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Developing Standards for
Breakthrough Therapy Designation



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Conference on Clinical Cancer Research

**Developing Standards for
Breakthrough Therapy Designation**

Daniel A. Haber, M.D., Ph.D.

Massachusetts General Hospital Cancer Center

“Breakthrough Therapies” - History

- Recent notable examples of novel drugs showing unprecedented activity in Phase I studies for diseases with poor outcomes:
 - **vemurafenib** in BRAF-mutated metastatic melanoma
 - ~50% melanoma
 - Trial comparing vemurafenib with “standard” chemo
 - Dramatic but transient responses, rapidly evolving new Rx
 - **crizotinib** in ALK-positive non-small cell lung cancer
 - ~4% of NSCLC
 - Need for upfront genotyping to identify rare subset

“Breakthrough Therapies” - Concept

- Is the current paradigm of Phase I,II, and III trials appropriate when exceptional results are observed in early phase trials?
 - **Phase I:** Defining appropriate drug dose in patients with drug-responsive tumors, rather than in those unlikely to benefit?
 - **Phase III:** Randomizing large numbers of patients to suboptimal SoC, when early results point to effective and low toxicity targeted agent?
 - **Timeline:** Speed of discovery, development and testing for targeted agents with scientific rationale

“Breakthrough Therapies” - Rationale

Why now?

- Compelling preclinical science
- Multiple small subsets of patient populations identified by diagnostic biomarker
- Rapid and dramatic responses with relatively modest toxicity
- Multiple drugs in pipeline with need for rapid and more economical testing

FDA's Existing Expedited Pathways

	Accelerated Approval	Fast-track Designation	Priority Review
When Appropriate	Drugs with the potential to fill an unmet need for serious or life-threatening diseases, and whose activity can be assessed using a qualified surrogate endpoint	Drugs intended to fill an unmet need for serious diseases	Drugs with potential to provide major advance over existing therapies
How it Helps	Makes potentially useful new agents rapidly available to patients	Enables more efficient development through frequent communication between FDA and sponsor	Shortens FDA review time by 4 months
Limitations	Requires additional randomization of patients in confirmatory trials	Does not condense or abbreviate clinical development	Does not condense or abbreviate clinical development

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“Breakthrough Pathways” aiming to provide path for abbreviated development

- Concept initiated at Friends-Brookings Conference
 - “Development Paths for New Drugs with Large Effects Seen Early”
- **Advancing Breakthrough Therapies for Patients Act**
 - Component of 2012 re-authorization of the Prescription Drug User Fee Act (FDA Safety and Innovation Act; FDASIA)
 - “An investigational drug may be designated as a “Breakthrough Therapy” if it treats a serious disease and **early clinical evidence** suggests that it provides a **substantial improvement** over existing therapies”




Benefits of Breakthrough Therapy Designation

- More frequent and interactive **communication** between sponsor and review team throughout drug development
 - Involvement of **senior managers** and experienced review staff in a collaborative, cross-disciplinary review
 - Expedited development and review- FDA provides timely advice so that **clinical trials are as efficient as possible**, when scientifically appropriate, and the number of patients exposed to a potentially less efficacious treatment is minimized
- 




Charge to this Panel

- Propose **criteria** that must be met for a new drug to obtain Breakthrough designation
 - Discuss **how** a Breakthrough designation could be requested and granted
 - Describe **issues** needing consideration to expedite the development of a Breakthrough product, and propose ways those issues could be resolved
- 



