# Defining the Accelerated Approval Mechanism

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  - Aravive, AZ, Caris, Clovis, Eisai, Epsilogen, Genelux, Genentech, GSK, Merck

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# THE HISTORY of DRUG REGULATION in the UNITED STATES

# 1848 IMPORTED DRUGS

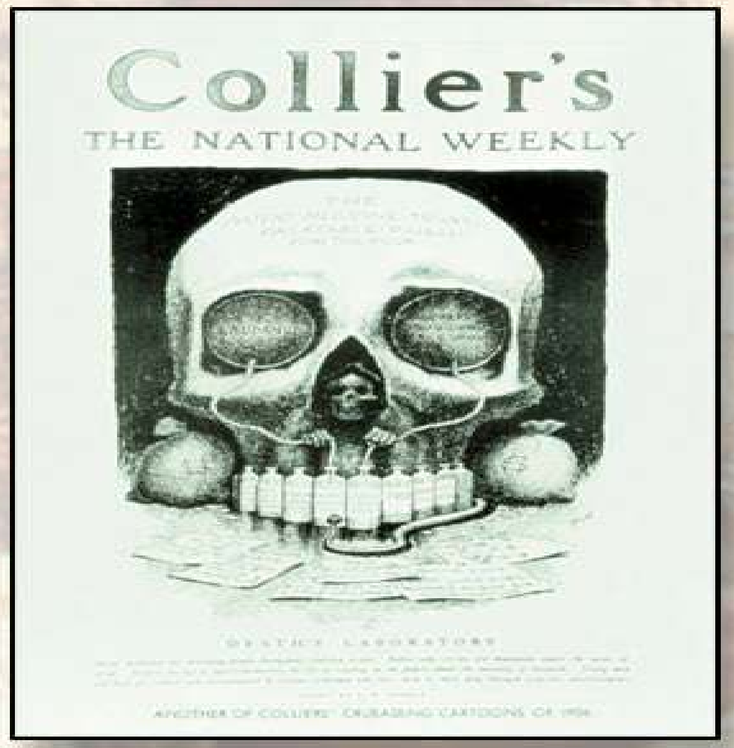
- Most U.S. drugs were imported
- Education & standards were established

