Accelerating Breakthrough Molecules…
… to Breakthrough Medicines

Karl Graham-Siegenthaler - F. Hoffmann-La Roche Ltd.

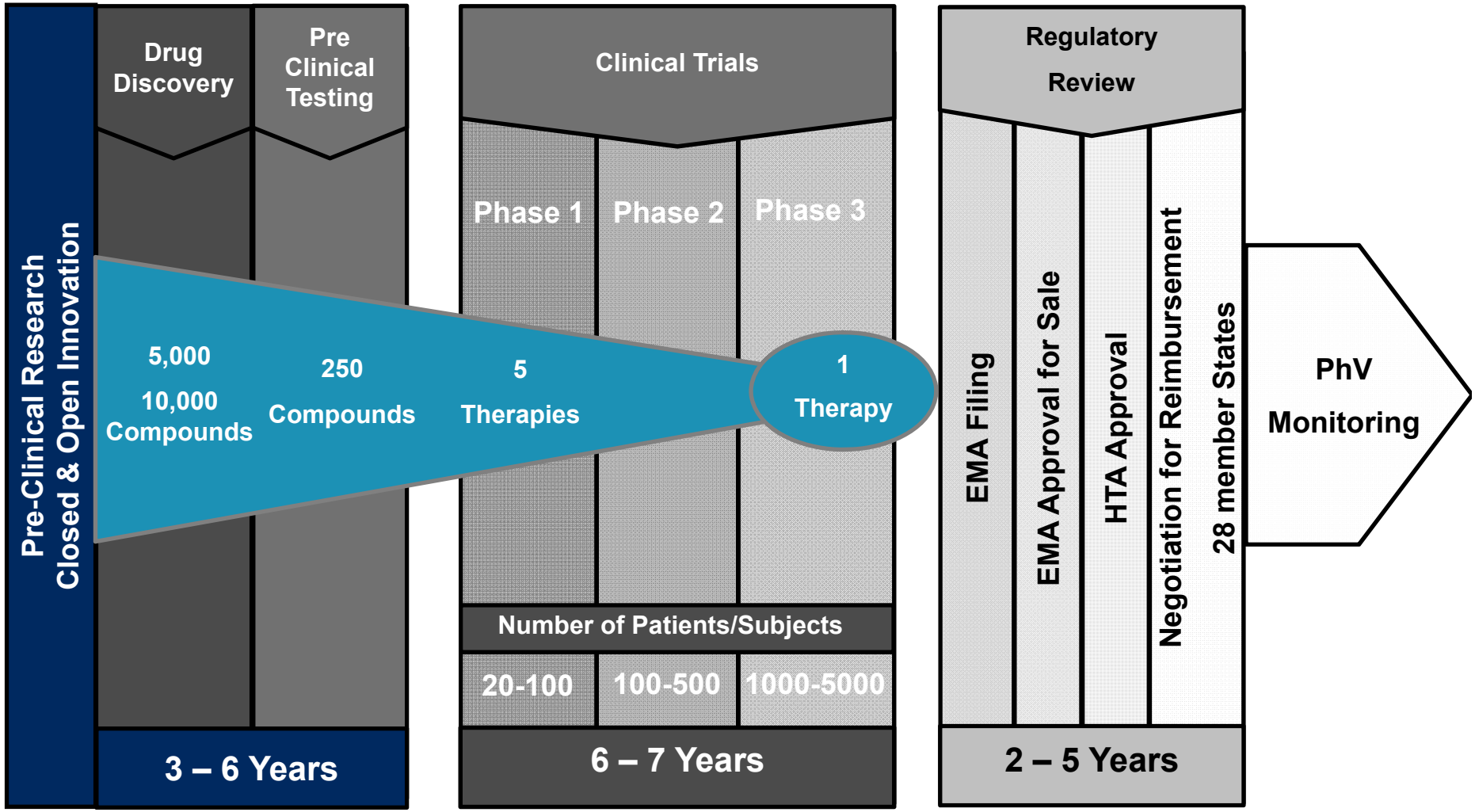
Overview

- “The Problem”
- US Response to The Problem
  - Existing Procedures
  - BTD
  - BTD experience and learnings
- EU Response to The Problem
  - Existing Procedures
  - PRIME
    - Intro
    - Experience to date
    - Areas to address

“THE PROBLEM”

The Medicines Access Problem…

…Too long & too expensive



Total Cost: → **€ 1.5 Billion**

Shifting Landscape of Drug Development

What is expected to change in the future?

Transition from…	To…
• Magic moment • RCT only • Prediction • Big populations • Focus on licensing • Regulators only • Open utilization	• Life-span management • Toolkit for evidence generation • Monitoring • Small populations • Focus on patient access • Regulators, HTAs, Payers • Outcome-based reimbursement

REGULATORY PATHWAYS:
US TOOLS FOR ACCELERATING DEVELOPMENT

US: Accelerated Approval

- Allows the **earlier approval** of a product **based on a surrogate endpoint**, if the product:
  - (1) is for a serious or life threatening disease or condition, and
  - (2) the product has an effect, in an adequate and well controlled study,:
    - on a surrogate endpoint likely to predict clinical benefit
    - on an intermediate clinical endpoint
- **Confirmatory trial underway at the time of submission**
  - If confirmatory trial does not show clinical benefit, FDA has regulatory procedures that can lead to:
    - removal of the drug from the market
    - modification of the label

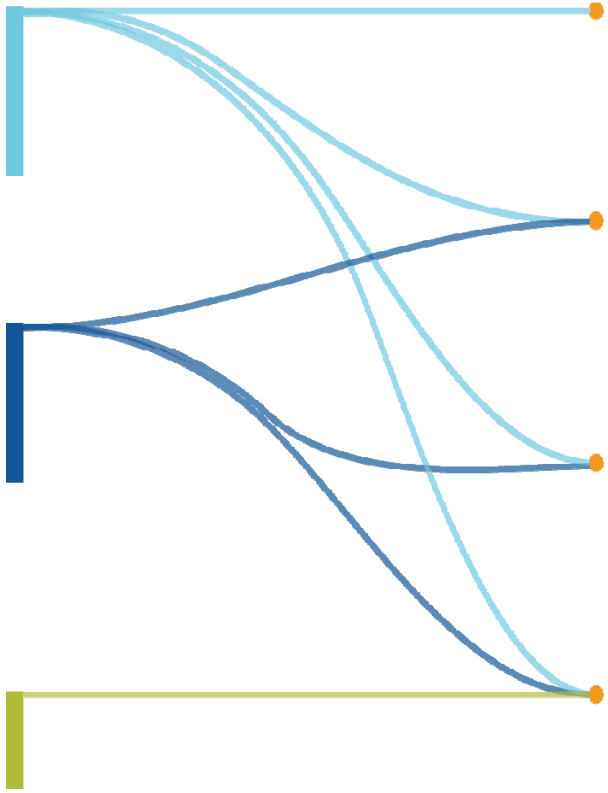
US Expedited Development and Review Paths

