Approval Stages

1. **Start**: target validation, in silico & HT screening (>10,000 compounds), lead optimization (~250 drug candidates)
2. **Pre-clinical testing** (3-6 years): SAR, drug-like properties, solubility, permeability, ADME, plasma PK, efficacy, toxicity (involves animal testing, ~10-20 drug candidates)
3. Filing and Investigational New Drug Application (IND): reviewed by FDA and a local Institutional Review Board (IRB)
4. **Clinical trials:**
   - **Phase 0**: micro-dosing (sub-therapeutic amounts), basic PK&PD, toxicity (few days, <15 healthy individuals) [preliminary SAFETY]
   - **Phase 1**: PK, toxicity, side effects, metabolism, excretion, dose escalation (~1.5 years, 20-80 healthy individuals) [SAFETY]
   - **Phase 2**: assessing therapeutic effect (~2.5 years, few dozen to ~300 patients) [EFFICACY]
   - **Phase 3**: safety and efficacy, different populations & dosages, drug combinations (~2.5 years, several hundred to ~3,000 patients) [EFFICACY&SAFETY]
5. Filing a New Drug Application (NDA): FDA has 60 days to decide if it will be reviewed;
6. **The Review**: 90% of application are reviewed within max 10 months (6 months for priority drugs)
7. Post-approval safety studies (“Phase 4”): months to years after approval

Rates of Success, Cost and Time

- Success rate: ~10% at the clinical stage
- Cost: $1-2 billion/drug
- Time to deliver a drug to the market: 10-15 years

FDA Approval Framework

- Analysis of the target condition/illness and available treatments: weighing the risks & benefits
- Assessment of the benefits and risks from clinical data: taking into account uncertainties (incomplete or imperfect data), deciding how many clinical trials are needed etc.
- Strategies for managing risks: type of side effects, detection and management

Drug Development Designations

- **Fast track**: speeds up the approval process for drugs for serious conditions and unmet medical needs
- **Breakthrough Therapy**: speeds up the approval process for drugs for serious conditions and that demonstrate substantial improvement over available therapies
- **Priority Review**: shortens the NDA review to 6 months for drugs that significantly improve treatment, diagnosis or prevention of serious conditions
- **First-in-class**: drugs that use a new and unique mechanism of action to treat an illness
- **Orphan**: drugs to treat rare diseases (<200,000 worldwide), provides various incentives: 50% tax credit for clinical trials, exemption from user fees, up to 7 years of market exclusivity
- **First-cycle Approval**: drugs that were approved without any re-submissions
- **Accelerated Approval**: drugs that were approved by a predicted clinical outcome based on some surrogate endpoint
- **Emergency Authorization**: non-approved therapeutics authorized for temporary use for example, during a pandemic.
- A drug can have multiple designations. In 2020 the 53 approved novel therapeutics had the following number of designations:

<table>
<thead>
<tr>
<th>Designation</th>
<th>Number of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast Track</td>
<td>17</td>
</tr>
<tr>
<td>Breakthrough Therapy</td>
<td>22</td>
</tr>
<tr>
<td>Priority Review</td>
<td>30</td>
</tr>
<tr>
<td>First-in Class</td>
<td>21</td>
</tr>
<tr>
<td>Orphan</td>
<td>31</td>
</tr>
<tr>
<td>First-Cycle</td>
<td>49</td>
</tr>
<tr>
<td>Accelerated approvals</td>
<td>12</td>
</tr>
</tbody>
</table>

1) FDA online resources; 2) www.cancer.org (Am. Cancer Society)  
3) Acta Pharm. Sinica B, 2022, 12(7), 3059-3062;
General

- A total of 99 therapeutics were approved by FDA in 2020.
- This does not include: 1) vaccines, 2) allergenic products, 3) blood & blood products, 3) plasma derivatives, 4) cellular & gene therapy products (see Center of Biologics Evaluation and Research for more info)
- 53 therapeutics were approved as New Molecular Entities (NMEs)
- The remaining 46 were approved as “efficacy supplements”: modified and/or expanded use of previously FDA-approved drugs.