# 1848 IMPORTED DRUGS


- Legislative responses to the problem

# 1906

## LABELING DRUGS

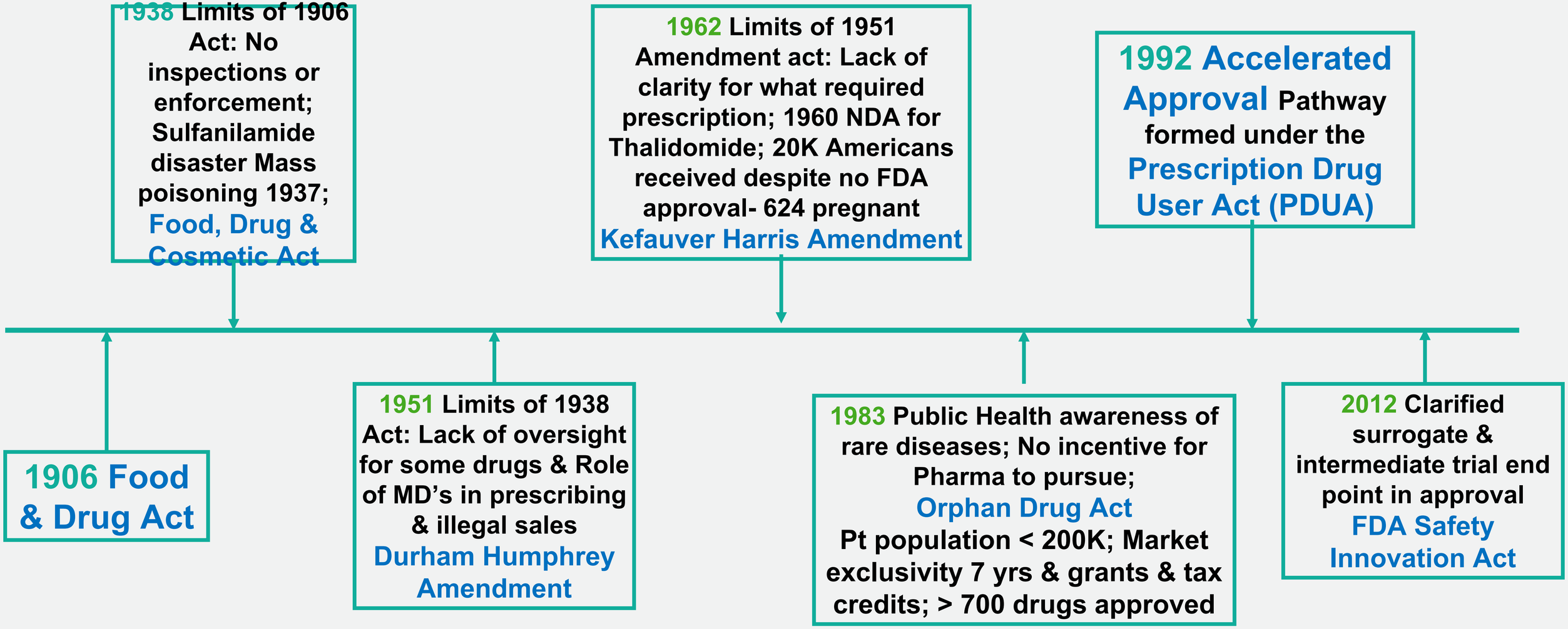



- **Journalists expose abuses as manufacturers cont. to sell unsafe drugs**
  - ***Collier's*** **magazine**
  - **Upton Sinclair's novel,** ***The Jungle***

# 1906 LABELING DRUGS

- **1906 Pure Food & Drugs Act**
  - **Prohibited interstate commerce of unsafe drugs**
  - **Required proper labeling**
  - **Identified official standards for drugs**
- **Harvey Wiley- head of Bureau of Chemistry in USDA- major champion of reform**

# Other Notable Drug Regulatory Historical Landmarks



# Key Programs In Accelerating Drug Development

Fast Track

Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.
**Fast Track**

**Established 1997**

Breakthrough Therapy

A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.
**Breakthrough Therapy**

**Established 2012**

Accelerated Approval

These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint.
**Accelerated Approval**

**Established 1992**

Priority Review

A Priority Review designation means FDA's goal is to take action on an application within 6 months.
**Priority Review**

**Established 1992**

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# Priority Review

- **Priority Review-** introduced in 1992 as alternative to **Standard review**
- Designed to speed approval times
- Take action on application within 6 mos. vs. 10 mos. with Standard Review
- Must still meet same scientific standard for approval & Pharma must request (60 d Decision)
- **Guide for Industry** for Expedited Programs for Serious Conditions – Drugs and Biologics

# FDA Fast Track (1997)

- To facilitate development, & expedite review of drugs to treat **serious** conditions & fill **unmet medical need** (no option or better option)
- **Serious:** survival, day-to-day functioning, or likely condition will progress; Cancer
- Pharma request anytime & FDA response < 60 d
- Benefits:
  - More frequent meetings & written communications
  - Implicit approval of trial design, endpoints, biomarkers
  - Eligible for **Accelerated Approval** & **Priority Review**
  - **Rolling review** (can submit sections for approval such as BLA or NDA rather than waiting for all sections

# FDA Breakthrough Therapy (2012)

- Preliminary clinical evidence the agent or combination demonstrates ”substantial” benefit over existing therapy on one or more clinically significant endpoints
  - Established surrogate endpoint considered reasonably likely to predict a clinical benefit
  - Effect on a pharmacodynamic biomarker(s) that suggests the potential for a clinically meaningful effect on the underlying disease
  - Significantly improved safety profile compared to available therapy
- BTD is eligible for the following:
  - All Fast Track designation features
  - Intensive guidance on an efficient drug development program, beginning as early as Phase 1
  - Organizational commitment involving senior managers
- Sample: 30-40 patients
- Efficacy bar is higher than Accelerated Approval targets
- 15-30% of BTD applications are approved annually

# FDA Accelerated Approval (AA): 1992

- It is full, rigorous FDA approval: Data standards are as high for AA as for conventional approval pathways
- Science around surrogate endpoints is accepted & appropriate.
- Two important features: Speeds approval process & incentivizes investment in novel therapies
- Serious or life-threatening diseases
- Must provides a benefit over existing therapies
- A surrogate reasonably likely to predict clinical benefit
- Subject to the requirement to verify benefit
- Confirmatory trial(s) would usually be underway
- Applicant should carry out studies with due diligence
- Since introduction of AA, >250 drugs have received AA, with roughly 42% rare diseases or conditions & 65% for oncology drugs. Over 50% of AA converted to full FDA approval.