Speakers

- **Daniel A. Haber, M.D., Ph.D.**, *Panel Moderator*
Mass General Hospital Cancer Center
 - **Wendy K.D. Selig**, Melanoma Research Alliance
 - **Percy Ivy, M.D.**, National Cancer Institute
 - **Sandra J. Horning, M.D.**, Genentech
 - **Robert Temple, M.D.**, FDA
- Co-moderator:* **Charles L. Sawyers, M.D.**,
Memorial Sloan Kettering Cancer Center
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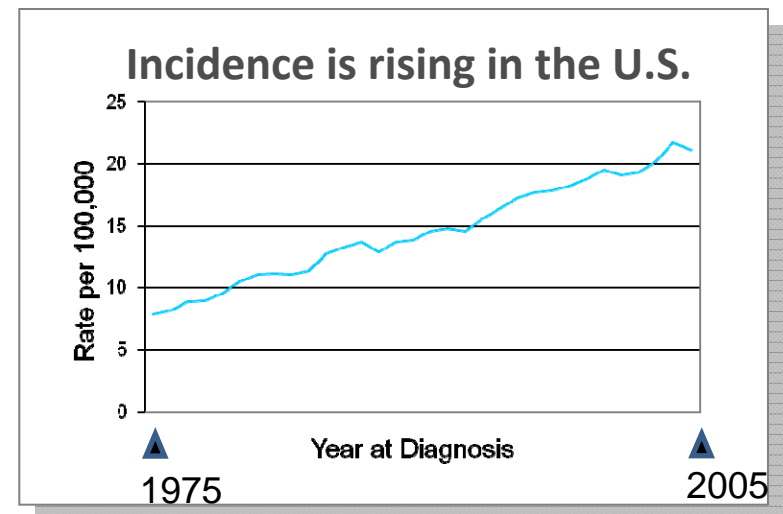
Conference on Clinical Cancer Research

**Developing Standards for
Breakthrough Therapy Designation**

Wendy K.D. Selig
Melanoma Research Alliance

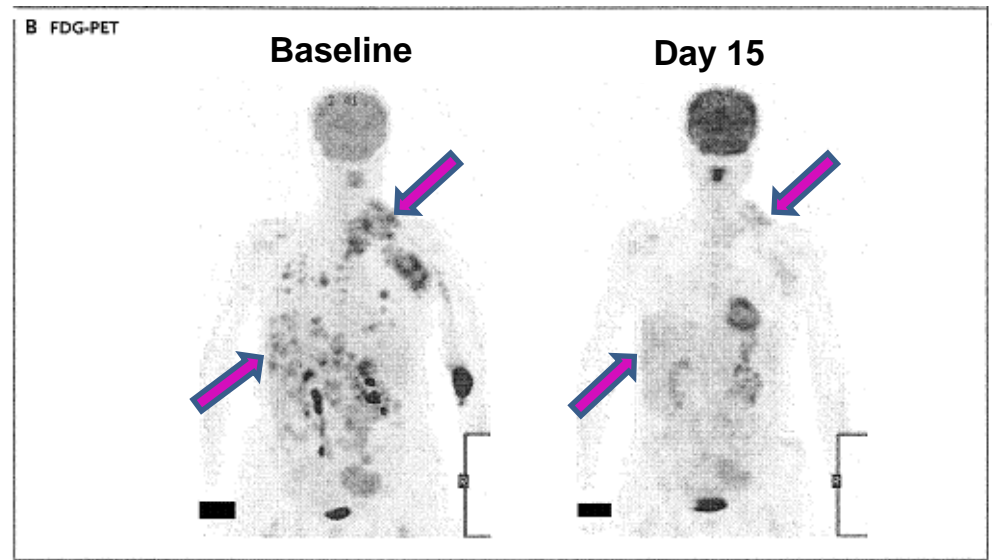
Melanoma: An Ideal Case Study

- **Need for new treatments:**
Aggressive cancer, poor prognosis in late stage, incidence rising dramatically
- **Scientifically and clinically:** At crossroads of molecular biology and immunology
- **New drug approvals:** Lessons learned?



Recent Clinical Advances

- Vemurafenib: Molecularly targeted drug against mutant BRAF
 - Less than 5 years from IND to FDA approval
 - Response rates >50%
 - Improved overall survival
 - Simultaneous approval with companion diagnostic

