(10):979–980. doi:10.1001/jama.2016.0416
- Patil S. Early access programs: Benefits, challenges, and key considerations for successful implementation. Perspect Clin Res 2016;7:4-8
- http://www.appliedclinicaltrialsonline.com/integrating-managed-access-programs-global-considerations
- https://www.thepharmaletter.com/article/early-access-programs-in-europe-a-regulatory-tool-with-pre-marketing-impact

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