# FDA Accelerated Approval: Nuances

- High unmet medical need (effective therapy absent)
- Surrogate of clinical benefit as endpoint
  - Single agent studies: ORR; combination studies: PFS
    - ORR: Investigator or BICR assessed; PFS: BICR and placebo-controlled (preferred)
    - Duration of response (DOR) required (target: 2 assessment cycles) with minimum follow-up of 6 months from last response
    - Number of complete responses (CR) considered
- Sample size of 100 homogeneous evaluable, well-defined subjects
- Safety database of 200-300 subjects
  - Tolerability is an important review issue
- Confirmatory study in same tumor type significantly enrolled at time of accelerated approval

# Thoughts About Combinations

- Single arm trials can lead to accelerated approval
- Must sort out the relative contribution
- Can utilize historical studies to sort out relative contribution
- The “official FDA opinion” is that randomized trials are needed to sort out relative contribution
- Substantial activity in single arm trials can lead to FDA approval

# Recent Example: Combination & Project ORBIS

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## Simultaneous review decisions for pembrolizumab plus lenvatinib in Australia, Canada and US

## Brazil, Singapore, Switzerland added 2020 & Israel, UK 2021

**Resources for Information on Approved Drugs**

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

**Approved Drug Products with**

On September 17, 2019, the Food and Drug Administration granted accelerated approval to the combination of pembrolizumab (KEYTRUDA, Merck) plus lenvatinib (LENVIMA, Eisai) for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation.

This review was conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence. Project Orbis provides a framework for concurrent submission and review of oncology drugs among international partners. The FDA, the Australian Therapeutic Goods Administration, and Health Canada collaborated on this review, allowing for simultaneous decisions in all three countries.

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# AA Under Scrutiny

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## The FDA's accelerated approval process: When drugs are cleared for sale based on limited evidence

*Accelerated approval is an important topic for journalists to consider in their ongoing coverage of drug costs in America. This article explains how the process works -- including examples of successes and controversies. Plus: 5 reporting tips.*

by Kerry Dooley Young | October 18, 2021 |

# FDA's accelerated drug approval process plagued by missing efficacy data and questionable evidence

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*Reviewed by Emily Henderson, B.Sc.* Jul 31 2021

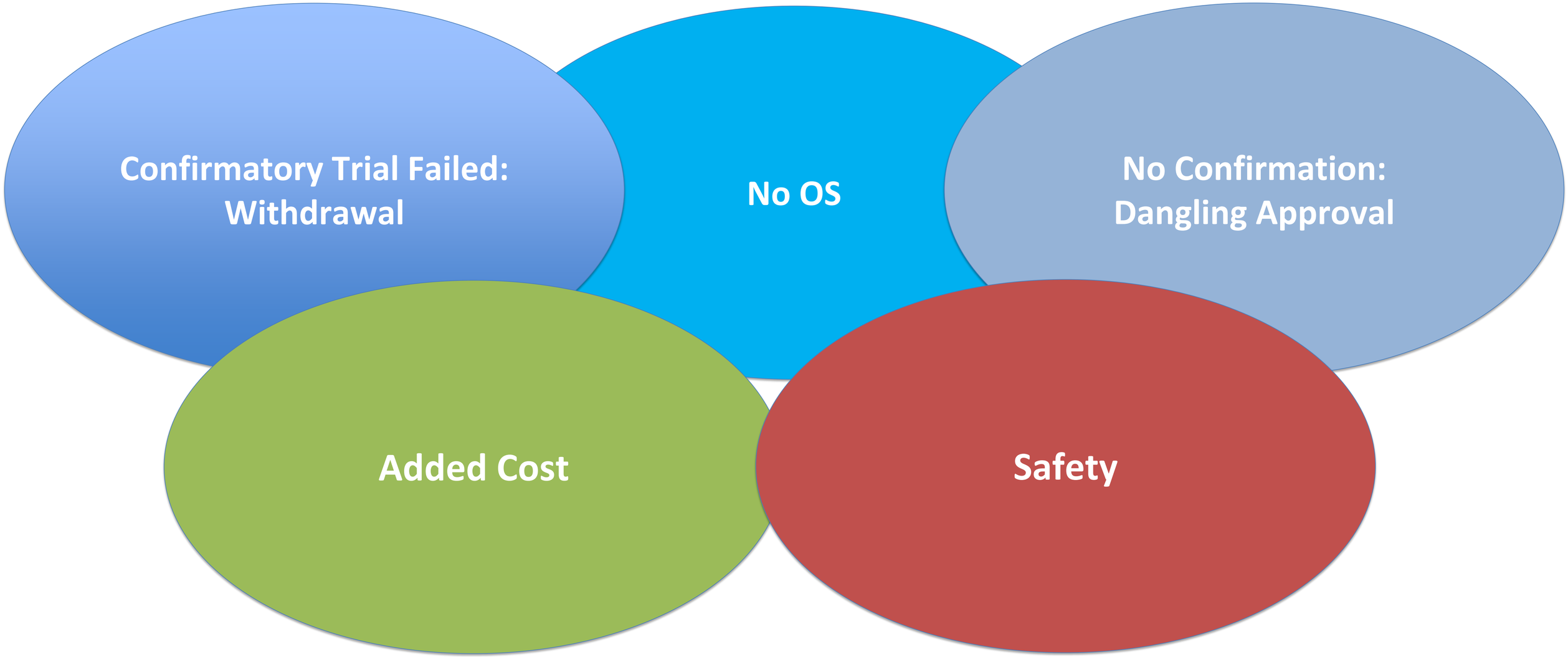
Since the US Food and Drug Administration (FDA) established its accelerated approval pathway for drugs in 1992, nearly half (112) of the 253 drugs authorized have not been confirmed as clinically effective, an investigation by The BMJ has found.