Efficacy Supplements

- A total of 46 Efficacy Supplements
- 22 were small molecules
- 24 biologics

Type of Modification/Expansion

- New uses (drug repurposing)
- New populations (expansion of patient population e.g. age or stage of disease)
- New formulations (intravenous vs subcutaneous injection; liquid vs powder)
- Combinations (combining already FDA-approved drugs)
- New dosage forms (make dosage easier or more accurate etc. nasal spray, oral suspension vs tablets)
- Biosimilars (biologics that are highly similar and have no clinically meaningful differences)
- New manufacturer

New Molecular Entities (NMEs)

- A 53 novel drugs in total
- 38 small molecules
- 15 biologics

Biologics

- 80% were monoclonal antibodies (mAbs)
- One RNA (Lumasiran, Oxlumo)
- One Phosphorodiamidate Morpholino Oligonucleotide (PMO) (Viltolarsen, Viltepso)
- One growth hormone (protein) analog (Somapacitan, Sogroya)
- Therapeutics areas and diseases:
  - Oncology:
    1. Margetuximab, Margenza® (breast cancer)
    2. Sacituzumab Govitecan, Trodelvy® (breast cancer)
    3. Naxitamab, Danyelza® (neuroblastoma)
    4. Belantamab Mafodotin, Blenrep® (multiple myeloma)
    5. Isatuximab, Sarclisa® (multiple myeloma)
    6. Tafasitamab, Monjuvi® (B-cell lymphoma)
  - Neurology:
    7. Viltolarsen, Viltepso® (Duchenne muscular dystrophy)
    8. Eptinezumab, Vyepti® (migraine)
  - Ophthalmology:
    9. Teprotumumab, Tepezza® (thyroid eye disease)
    10. Satralizumab, Enspryng® (neuromyelitis optica spectrum disorder)
    11. Uplizna, Inebilizumab® (neuromyelitis optica spectrum disorder)
  - Viral Infectious Diseases:
    12. Ansuvimab, Ebanga® (ebola)
    13. (Atoltivimab, Maftivimab, and Odesivimab), Inmazeb® (ebola)
  - Endocrinology:
    14. Somapacitan, Sogroya® (growth hormone deficiency)
  - Renal Diseases:
    15. Lumasiran, Oxlumo® (hyperoxaluria type 1)
Oncology drugs accounted for 29% 
Followed by Neurology – 13%, Medical Imaging agents – 11%, Dermatology – 8%, Infectious Diseases (viral and nonviral) – 10%, and Gastroenterology – 5%

Other:
• Allergy – 1
• Analgesia – 1
• Anesthesiology – 1
• Cardiovascular – 1
• Endocrinology – 1
• Metabolism – 1
• Psychiatry – 1
• Urology – 1
• Other – 1

How does this compare to the European Medicine Agency (EMA)-approvals?
- A total of 20 small molecule NMEs were EMA-approved in 2020
- 70% of them were delivered by USA-based companies.
- FDA and EMA concordance on drug approvals is over 90% (2014-2016)1

1) By company’s headquarters:
- A total of 38 small molecule NMEs were approved
- USA-based companies accounted for 68% of drugs:
  - In the USA, California- and Massachusetts-based companies accounted for 43% of FDA-approved drugs in 2020

2) Therapeutic Area:
- Oncology drugs accounted for 29%
- Followed by Neurology – 13%, Medical Imaging agents – 11%, Dermatology – 8%, Infectious Diseases (viral and nonviral) – 10%, and Gastroenterology – 5%
- Other:
  - Allergy – 1
  - Analgesia – 1
  - Anesthesiology – 1
  - Cardiovascular – 1
  - Endocrinology – 1
  - Metabolism – 1
  - Psychiatry – 1
  - Urology – 1
  - Other – 1