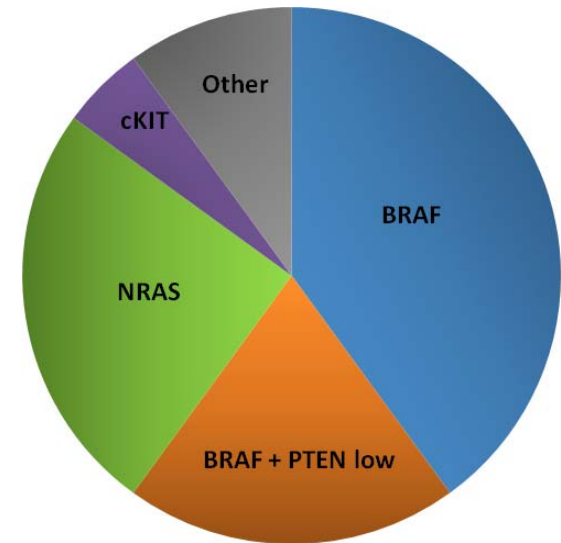


Adapted from Flaherty et al., NEJM 2010

- Ipilimumab: Antibody against an immune checkpoint
 - Durable responses for those that benefit
 - Improved overall survival


Next Generation Therapies

- Explosion of opportunities: 108 drugs in the melanoma pipeline (Datamonitor 8/15/12)
- New molecular targets: BRAF “wild-type” mutant tumors
- New immunotherapies (e.g., anti-PD-1)
- Combinations (e.g., BRAF+MEK): Address drug resistance and improve effectiveness






Non-Profit/Foundation Role

- Provide critical funding for cutting-edge, translational science for near-term impact. Willingness to invest in high-risk, high-reward projects. Finance multi-disciplinary teams.
 - Lead the scientific and clinical agenda for the field.
 - Participate in contributing scientific expertise to the policymaking process.
 - Speak to what patients need to accelerate new tools and treatments to market.
- 



Breakthrough Designation is Important for Patients

- “All hands on deck” mindset is critical in an area like melanoma with serious unmet need
 - Late stage cancer patients don’t have time to wait for a lengthy process
 - Ability to “break through” the status quo and streamline process could limit numbers of patients needing to participate in clinical trials and bring options to the market more quickly
- 



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**Developing Standards for
Breakthrough Therapy Designation**


S. Percy Ivy, M.D.
National Cancer Institute

What is a “Breakthrough Therapy”?

- “You know it when you see it”
- Pathway should be reserved for exceptional new drugs that have the potential to profoundly change how a disease is treated
- We have proposed qualitative criteria for Breakthrough designation, and described potential categories that future Breakthroughs may fit into



Criteria for Breakthrough Designation

1. The diseases under study will be serious and either have no established standard-of-care, or a standard-of-care that yields poor clinical outcomes
 2. Compelling early clinical evidence suggesting substantial improvement in efficacy over existing therapies, or a superior therapeutic index
 3. Compelling scientific rationale and promising mechanism of action
- 

Categories of Breakthrough Therapies

1. Drugs that address conditions with poor outcomes with no established standard of care
2. Drugs show substantial therapeutic improvement over an existing standard of care in conditions with poor outcomes
3. Drugs with substantial therapeutic index advantage over a well-characterized SoC in similar population
4. Drugs that dramatically enhance activity or tolerability of existing regimen
5. Drugs with previously demonstrated efficacy in a tumor type with identified mutation/pathway alteration could be eligible in different tumor type with same mutation/ alteration

Examples of Potential Breakthroughs

1. Drugs that address conditions with poor outcomes with no established standard of care
 - Recent examples- vismodegib in basal cell carcinoma, ivacaftor in G551D cystic fibrosis
 - A drug in this category might show unprecedented response rates in Phase I and could potentially be developed through a single-arm pivotal trial

Examples of Potential Breakthroughs

2. Drugs show substantial therapeutic improvement over an existing standard of care in conditions with poor outcomes
 - Could include drugs that act through a novel pathway (ex: vemurafenib, crizotinib), or potentially second generation drugs
 - A drug in this category might show substantial, durable responses in Phase I that clearly exceed those offered by existing therapies, and could potentially be developed through a small randomized study



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**Developing Standards for
Breakthrough Therapy Designation:
Perspective on Process**

Sandra J. Horning, M.D.
Genentech

Breakthrough Therapy Designation

Importance to Industry

- Addresses substantial risk and uncertainty
 - Provides expectations and standards
 - Affords alignment on internal prioritization
- Enables better use of resources through consistency and clarity in process
 - Opportunity cost for failed submission
 - Real cost: patients, trials, CMC, etc
- Provides new avenue of real time communication for sponsor and FDA for breakthrough medicines