Elisabeth Mahase, clinical reporter at The BMJ, carried out an in depth analysis of FDA data up to 31 December 2020 and found that of these 112 drugs approved in the last 28 years a fifth (24) have been on the market for more than five years and some have been on the market for more than two decades - often with a hefty price tag.

The accelerated pathway allows drugs onto the market before efficacy has been proven, she explains. But as part of this approval, the manufacturer must conduct post-approval studies—known as phase IV confirmatory trials—to "verify the anticipated clinical benefit." If these trials show no benefit, the drug's approval can be cancelled.

Mahase E, BMJ 2021

# Criticisms of Accelerated Approval Process



# Accelerated Approval Pushback


JAMA Intern Med. 2019 Jul; 179(7): 906–913.
PMCID: PMC6547118
Published online 2019 May 28. doi: 10.1001/jamainternmed.2019.0462
PMID: 31135808

## Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval

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- 20% (19 of 93) of Accelerated Approvals had confirmatory trials showing OS benefit in first 25 yrs of AA Program: 1992-2017.

# Gyn Accelerated Approvals-Completed

| Accelerated Approval | Drug | Indication | Full Approval |
|---|---|---|---|
| 6/28/1999 | PLD | Metastatic ovarian carcinoma refractory to paclitaxel and platinum-based chemotherapy | 6/10/2008 |
| 12/19/14 | Olaparib | Mutated BRCA genes (gBRCAm)-associated ovarian cancer who have received three or more chemotherapy treatments accompanied by approval of the companion BRACAnalysis CDx (Myriad) | 8/17/17 |
| 12/9/2016 | Rucaparib | Deleterious BRCAmut (germline &/or somatic) associated adv ovarian cancer treated with 2 or more chemotherapies | 4/6/2018 |
| 6/12/2018 | Pembro | Treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS >/=1) as determined by an FDA approved test | 10/13/2021 |
| 9/17/2019 | Pembro Lenvatinib | In combination with lenvatinib for advanced endometrial carcinoma not MSI-H or dMMR, with progression following systemic therapy and not candidates for curative surgery or radiation | 7/21/2021 |

# Gyn Accelerated Approvals: Full Pending

| Date | Drug | Indication | Orig projected completion: |
|---|---|---|---|
| **5/23/2017** | **Pembro** | Treatment of adult & pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, | 3/31/2023 |
| **6/16/2020** | **Pembro** | Treatment of adult &pediatric patients with unresectable or metastatic tumor mutational burden high (TMB H) [=10 muts/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. | 12/31/2025 |
| **4/22/2021** | **Dostarlimab** | Treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a plat-containing regimen. | 7/31/2022 |
| **8/17/2021** | **Dostarlimab** | Treatment for adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options | 10/31/2022 |
| **9/20/2021** | **Tisotumab Vedotin** | Treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy | 11/30/2024 |

