Accelerated Approvals –
An Industry Perspective

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South African Expedite Review Process

Expedited Review Process (Fast Track)- ZA

- The Act provides for expedited review for items on the EML (Essential Medicines List) or innovative medicines (first in class) that meets an unmet health need.
- An expedited review request must be submitted to the Minister of Health for the attention of the Registrar of Medicine at least two months prior to the submission of the dossier for evaluation.
- The submission of the application for registration can only proceed once the outcome to the expedited review application is received. The Registrar will respond to the applicant within 30 days.
- The following data should be submitted with the expedited review application:
  - *A motivation for an expedited review of a specific product*
  - *An expert report (which is not more than 2 (two) years old;*
  - *An approved copy of the prescribing information/SPC from a country where the product has been registered (if available)*
  - *KOL expert report supporting the use of the new product (if available)*
- If expedited review is granted for a specific product, the MCC is obliged to provide feedback (positive or negative) to an application for registration within 9 months of the submission.
- Average approval time for fast track: 24 months
- Aim: To ensure that patients have access to essential and innovative therapies quicker

FDA Expedited Pathways: Special Focus on Breakthrough Designation

FDA Expedited Pathways

Overview

	Accelerated Approval	Fast-Track Designation	Breakthrough Designation	Priority Review
Eligibility	1. Treat serious or life-threatening diseases 2. Provide meaningful therapeutic benefit over existing therapies 3. Surrogate endpoint reasonably likely to predict clinical benefit	1. Intent to treat broad range of serious or life-threatening diseases 2. Potential to fill an unmet medical need	1. Treat serious or life-threatening diseases 2. Early clinical evidence of substantial improvement over existing therapies	Offer major advances in treatment over existing therapies
Designation	No formal process	Can be requested by sponsor at any time	Can be requested by sponsor at any time after IND submission	Requested by sponsor at time of NDA/BLA submission
FDA Review-Response	N/A	60 days	60 days	45 days
Clinical Development	Conditional approval granted using surrogate endpoint from phase II trials or interim phase III data; controlled trials with hard clinical endpoints required to confirm clinical benefit	Earlier and more frequent Communication	Abbreviated or condensed development; earlier and more frequent communication; delegation of senior reviewers and cross-disciplinary review team	N/A
Review Process	NDA/BLA data submitted in one package; standard 10-month review	Option for Rolling NDA/BLA submission. Official review clock begins when last module is submitted	NDA/BLA data submitted as they are accumulated; review time shortened	NDA/BLA data submitted in one package; review time shortened to 6 months

Breakthrough Designation vs. Fast Track

	Breakthrough	Fast Track
Criteria		
Serious life threatening diseases	√	√
Unmet medical need	√	√
Superior to existing therapy	√	√
Substantial early clinical treatment effect	√	-
Enhanced Interactions		
Frequent meetings with FDA & timely advice	√	√
Advice throughout drug's development	√	√
Optimize efficiency of clinical trials	√	?
FDA Senior management involvement	√	?
Cross functional scientific liaison support	√	?
Optimize review process	√	?

BTDs by the Numbers

- 293 BTD Requests
- 82 BTDs requests granted – approx 40% are Oncology & Hematology
- 155 denied
- 23 BTD approvals (2 Novartis)
- 2 BTDs rescinded by FDA
  - Merck – grazoprevir/elbasivir for HCV (January 2015)
  - BMS – daclatasvir/asunaprevir HCV (February 2015)
- Novartis – remains a leader in BTD (5 designations)
  - Bexsero (approved); Zykadia (approved)
  - BYM338, CTL109, Serelaxin

BTD – Current Status

- Program commitments are resource intensive for FDA
  - Number of requests and designations have exceeded expectations
  - Dedicated resources for BT program were not provided under FDASIA
  - FDA states that it is working to minimize adverse impact on other programs
- Common reasons for denial of BT requests
  - Evidence does not include clinical data
  - Evidence is too preliminary to be considered reliable; e.g., small numbers of patients treated or inadequate duration of follow up
  - Failure to demonstrate “substantial” improvement over available therapy vs “expected” incremental benefit of development programs
  - Reliance on a novel biomarker or surrogate endpoint without sufficient evidence to support benefit to patient
  - Post-hoc analyses of failed studies
- FDA plans to issue BTD best practices