Perspective on Breakthrough Process

Areas for Regulatory Clarity

- Breakthrough Designation
 - Request, evaluation, decision making
- Expedited Development
 - Process, timelines
 - Issues that could delay acceleration (eg. manufacturing, companion diagnostics)
 - Post-marketing commitments

Perspective on Breakthrough Process

Regulatory Clarity in Request & Evaluation

Designation Request

- **Content of package**
- **Timing**
- **Meeting type**

Required Observed Effects

- **Focused expertise could be available to FDA**

For Denied Requests

- **Basis for non-designation**
- **What could constitute designation in the clinical setting**
- **If external experts used**

Additional Questions

- **How change in SoC* may effect breakthrough evaluation**
- **How preclinical data may constitute breakthrough potential**

* Standard of care

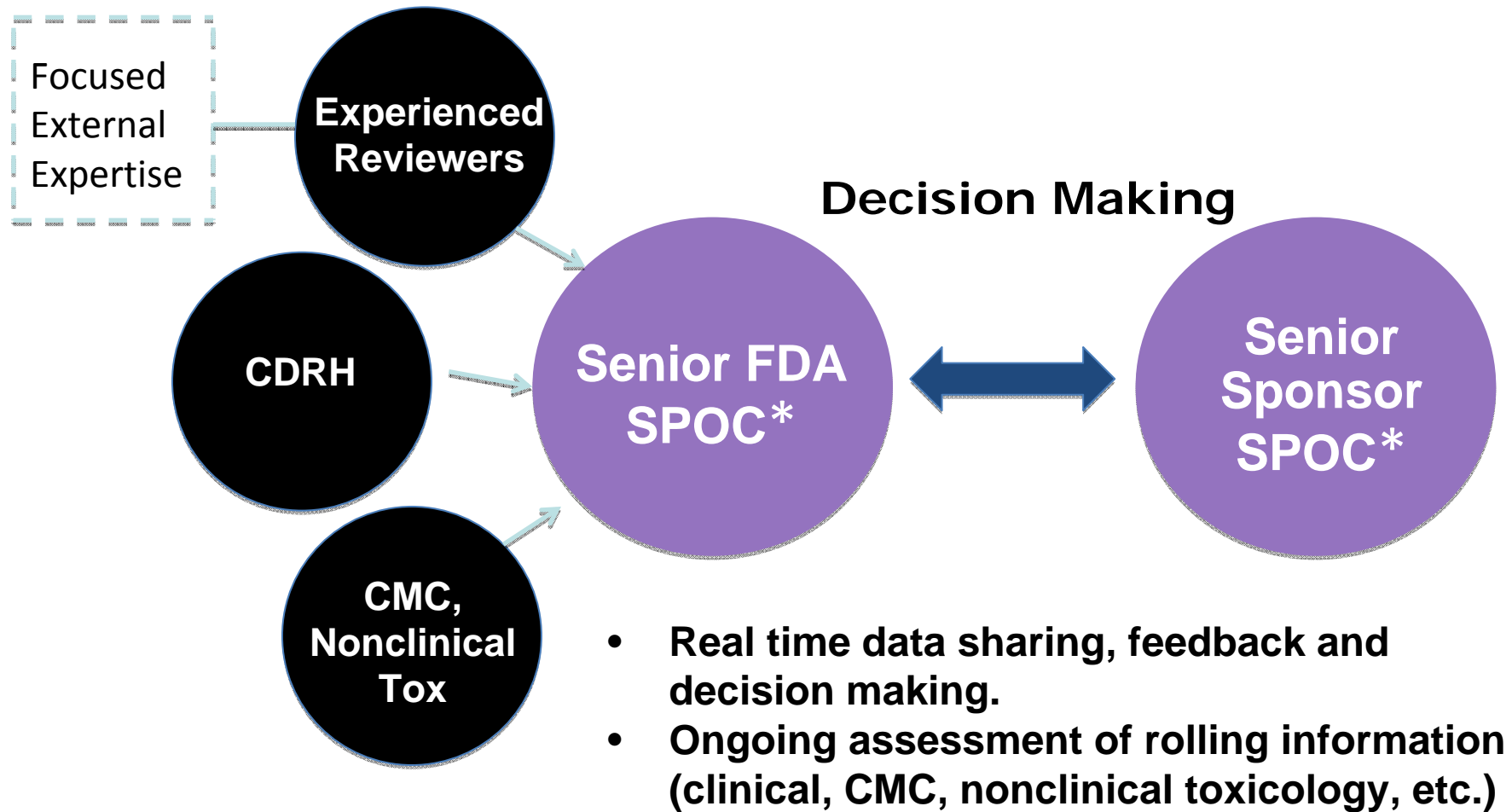
Perspective on Breakthrough Process

Expedited Development: Interactive Communication

- FDA has 60 days to respond to Breakthrough Designation request. Senior officials conduct review.
- If designated, FDA philosophy of “all hands on deck” for *real-time interaction* to share data, provide feedback and advice, make decisions, and ensure efficient, high quality development. For consideration:
 - New meeting type held between the single-points-of-contact of sponsor and FDA to create a “hotline.”
 - Weekly teleconferences throughout the review as sections of the BLA/NDA are submitted.
 - 3 month review period.