For serious and life-threatening diseases, like cancer, the FDA can grant designations to certain medicines that may help accelerate the time to approval

Breakthrough Therapy Designation
Drug makers can apply based on clinical data indicating substantial improvement in one clinically significant endpoint over available medicines

FAST TRACK
Drug makers can apply based on pre-clinical or clinical data for a serious condition with a need for new medicines

PRIORITY REVIEW
The FDA grants priority review to drugs deemed major advancements



Dedicated Senior Management Team
At the FDA helps companies streamline the clinical trial process

Frequent FDA Meetings
Help drug makers design clinical trials that are as efficient as possible and meet FDA expectations

Rolling Review
Allows drug makers to submit data as they become available

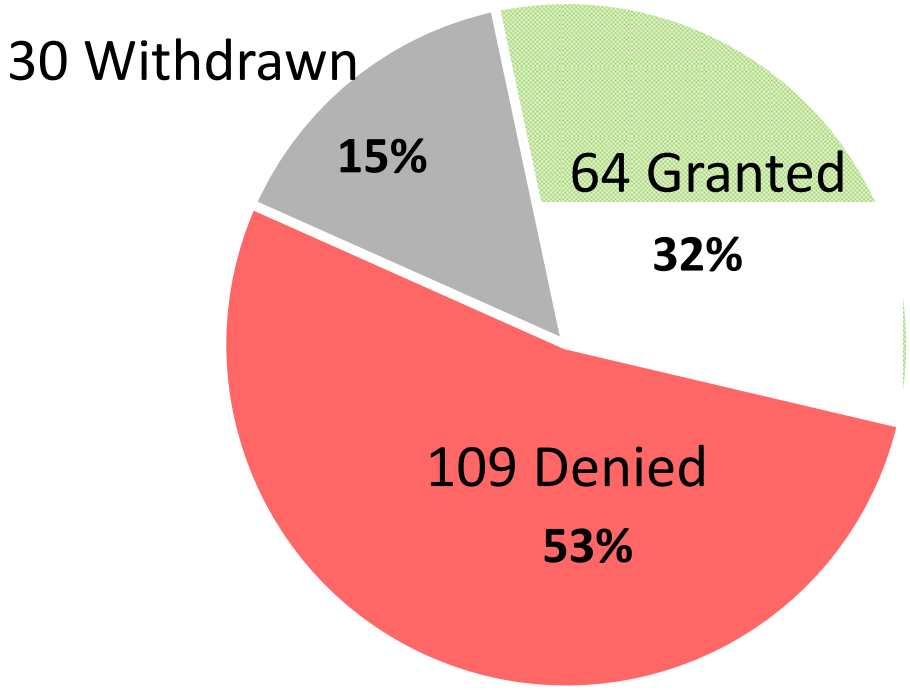
Shortened Application Review Time*
Shortens the FDA's review time by 4 months

*Breakthrough Therapy and Fast Track designations have the possibility of shortened review times; it is not guaranteed.

Breakthrough Therapy Designation

- Drugs granted Breakthrough Therapy Designation will be eligible for:
  - All features of the **Fast Track Program plus:**
    - More intensive FDA guidance
    - Organizational commitment involving senior FDA managers
    - Eligibility for rolling review and priority review
- Qualifying Criteria
  - Serious condition
  - Improvement over existing (or available) therapies
  - Preliminary clinical evidence
    - Evidence sufficient to indicate that the drug may demonstrate substantial improvement in effectiveness or safety over available therapies, but in most cases not sufficient to establish safety and effectiveness for approval
    - Must be clinical evidence- not just theoretical/mechanistic rationale
- Can be revoked by FDA

Outcome of BTD Requests (2013-2015)

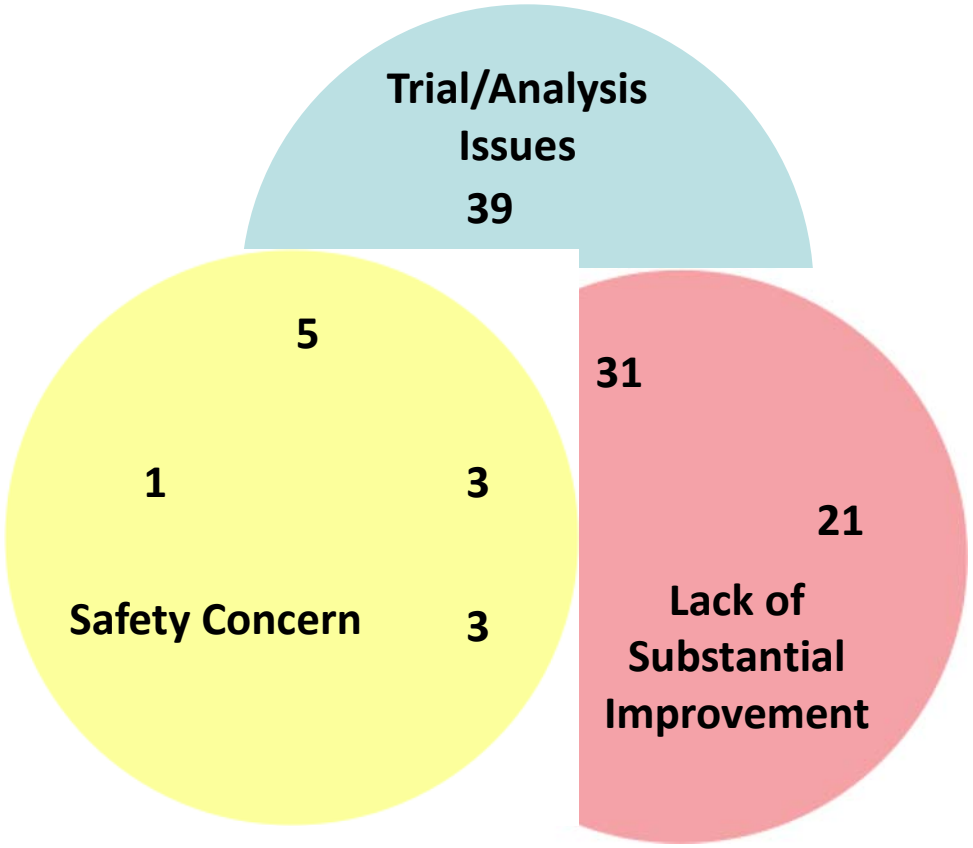


Heme/Onc ONLY
86 BTDRs (42%)