Overview of accelerated regulatory procedures in Europe with a focus on the new EMA Adaptive pathways (previously known as adaptive licensing) pilot

EMA Pilot on Adaptive Pathways

Aims and criteria

- Aims to support selection of pathway for product development and (potential) earlier access to medicines involving all stakeholders (regulators, HTAs, payers, patients..)
- Involves early brainstorming with EU HA in a safe harbour environment with these stakeholders to optimise development, potentially accelerating patients access to medicines
- Followed by a request for parallel EMA/HTA advice to discuss requirements in depth and formalise advice

Criteria for candidates

- Unmet medical need, serious conditions
- An iterative, prospective development plan (start in a well defined subpopulation and expand, or have a conditional approval, maybe surrogate endpoints and confirm
- Real world data (safety and efficacy) can be acquired to supplement clinical trials
- Input of all stakeholders, particularly HTAs, is fundamental

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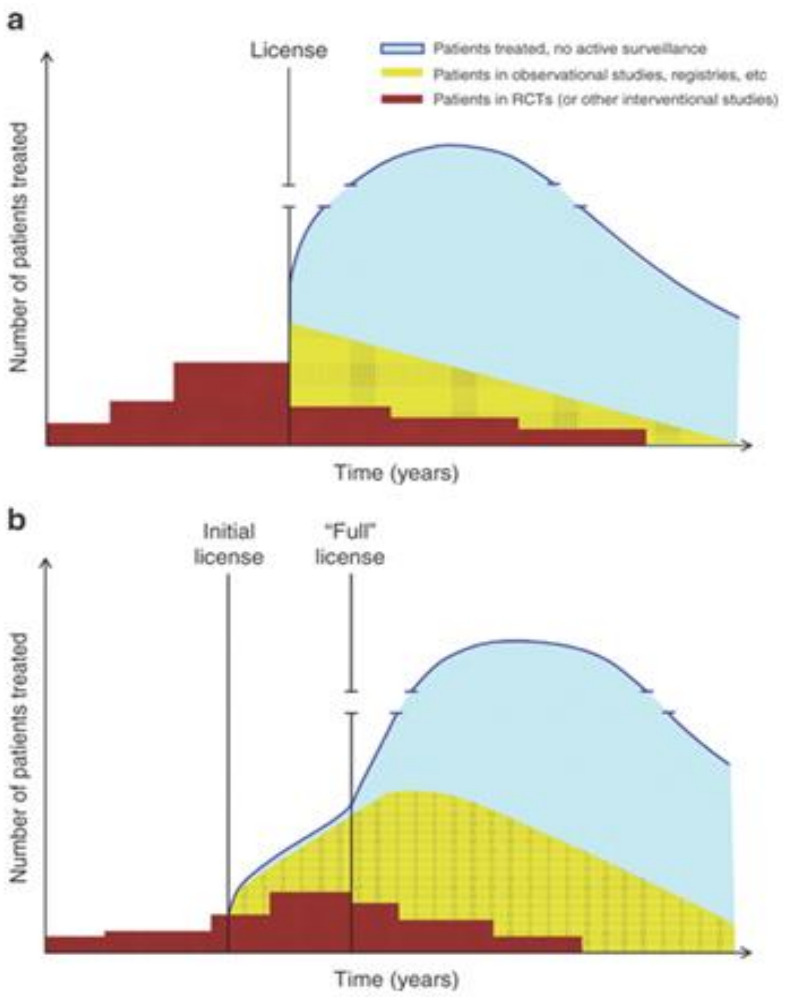
Comparison between traditional exposure to new drug and time to MA (a) and adaptive pathway approach (b)



a) Traditional: *all pts are treated in CTs and once the MA granted treatment population expands rapidly. Real-world prescribing data (RWD) is usually not contributing to evidence generation pre-authorization*

b) AP: 1st license can be granted based on lower number of pts in CTs and earlier than in (a), but for a limited indication. Later, the number of pts doesn't increase so dramatically and RWD can contribute to effectiveness evidence. Patients are also treated under active surveillance