3) Target type:
- Receptors 30%
- Kinases 24%
- Other Proteins 14%
- DNA 5%
- Non-kinase Enzymes 27%

4) Molecule type

- 25 (66%) were heterocycles
- 4 contained a radionuclide (11%)
- Other:
  - natural product derivatives – 3
  - cyclic peptides – 2
  - fatty acids/esters – 2
  - w/ phosphorous – 2
  - sugars – 1
- 55% are chiral (only 1 racemate)

**Synthesis**

**Vibegron**
(Gemtesa®, Urovant Sciences Inc, USA)
(overactive bladder, β-3 adrenergic receptor agonist)

Org. Lett. 2013, 15, 1342-1345

- 1. PhClO2
- 2. (Boc)2O cat. DMAP MeCN
- [Chan-like rearrangement]
- KOBu
- 90%, 99% ee
- 98% yield
- (HWE reaction)
- NaOCl, cat. TEMPO cat. KBr
- 88%
- LiBr, i-Pr2NEt MeCN, 0-20 °C
- (TMS)3NH, then H2, Pd/A2O3, THF, 95%

**Relugolix**
(Orgovyy®, Myovant Sci, USA)
(advance prostate cancer, GnRH agonist, IC50=0.1 nM)

- 1. 150 °C
- 2. LiOH, H2O MeOH
- (Gewald reaction)
- K2CO3, KI, DMF 95%

**Med. Chem. 2011, 54, 14, 4998–5012**
cont.

NOTE: In process e.g., US10344034B2, the N(Me)₂ is installed directly.

Berotalstat
(Orfadye®, Biocryst, USA)
(hereditary angioedema, Plasma kallikrein inhib, IC₅₀=0.44 nM)

Lactitol
(Pizensy®, Braintree, US)
(osmotic laxative)

NOTE: In process e.g., US10344034B2, the N(Me)₂ is installed directly.
FDA Drug Approvals: 2020

Mike Bielecki

DNA alkylating agent

- A derivative of the natural product Trabectedin (from bacteria found in a sea squids)
- 1969 - anticancer properties of extracts

Lurbinectedin

(Zepzelica®, Jazz Pharm., Ireland)

(metastatic lung cancer, DNA alkylating agent)

- 1984 – structure determined by KL Rinehart (University of Illinois)
- Over 1 ton of squids needed to make 1 g
- 1996 – total synthesis by EJ Corey synthesis (43 steps, 0.25% yield, 0.5 mg)
- 2000 – industrial; semisynthesis from Cyanosafacin B (21 steps, 1% yield)
- 2019 – Improved total synthesis (26 steps, 1.6%) from Cbz-protected (S)-tyrosine:

Pictet-Spengler reaction)

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1969</td>
<td>anticancer properties of extracts</td>
</tr>
<tr>
<td>1984</td>
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</table>

FDA Drug Approvals: 2020

Mike Bielecki

Inhibits metalloproteases crucial to hatching of lice eggs
Strong complexing agent
Typical route:

Pd(ACO2) (5 mol%), K2CO3 (1 eq), TBAB 0.5 eq.
DMF, H2O, 95-100 °C, 48h

Hydrazine as a "traceless mediator":

N(Br) + Br + N(Br) → N2 + H2

Abatemapir

(Xeglyze®, Hatchtech, Australia)
(head lice, metalloproteinase inhib)

Artemunate

(AMivas® , US)
(malaria, parasite proteins)

Artemisinin

$1.5/1g
(1PlusChem)

Artemisine

$3.6/1g

Artemesine


Opicapone

(Ongentys®, Neurocin, US)
(Parkinson’s disease, Catechol O-methyltransferase inhib, IC50 <0.01 nm)

Artemesine can be synthesized from the natural product artemisinin:

WO 2015/007693 A1


Artemesine


Fluoroestradiol F18

(Cerinana® Ziaex, France)
(Breast cancer, estrogen receptor binder, Kd ~0.13 nM)

Drug Design,
Development and
Therapy. 2016, 10, 3575-
3590.