Industry (n=203)

Reason for Denials (2013-2015)

Reliability of clinical evidence biggest reason



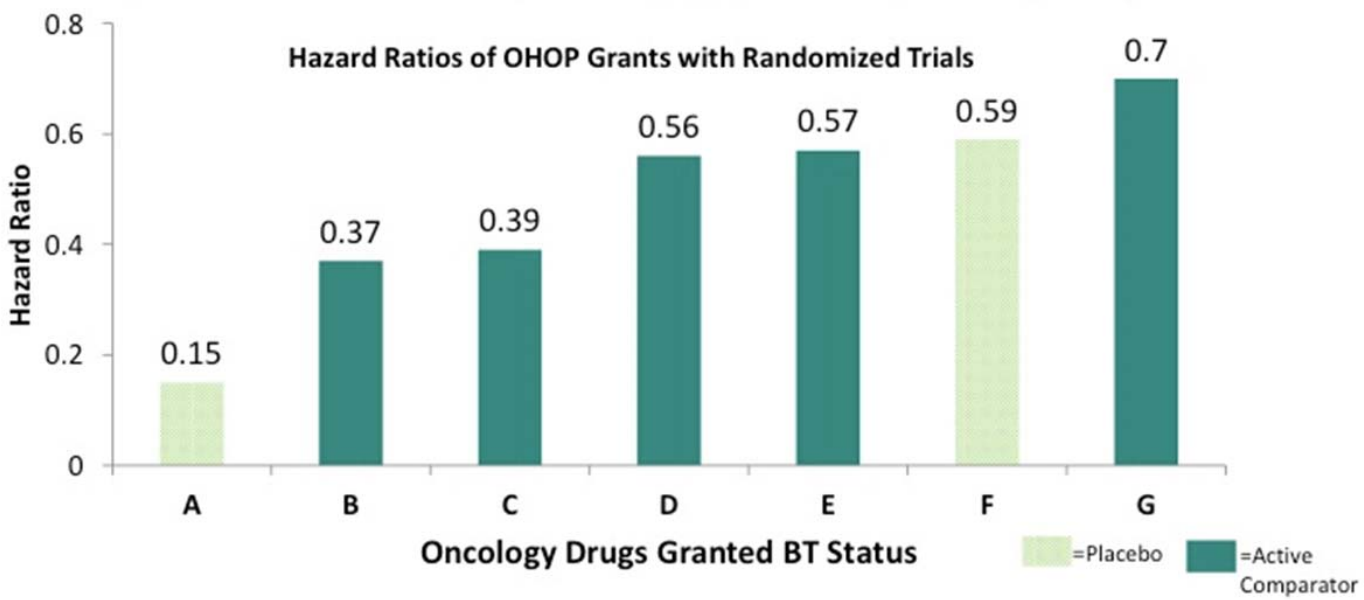
Denials N=109	
Reasons for Denial[1]	
Trial/analysis issues	**78 (72%)**
Trial design issues	45 (41%)
Sample issues	39 (36%)
Endpoint issues	29 (27%)
Results too preliminary	19 (17%)
Flawed post-hoc analysis	17 (16%)
Lack of substantial improvement	**58 (53%)**
Lack of data	**18 (17%)**
No clinical data	4 (4%)
Incomplete data	14 (13%)
Safety concern	12 (11%)
Miscellaneous	**14 (13%)**
Not serious condition	2 (2%)
Other	12 (11%)

[1]Totals exceed 100% as many denials cited multiple reasons for denia

1. **Trial design issues**: Treatment effect not isolated, inappropriately uncontrolled or unblinded trial, etc. **Endpoint issues:** lack of a defined endpoint, faulty/flawed endpoint, or primary endpoint not supported or predictive of clinical benefit. (Note that failing a primary endpoint does not constitute this rationale.)

BTD Associated with Truly Breakthrough Data (2013-2015)

- Average improvement in ORR *over best available therapy*: 55% (38% to 400%)
- Average ORR *without available therapies: 54% (range* 29% to 87%)