Perspective on Breakthrough Process

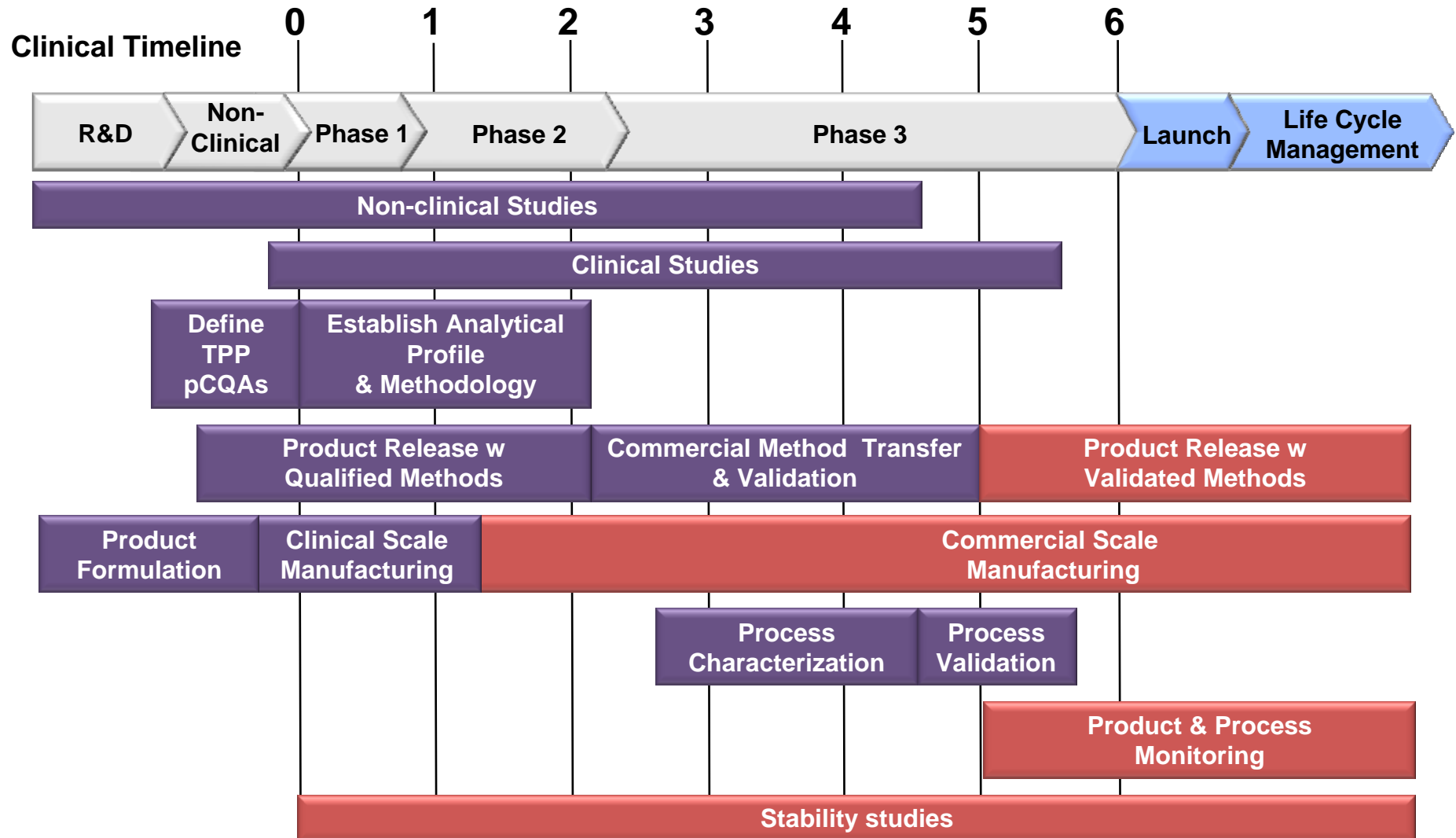
Expedited Development



* Single point of contact

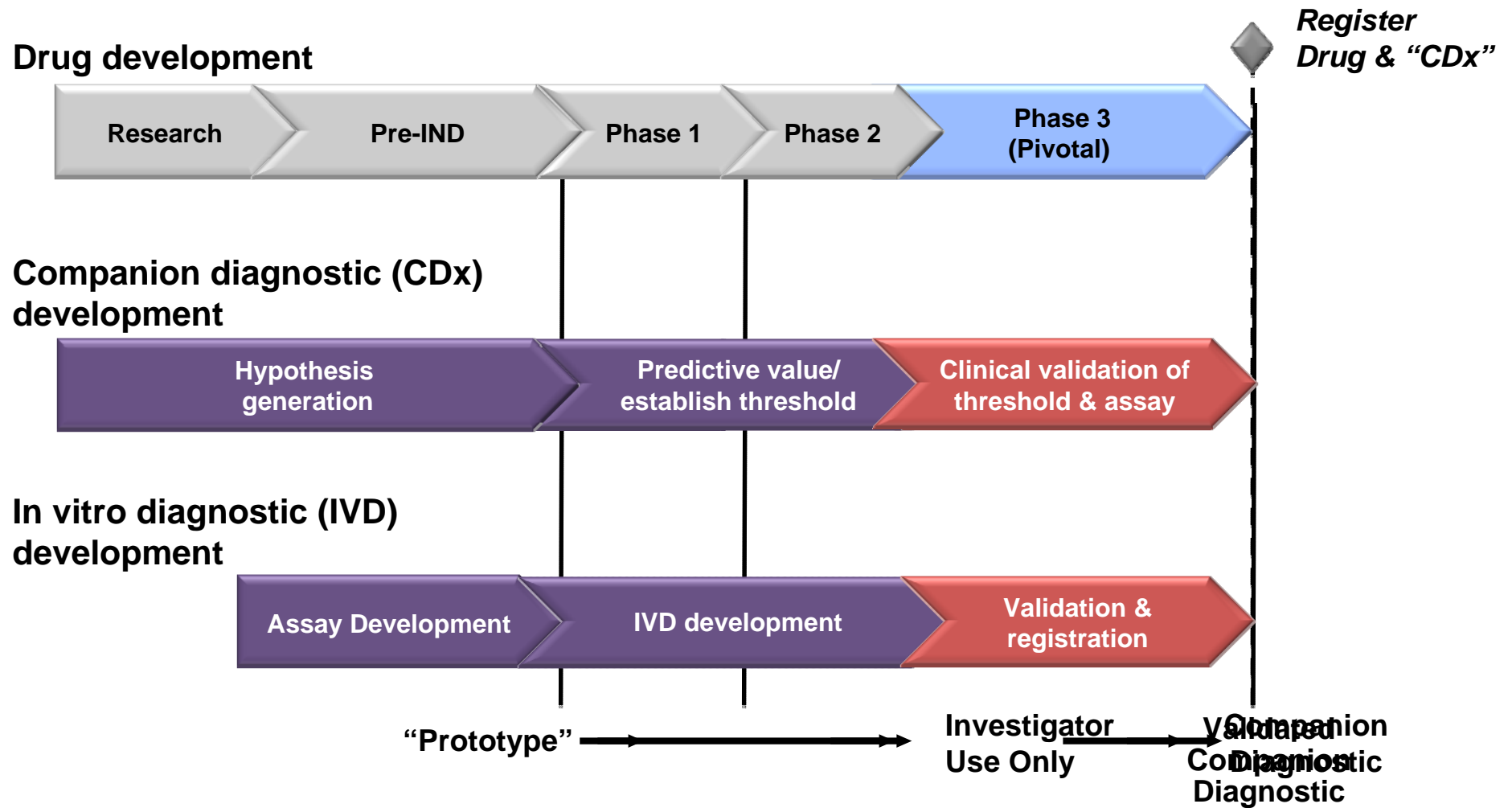
Perspective on Breakthrough Process

Chemistry, Manufacturing and Control



Perspective on Breakthrough Process

Companion Diagnostic Development



Perspective on Breakthrough Process

Key Considerations for Acceleration

- Focus on objectives of Breakthrough Therapy – what's important for patients, safety of the product, and responsible identification of appropriate patients
- Flexibility in regulatory expectations for CMC, companion diagnostics; for consideration:
 - Defer certain process validation requirements not directly related to safety
 - Leverage prior knowledge and data
 - Enable bridging studies with adequate analytic criteria
 - Conditional process for PMA may be needed if prototype kit not ready

Perspective on Breakthrough Process

Conclusions

- Breakthrough Therapy designation provides an important new avenue for expedited drug development with assurance of substantial evidence standards.
- Interactive, timely communication process between Sponsor and FDA is critical to achieve the Breakthrough Therapy goals.
- Flexibility in regulatory expectations for CMC and companion diagnostics is needed for expedited development.
- Additional considerations for industry include post-marketing commitments and the need for harmonization with other regulatory agencies (eg. European Medicines Agency) for global development programs.

Perspective on Breakthrough Process

Expedited Development Programs will put CMC / GMP Issues on Critical Path