# FDA Approved ADC's through 7/2021

| ADC | Target | Antibody | Linker | Payload | Indication | Manufacturer | Approval Yr |
|---|---|---|---|---|---|---|---|
| Adcetris® | CD30 | Chimeric IgG1 | Valine-citrulline | MMAE | Untreated classical Hodgkin's Lymphoma (cHL); relapsed or refractory cHL | Seattle Genetics (Seagen) | 2011 |
| Kadcyla® | HER2 | Humanized IgG1 | SMCC | DM1 | HER2-positive, metastatic breast cancer | Genentech | 2013 |
| Besponsa® | CD22 | Humanized IgG4 | ActBut | Calicheacmicin | Monotherapy in adults with relapsed or refractory B-cell ALL | Pfizer | 2017 |
| Mylotarg® | CD33 | Humanized IgG4 | ActBut | Calicheacmicin | Single-agent & combo therapy in newly-diagnosed CD33-positive AML | Pfizer | 2000; 2017 |
| Polivy® | CD79b | Humanized IgG1 | Valine-citrulline | MMAE | Combo with benda-mustine & rituximab diffuse B-cell lymphoma | Genentech | 2019 |
| Padcev® | Nectin-4 | Human IgG1 | Valine-citrulline | MMAE | locally adv or metast urothelial cancer | Astellas Pharma, inc. | 2019 |
| Enhertu® | Her2 | Humanized IgG1 | Tetrapeptide | exatecan-derivative topo I inhibitor (DXd) | Metastatic HER2-positive breast cancer | Daiichi Sankyo | 2019 |
| Trodelvy® | Trop-2 | Humanized IgG1 | Hydrolysable CL2A | SN-38 Topo I inhibitor | Mets triple-neg Br cancer | Immunomedics | 2020 |
| Blenrep® | BCMA | Humanized IgG1 | maleimidocaproyl | MMAF | Multiple myeloma after at least 4priors | GSK | 2020 |
| Zynlonta™ | CD19 | Humanized IgG1 | Valine-alanine | SG3249 PBD dimer | Relapsed or refractory large B-cell lymphoma after ≥ 2 lines of | ADC Therapeutics | 2021 |