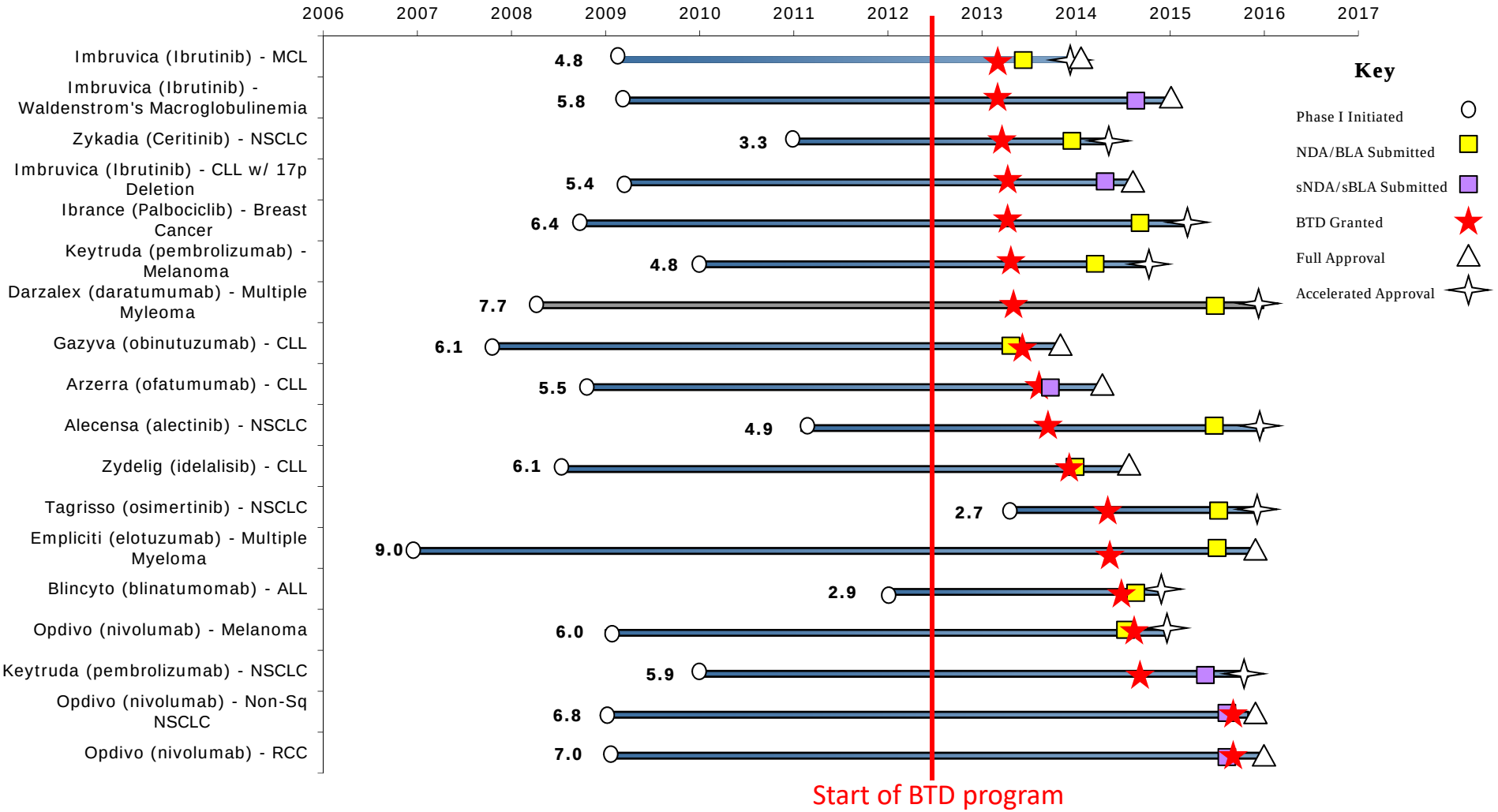
BTD Granted: Average HR: 0.48

BTD Denied: Ave. HR: 0.68

[1]Endpoints included progression-free survival (PFS), event-free survival (EFS) and OS; All but one drug were for indications with available therapies; One drug had an improved safety profile over available therapy

BTD: Phase 1 Initiation to FDA Approval (2013-2015)

5.5 years on average to date



Only oncology drugs approved on the market 2013-2015 granted BTD are presented

FDA BLA/NDA Approval – Some BTD Statistics

18 approvals received in 2013-2015 for drugs with BTD

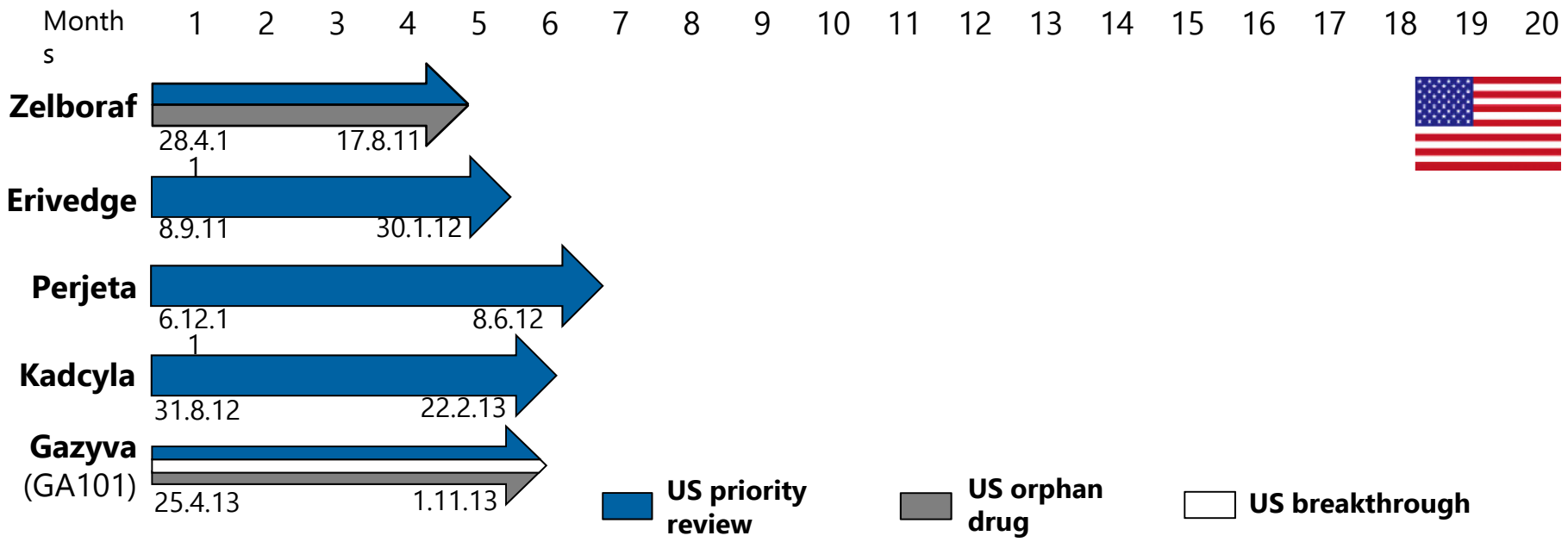
- All received priority review
- 4 drugs (22%) had fast track with rolling BLA/NDA
- 56% received accelerated approval with relatively small phase 1-2 studies (Average trial size: 131 patients - range: 61-198 patients)
- No ODAC meetings
- Average duration of Phase 1 initiation to approval: 5.5 years
- Average approval timing ahead of PDUFA date: 2.5 months