Eichler et al. 2012

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EMA Initial Experience & Next Steps

- 34 products submitted as candidates (from start of pilot March 2014 – Dec 2014)
  - 11 SMEs, 12 orphans, 6 ATMPs
  - 10 selected for discussion with companies (Phase I)
- 6 proposals for phase II pilot – in depth face to face meeting
- Phase I of the pilots ended on 28th Feb, but EMA will consider applications with 'well developed proposals' for phase II
- Aim to produce an evaluation after at least 6 procedures have gone through parallel EMA/HTA advice
- Novartis approach - internal discussion group formed and 3 possible candidates identified (QAX, DEB, BYM) but were not submitted due to project re-prioritisations
- We continue to proactively solicit input for more potential candidates as we would like to gain experience with this process

EU Expedited approvals / reviews

Overview

	Conditional approval	Approval under exceptional circumstances	Accelerated review	Adaptive pathway (in pilot stage)
Requirement/ Criteria to qualify	-High unmet medical need -Chronically/seriously debilitating or life-threatening diseases -Public health interest	-Very rare indication so full data can't be collected -Present state of scientific knowledge or ethical concerns doesn't allow full data package	- Unmet need - Therapeutic innovation - Major added value - Major public health interest	Unmet medical need, serious conditions Input of all stakeholders, particularly HTAs possible
Eligibility	Agreed at time of submission of MAA	To be discussed at Scientific Advice Agreed at time of submission of MA	Agreed at time of submission of MAA	Determined by EMA
Clinical Development	- Abbreviated development - MAA granted on incomplete data - Full data to be provided after approval => MA converted into "normal" MA - Other specific obligations (SO) e.g. Pharmacovigilance (PV) activities	-MAA despite lack of comprehensive data -Full data will not be provided -SO to be fulfilled post- approval e.g. PV activities ,additional studies		An iterative development plan - start in a well defined subpopulation and expand, - or conditional Authorisation, maybe surrogate endpoints and confirm - Real world data can supplement clinical trials
HA interaction/ Review Process	-Standard 210 days for CHMP opinion -Conditional MA valid for 1 year – will be reassessed every year	-Standard 210 days for CHMP opinion. - MA valid for 5 years – reassessed every year -not expected to be converted into a "normal" MA even if SOs fulfilled - new indications can be added but MA will remain EC	-210 days assessment period is reduced to **150 days** -in practice difficult to be applied in case of extensive list of questions -CHMP can decided to revert to 210 days review at any time	-Early and frequent HA/HTA interactions during development -Standard 210 days for CHMP opinion or accelerated 150 day review -could use conditional approval
Novartis example	Votubia (oncology)	Ilaris (CAPS)	Glivec , LZC696	No drug authorized as yet . No NVS product in the EMA pilot .

Expedited approvals / reviews pathways -Comparison **EU** and **US**

US FDA	EMA
Accelerated approval • Allows approval of a drug for serious or life threatening conditions based on an effect observed on a surrogate endpoint that is reasonably likely to predict clinical benefit.	**Conditional approval** • Allows approval of a drug for serious or life threatening conditions based on less complete data than is normally required, subject to certain specific obligations to be reviewed annually
No direct equivalent procedure	**Approval under exceptional circumstances** • Applicants must demonstrate that they are unable to provide comprehensive data on the efficacy and safety under normal conditions of use (e.g. rare diseases)
Priority review • Regulatory review period shortened from standard 10 months to 6 months	**Accelerated assessment** • CHMP opinion given within 150 days as opposed to 210 days
Fast track designation • Facilitate development and expedite review of drugs through more frequent FDA interaction and rolling review of data	No Fast track designation, some similar supportive mechanisms • Innovation task force/ SME office/ CHMP scientific advice & protocol assistance/ Qualification of novel methodologies for medicine development
Breakthrough designation • Expedite the development and review of drugs through more intensive FDA guidance and commitment to involve senior management	**No specific breakthrough designation, some similar supportive mechanisms** • Adaptive pathways, innovation task force/ SME office/ CHMP scientific advice & protocol assistance/ Qualification of novel methodologies for medicine development,