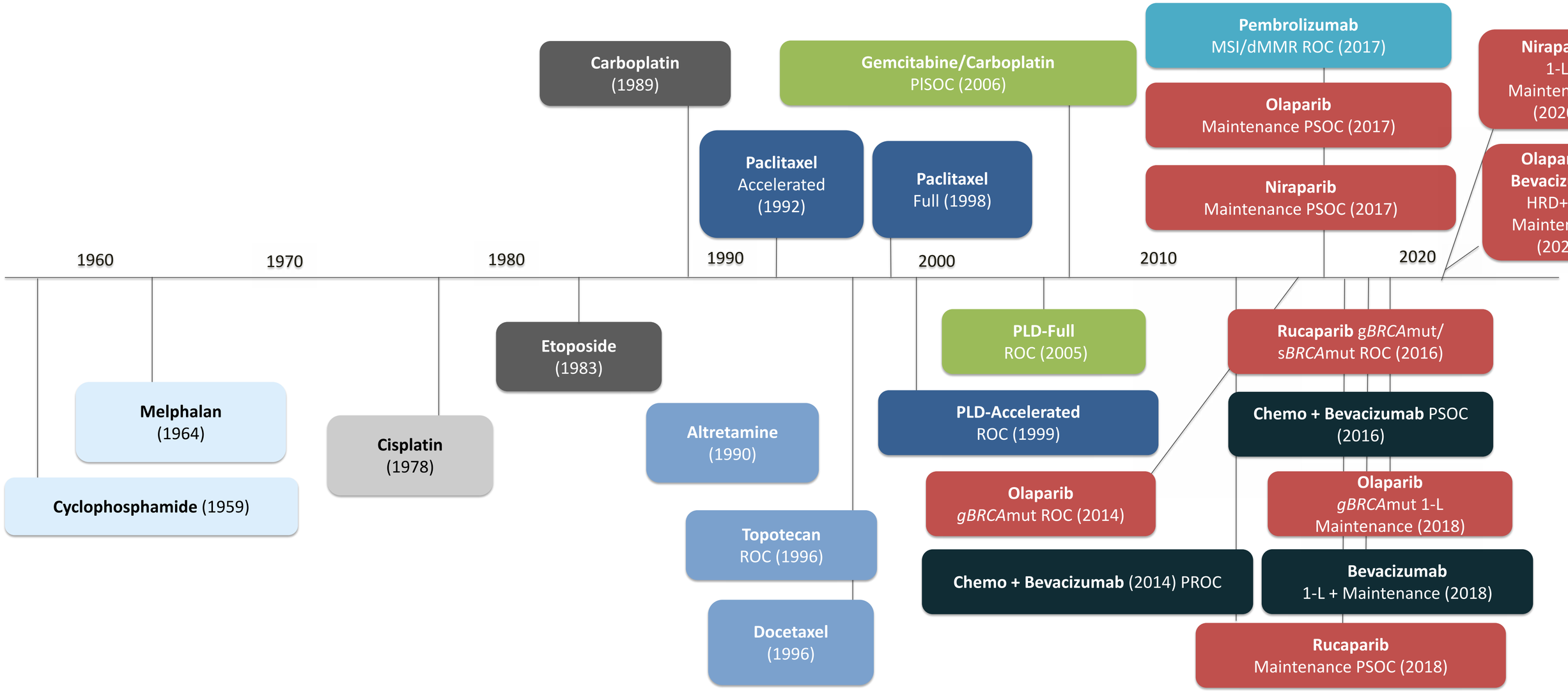
Dean AQ mAbs Vol 13, 2021

# FDA Approved ADC's: 1/2021

| Drug | Maker | Condition | Trade name | Target | Approval Year |
|---|---|---|---|---|---|
| Gemtuzumab ozogamicin | Pfizer/Wyeth | relapsed acute myelogenous leukemia (AML) | Mylotarg | CD33 | 2017;2000 |
| Brentuximab vedotin | Seattle Genetics, Millennium/Takeda | relapsed HL and relapsed sALCL | Adcetris | CD30 | 2011 |
| Trastuzumab emtansine | Genentech, Roche | HER2-positive metastatic breast cancer (mBC) following treatment with trastuzumab and a maytansinoid | Kadcyla | HER2 | 2013 |
| Inotuzumab ozogamicin | Pfizer/Wyeth | relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia | Besponsa | CD22 | 2017 |
| Moxetumomab pasudotox | Astrazeneca | adults with relapsed or refractory hairy cell leukemia (HCL) | Lumoxiti | CD22 | 2018 |
| Polatuzumab vedotin-piiq | Genentech, Roche | relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) | Polivy | CD79 | 2019 |
| Enfortumab vedotin | Astellas/Seattle Genetics | adults with locally adv or metastatic urothelial cancer who have received a CKI & Pt-containing therapy | Padcev | Nectin-4 | 2019 |
| Trastuzumab deruxtecan | AstraZeneca/Daiichi Sankyo | Adults with unresectable or metastatic HER2-positive breast cancer who have received ≥2 prior anti-HER2 based regimens | Enhertu | HER2 | 2019 |
| Sacituzumab govitecan | Immunomedics | adults with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for patients with relapsed or refractory metastatic disease | Trodelvy | Trop-2 | 2020 |
| Belantamab mafodotin-blmf | GlaxoSmithKline (GSK) | adults with relapsed or refractory multiple myeloma | Blenrep | BCMA | 2020 |
| Loncastuximab tesirine-lpyl | ADC Therapeutics | Large B-cell lymphoma | Zynlonta | CD19 | 2021 |
| Tisotumab vedotin-tftv | Seagen Inc | Recurrent or metastatic cervical cancer | Tivdak | Tissue factor | 2021 |

Dean AQ mAbs Vol 13, 2021 & Biopharma PEG 2022

# Twelve New Approvals in the Last 6 Years

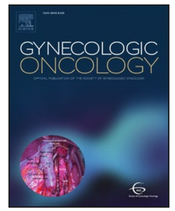


# Clinical Trial Endpoint Paper

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno




## FDA ovarian cancer clinical trial endpoints workshop☆

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# Endpoints & Study Settings

| | Frontline | Platinum-Sensitive | Platinum-Resistant |
|---|---|---|---|
| **OS** | Approve | Approve | Approve |
| **PFS** (Statistically significant) + Other (QoL/PRO) | Approve | Approve | Consider |
| **PFS** (Statistically significant) with clinically meaning MOE | Consider | Consider | Consider |
| **Response Rate/CBR** Overall- High grade serous | No | No | Consider |
| **Response Rate/CBR** Selected histologies (eg. Clear cell, Mucinous, Low grade serous) | Consider | Consider | Consider |

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# Summary

- Recent regulatory meetings with FDA for BTD and AA have been remarkably consistent in guidance:
  - Population clarity, Efficacy benchmarks single agents & combinations, Duration of response definition & follow-up, Methodology of assessment (INV vs BICR),Sorting out relative contribution, Sample size for efficacy &safety for AA, Ph III full approval trial guidance (at AA application)
- In Gyn Onc AA process has been effective
- Dec 1, 2021 Minisymposium with FDA on AA in Gyn Onc
- Expect more regulation on confirmatory trial

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# Thank You!

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