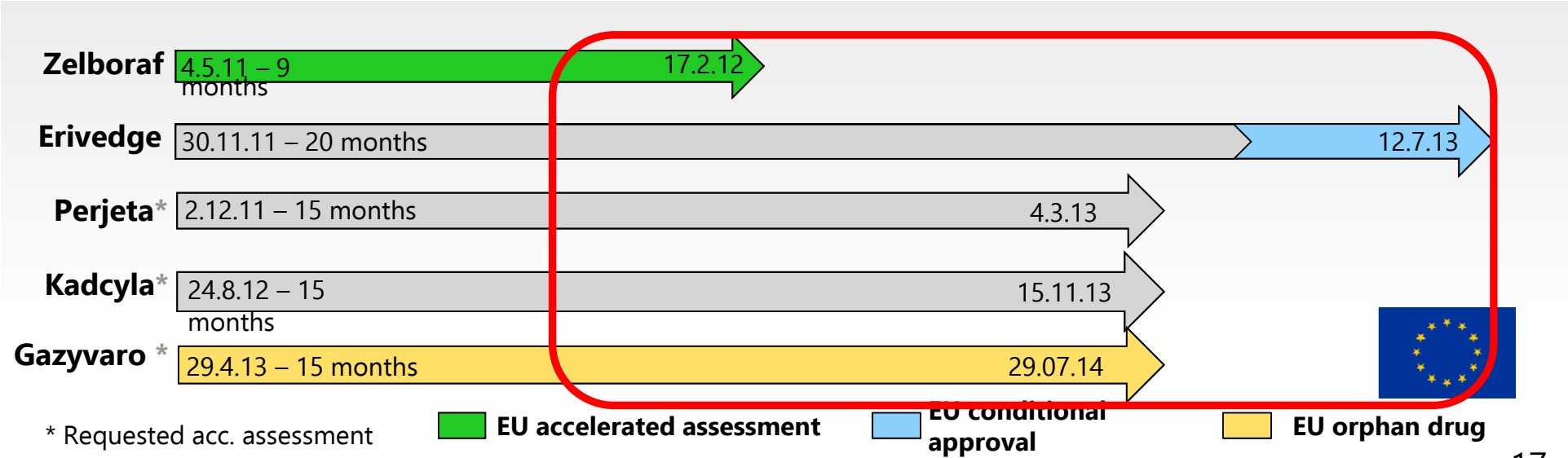
Key Success Factors Associated with BTD

- No distinction between SMEs and “Big Pharma” impacts BTD assessment – focus on breakthrough innovation
- Simple application approach allows for preliminary interaction with the FDA to discuss BTD intent before submitting formal request
- Rapid interaction with senior FDA decision-making stakeholders
- Application possible from any time after IND filing and initial clinical experience available up to the time of (s)NDA/(s)BLA filing
- Application for BTD (and Priority Review) granted on a per indication basis and is not limited to first indication

REGULATORY PATHWAYS:
EU TOOLS FOR ACCELERATING DEVELOPMENT

Some Recent NME Approvals





EMA support for early access

- European Medicines Agency (EMA) has committed to enabling early patient access to innovative new medicines using existing processes
- Current EU regulatory approaches to accelerate early access to medicines and lead to full marketing authorisation are:
  - Conditional Marketing Authorisation (CMA)
  - Exceptional Circumstances (EC)
  - Accelerated Assessments (AA)
  - PRIority MEdicines (PRIME) scheme

EU: Conditional Marketing Authorisation (CMA)

- **What is a CMA?**
  - Authorisation while the collection of comprehensive data is ongoing in order to address unmet medical needs.
  - Comprehensive data are generated post-authorisation in agreed timelines.
- **When can it be obtained?**
  - For a first approved indication (MAA) only
  - Product addresses debilitating or life-threatening disease, or is for an emergency situation or orphan disease;
  - Data show a positive risk-benefit balance and comprehensive data will be provided post-authorisation
  - Quality and non-clinical data required as for a normal authorisation
- **What's the impact?**
  - Encouraged to consider seeking accelerated assessment
  - CMA is valid for 1 year and must be renewed annually
  - Specific Obligations must be met to convert CMA to a full authorisation

EU: Exceptional Circumstances (EC)

- **What is an Authorisation under Exceptional Circumstances?**
  - Authorisation when comprehensive data on efficacy and safety cannot be obtained, but it is still appropriate to grant the authorisation due to exceptional circumstances.
- **When can it be obtained?**
  - Medicines without comprehensive data on efficacy and safety under normal conditions of use, respectively because:
    - So rare that cannot be expected to provide comprehensive evidence;
    - In the present state of scientific knowledge, comprehensive information cannot be provided, or it would not be ethical to collect such information.
- **What's the impact?**
  - Annual reassessment of benefit-risk for life time of MAA
  - Safety – ongoing notification required of any incident relating to product use
  - Does not lead to completion of a full dossier or to a 'standard' authorisation

EU: Accelerated Assessment (AA)

- **What is an Accelerated Assessment?**
  - Accelerated assessment reduces the CHMP review time for a MAA
- **When can it be obtained?**
  - For a first approved indication (MAA) only
  - Products with potential major public health interest, particularly from the point of view of therapeutic innovation.
- **What's the impact?**
  - Reduction of the MAA evaluation time from up to 210 days (+ clock stop time) to 150 days (+ 1 month clock stop time) – similar to US Priority Review duration
  - GMP inspection readiness of the manufacturer must be confirmed

Oncology Approvals (2006-2013)

	Standard MA (n=32)	Conditional MA (n=11)	P-value
Data			
Number of patients in pivotal study	662 (347)	265 (177)	<0.001
Pivotal study is RCT	29 (91%)	5 (46%)	0.004
Primary endpoint in pivotal study			
Overall survival	19 (59%)	0 (0%)	<0.001
Progression-free survival	7 (22%)	3 (27%)	
Time to progression	1 (3%)	1 (9%)	
Response rate	5 (16%)	7 (64%)	
Number of patients in safety population	980 (978)	453 (220)	0.006
Timelines			
Total assessment time in days	315 (77)	393 (84)	0.005
Active assessment time in days	197 (17)	201 (10)	0.809
Clock stop time in days	118 (68)	192 (76)	0.004
Accelerated assessment, n (%)	6 (19%)	0 (0%)	0.312
Procedures			
Scientific advice, n (%)	25 (78%)	8 (73%)	0.698
SAG-O meeting, n (%)	9 (28%)	8 (73%)	0.014
Consensus vote, n (%)	28 (88%)	6 (55%)	0.034
Appeal procedure, n (%)	0 (0%)	1 (9%)	0.256

Link to Escher 2014:

Escher. 2014. Improving the EU system for marketing authorisation of medicines.