- Accelerated clinical development timelines for breakthrough products will necessitate agreement on the statutory and regulatory requirements:
 - Needed to ensure safety and efficacy of product for commercial approval;
 - To be deferred post-approval
- Focus on the product & supply; then focus on the process
- Key Considerations
 - Use of initial product supply from clinical manufacturing process/site
 - Defer certain process validation requirements not directly related to safety
 - Leverage prior knowledge, platform data, and use of comparability protocols
 - Leverage use of stability data from representative pilot scale lots
 - Accept broader product quality acceptance ranges until further manufacturing experience is gained post-approval



Breakthrough Therapies What Is New?

Robert Temple, MD

Deputy Center Director for Clinical Science
Center for Drug Evaluation and Research
Food and Drug Administration

Friends of Cancer Research
November 14, 2012

Breakthrough Therapies

Long-Standing Interest, but new focus

For a long while FDA, not really surprisingly, has had a particular interest in treatments that make a real therapeutic difference – treat a serious disease with no treatment or treat it better. This is expressed in a regulation as overall concept (21 CFR 312.80) and in 3 specific regulations and guidances. I will briefly discuss what Subpart E calls for, then consider:

- Priority review
- Accelerated approval
- Fast-track designation

In all cases the severity of the disease, value of the treatment and lack of good alternatives is a recurring basis for the extra efforts and special considerations involved.

Subpart E – 21 CFR 312.80

Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses (Oct 1988)

Quite long ago, FDA wrote a regulation “to establish procedures... to expedite the development, evaluation and marketing of new therapies intended to treat persons with life-threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy exists.”

Without changing statutory standards for S and E, the diversity of drugs and the uses of those drugs has led FDA to determine that it is appropriate to exercise the broadest flexibility in applying the statutory standards.

This reflects the recognition that “physicians and patients are generally willing to accept greater risks or side effects from drugs that treat life-threatening and severely debilitating illnesses...[and] that... the benefits of the drug need to be evaluated in light of the severity of the disease being treated.

Subpart E (cont)

So, what did Subpart E offer?

1. Early consultation (312.82)

- Design of pre-clinical and clinical
- Can bring in outside experts or A.C. members
- Pre-IND meetings (needed annual studies, design of phase 1 studies)
- EOP1 studies: purpose is to “reach agreement on the design of phase 2 controlled trials, with the goal that such testing will be adequate to provide sufficient data on the drug’s safety and effectiveness to support a decision on its approvability for marketing.
- Discuss peds studies

2. Treatment protocols (312.83)

3. Risk-benefit analysis (312.84)

“... taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.”