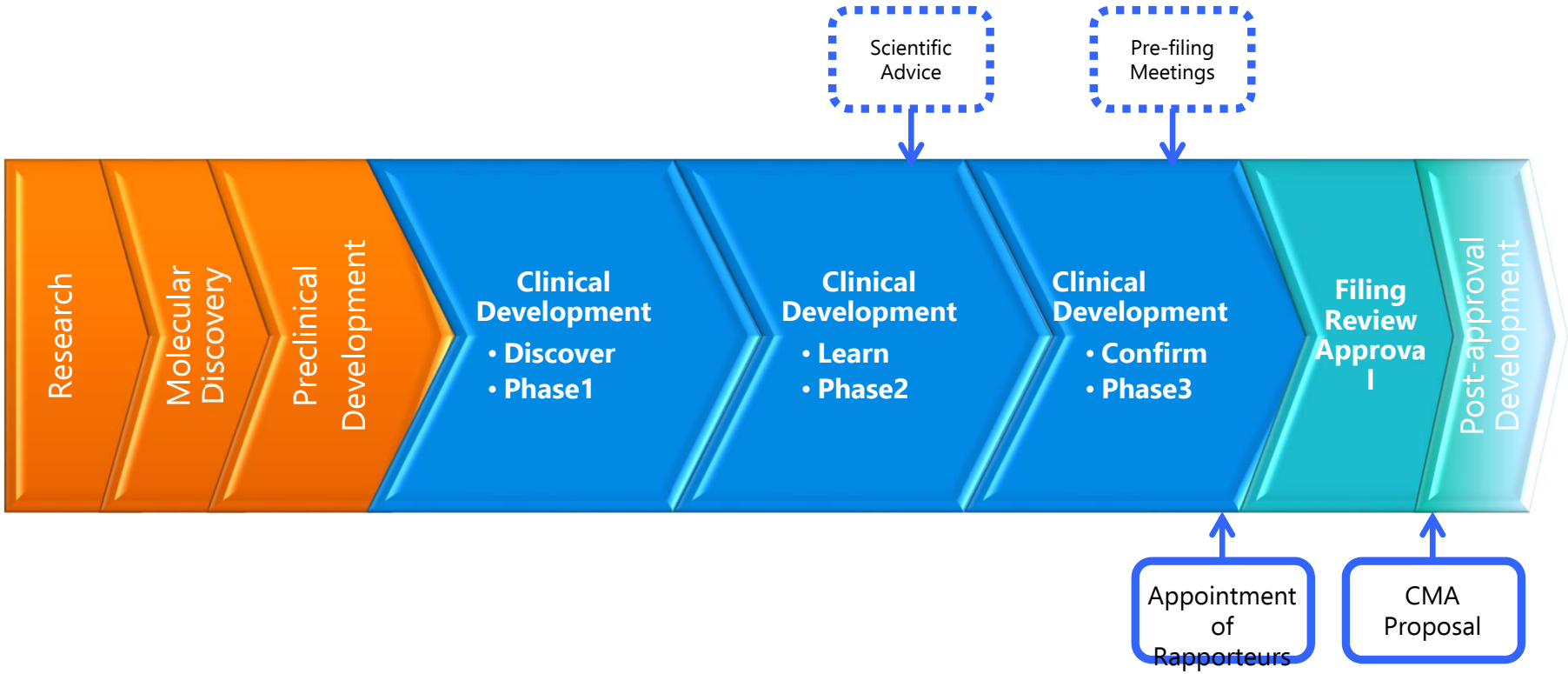
PRIME:

PRIORITY MEDICINES IN THE EU

What is PRIME?

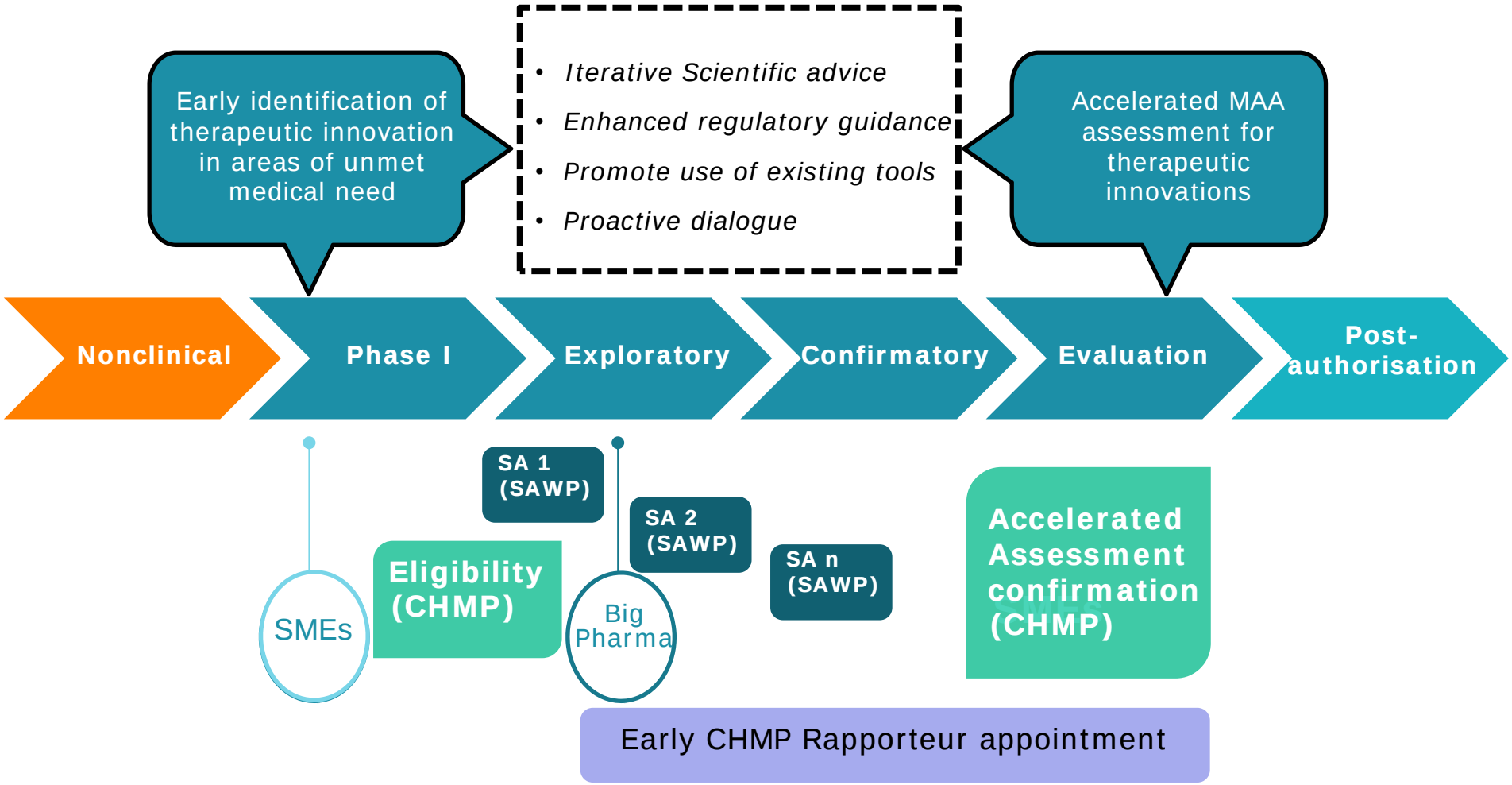
- EU PRIME introduced in March 2016 to support innovation and ensure timely access to “breakthrough” Priority Medicines
- The PRIME scheme:
  - Supports development of innovative medicines addressing unmet medical need and bringing major therapeutic advantage to patients
  - Builds on currently existing regulatory framework and procedures
  - Focuses on early regulatory support and scientific advice together with accelerated assessment of innovative medicines

Typical EU Clinical Drug Development

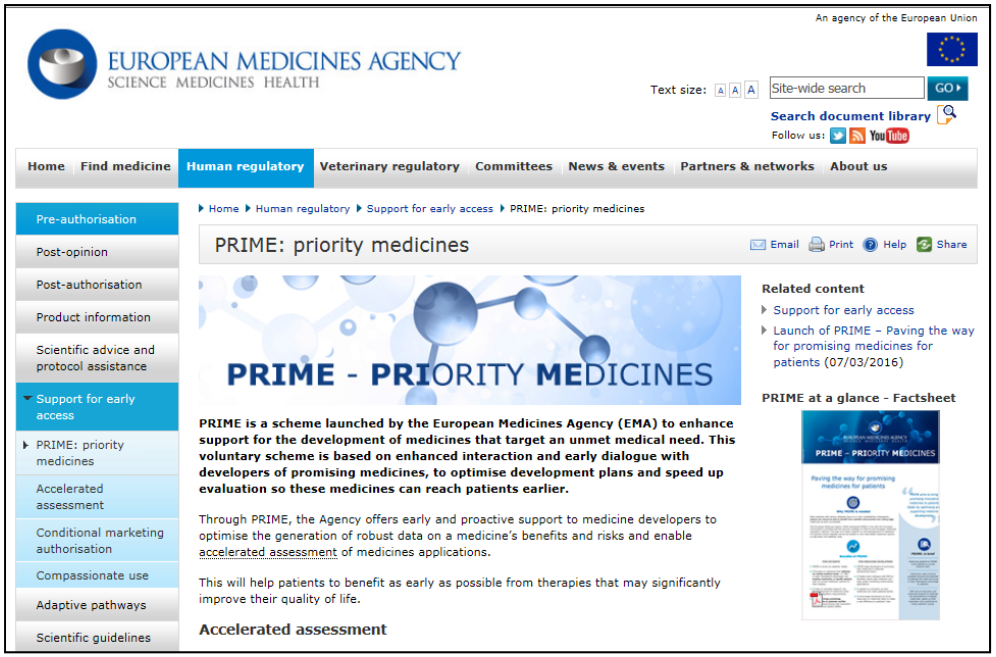


- Early and continual dialogue to validate the development plan is often lacking
- Long review times (ca. 14 months) with sequential responses
- Rescue use of Conditional Marketing Authorization or label restrictions

PRIME Concept to Support Innovative Medicines



Available EMA Support



EMA PRIME Mailbox:
prime@ema.europa.eu

PRIME eligibility criteria for “Big Pharma”

- Development in an area of Major Public Health Interest
  - No single definition of what constitutes major public health interest – this needs to be justified on a case-by-case basis.
- Potential to significantly address the Unmet Medical Need
  - no satisfactory method of diagnosis, prevention or treatment, or
  - the medicinal product offers potential for major therapeutic advantages over existing options
- Initial Proof of Concept evidence
  - Potential promising activity based on PoC clinical data
  - Appropriateness of data depends on magnitude, duration and relevance of the observed clinical effect

Eligibility Assessment for PRIME

- Submission of a PRIME Eligibility Request using EMA PRIME Template (Justification Briefing Package) and per submission timetable
- Assessment procedure:
  - Day 1 – Start of Procedure – SAWP
  - Day 30 – Discussion and recommendation during SAWP plenary meeting
  - Day 40 – CHMP recommendation on eligibility is adopted
  - Day 40 - EMA Contact appointed
  - Publication in CHMP Monthly Report of granted/denied applications (incl. type of product, indication, type of supportive data, type of applicant)
- CHMP Rapporteur assigned 1 month after PRIME eligibility confirmed (Co-rapporteur assigned prior to MAA filing)

After PRIME Designation is Granted

- Kick-off meeting is held ASAP:
  - to facilitate the initial interaction between the applicant and the multi-disciplinary assessment team of experts and EMA
- Kick-off meeting ASAP to facilitate interaction between the applicant and:
  - EMA, CHMP Rapporteur
  - Scientific Advice Working Party (SAWP)
  - Paediatric Committee (PDCO)
  - Committee for Orphan Medicinal Products (COMP)
  - HTAs (?)
- Kick-off meeting content:
  - Development program & regulatory strategy are presented
  - Recommendations are received on planning regulatory interactions

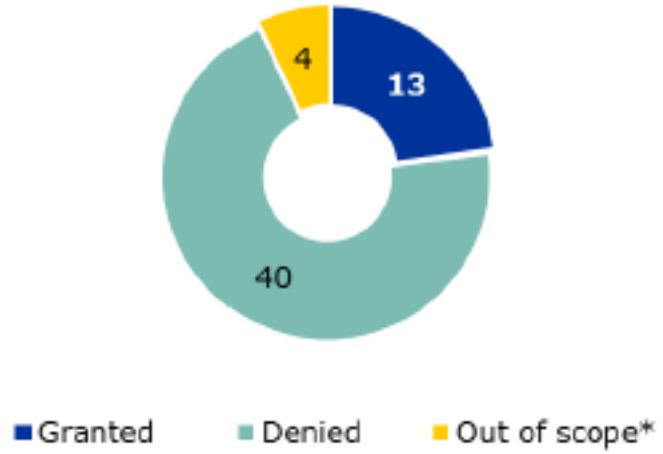
"Typical" PRIME Candidates

Current expectations for PRIME candidates:

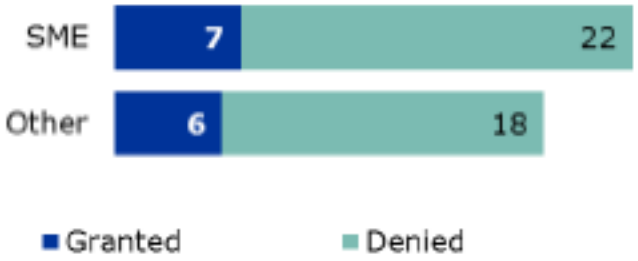
- Developing first indication
- Few to no therapeutic options available
- Proof of Concept data available
- Magnitude of benefit observed suggests potential for truly "breakthrough" status

"If you're thinking Breakthrough, think PRIME!"

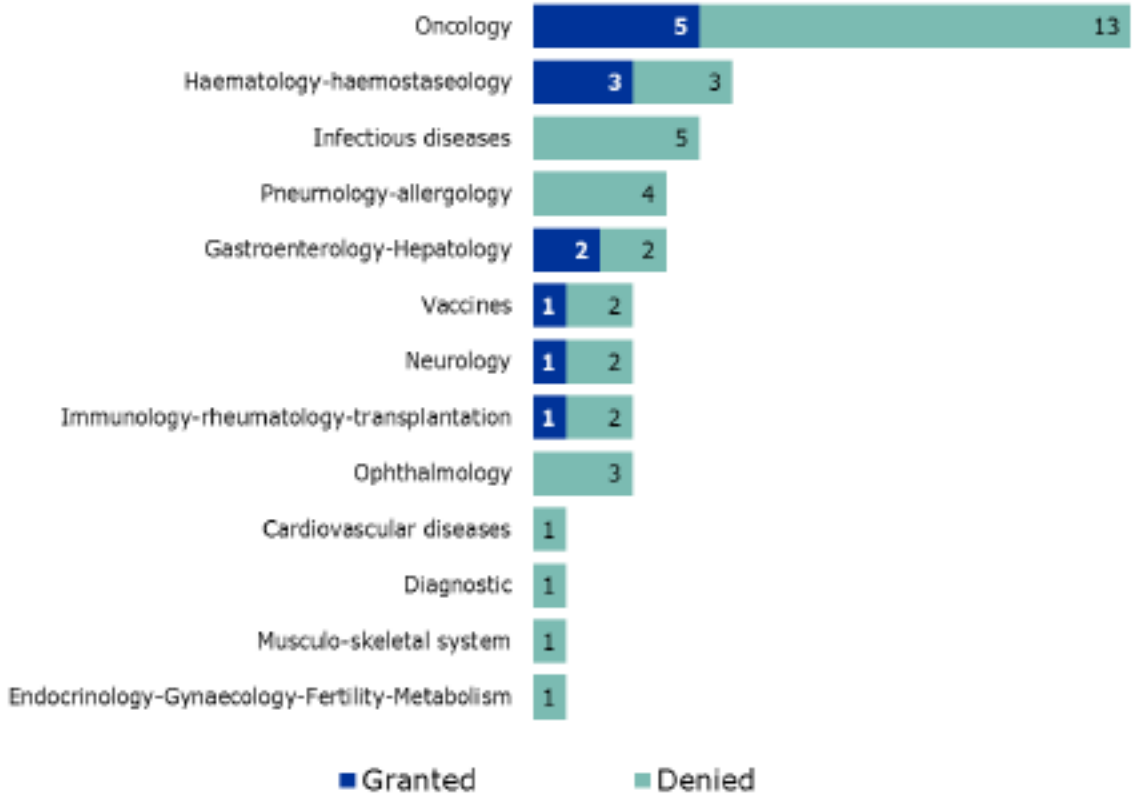
Learnings from the EMA – Status October



By type of applicant



By therapeutic area



* This indicates eligibility requests received but not scanned by EMA as they were deemed outside the scope of the scheme or with a format and content inadequate to support their review. These are not included in the breakdown by type of applicant or by therapeutic area.

Oncology PRIME Designations to Date

PRIME Designation	Name	Company	Substance type	Therapeutic indication	Data Phase (if known)	Type of applicant	BTD Status (at time of granting)
May 2016	KTE-C19	Kite Pharma	Advanced Therapy	Treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) who have not responded to their prior therapy, or have had disease progression after autologous stem cell transplant (ASCT)	1b	SME	Y
June 2016	CTL019	Novartis	Advanced Therapy	Treatment of primary haemophagocytic lymphohistiocytosis (HLH)	2	Other	Y
July 2016	Autologus CD4 and CD8 T-cells transduced with lentiviral vector containing an affinity-enhanced T-cell receptor to target the cancer-testis tumour antigen NY-ESO-1 (NY-ESO-1c259T)	Adaptimmune (with GSK)	Advanced Therapy	Treatment of HLA-A*0201, HLA-A*0205, or HLA-A*0206 allele positive patients with inoperable or metastatic synovial sarcoma who have received prior chemotherapy and whose tumor expresses the NY-ESO-1 tumor antigen.	1/2	SME	Y
July 2016	Adenovirus serotype 5 containing partial E1A deletion and an integrin-binding domain (DNX-2401)	DNAtrix	Advanced Therapy	Treatment of recurrent glioblastoma in patients for which a gross total resection is not possible or advisable, or for those who refuse further surgery	1/2	Other	N
September 2016	Autologous CD3+ T Cells Expressing CD19 Chimeric Antigen Receptor (JCAR015)	Juno Therapeutics	Advanced Therapy	Treatment of relapsed/refractory adult B-cell Acute Lymphoblastic Leukaemia (ALL)	1b	Other	Y

Key Learnings from PRIME to Date (1)

- SMEs are submitting many of the PRIME applications and only 1/3 - 1/4 of submission are receiving PRIME designations.
  - ➢ Is there a need for a pre-application contact mechanism?
- Different data requirements for SMEs and Pharma companies to support PRIME applications (PoP vs PoC data) may not best support healthcare innovation.
  - ➢ Does this discourage earlier partner dialogue to align on development?
- Requirements for POC data don't reflect non-standard development approaches often seen in oncology.
  - ➢ Is there a need to allow earlier PRIME dialogue to align

Key Learnings from PRIME to Date (2)

- EMA appears to be taking a narrower approach to granting PRIME designations than FDA is with BTD (BTD from PoP clinical data through to (s)BLA/(s)NDA submission).
  - ➢ Is this reducing opportunity for partner dialogue on breakthrough developments?
- PRIME is only available for first indications as Accelerated Assessment can only be granted for MAAs and not for new indications.
  - ➢ Should the formal groundwork be laid for extending Accelerated Assessments to subsequent filings for new indications?

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