Review Classification – Priority Review

Long ago we ranked applications, first as A, B, and C (in the 80's), later as P (priority) and S (standard), but a meaningful distinction effect on how P and S drugs were handled by FDA first appeared in PDUFA1 (1992), which set out a 4 month difference to action goals, currently 6 vs 10 months.

The basis for priority designation is:

“Preliminary estimates indicate that the drug product, if approved, has the potential to provide:

1. S & E therapy where there is no satisfactory alternative
2. A significant improvement compared to marketed products, such as
 - Increased effectiveness
 - Elimination or reduction of a treatment limiting drug reaction
 - Documented enhancement of patient compliance
 - Evidence of S and E in a new subpopulation

Evidence of such improvement can come from direct comparison but “can be based on other scientifically valid information.”

P/S designation is entirely about the timing of the NDA review process; there is no implication with respect to review standards

Accelerated Approval (21 CFR 314.500, Subpart H)

Although everyone attributes this to AIDS, the concept was actually being discussed before that and entered regulations in 1992. Accelerated approval

1. Allows approval based on a surrogate endpoint “reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence to predict clinical benefit (an explicitly lower level of evidence than would be needed for full approval based on surrogate).
2. Allows approval based on full approval of an endpoint other than survival or irreversible morbidity (but we regularly give such drugs so, by implication, there must be need for data on the ultimate endpoint. FDASIA has elaborated on that point to some extent.
3. Allows approval with restrictions to approve safe use.

In the first 2 cases there is a requirement to conduct studies post-marketing to confirm the expected clinical benefit. The required studies must be A & WC and “would usually be studies already underway [well, not exactly].

Fast Track - 1

Designed to facilitate the development and expedite the review of new drugs intended to treat serious or life-threatening conditions (but only a serious aspect of that condition) and that demonstrate the potential to address unmet medical need (unmet need still exists if the only approvals are accelerated).

FDAMA incorporated Fast Track, endorsed accelerated approval (21 CFR 314, Subpart H); and endorsed rolling review.

Fast track applies to a combination of the product and the specific indication.

It is mostly about the development process (except for rolling review, which we could always accept), and potential for priority review.

Fast Track - 2

Section 506

On sponsor request, “facilitate the development and expedite the review of a drug intended to treat a serious or life-threatening condition that “demonstrates the potential to address unmet medical needs for such a condition.” These products are “fast track products.”

Permits ordinary or accelerated approval (but this refers only to the surrogate endpoint, not limited distribution), and rolling review.

How is potential to meet an unmet need demonstrated?

- Pharmacologic, animal model data
- As data emerge, they should be consistent with what seemed supportive before
- Finally, the clinical trial data should support

Fast Track -3

So what do we do?

(In addition to P, rolling, AA)

We need to plan getting the needed evidence,

- Pre-IND – get appropriate pre-clinical data
- EOP1 (per 312.82) to see if the first phase 2 controlled studies case support S&E, with later data on S, D/R. It's very critical to discuss trials with mortality of major morbidity endpoints.
- EOP2 agree on design of phase 3 trials.

Other Mechanisms

1. Safety Database

The pre-marketing risk assessment guidance (2005) makes explicit what we all know: safety databases for drugs to treat life-threatening diseases are usually smaller (subpart E makes that clear also).

2. Reliance on a single study plus confirmatory evidence. (Evidence Guidance 1998)

Very common for orphan drugs, where mechanism is often well understood and for successful outcome studies, where a) p-value is often small and b) repetition is not ethical.

3. Historical Controls

Acceptance of such studies (long-standing) is itself evidence of appropriate flexibility. These trials are identified as a kind of well-controlled study in 312.126 and baseline control trials are common in oncology and orphan diseases, where effects are large and the course of untreated disease is well-understood.

So What Is New

As you can see, between priority review, accelerated approval, fast track, and Subpart E we have repeatedly expressed support for the efficient development of drugs that make a difference in a bad disease – i.e., breakthrough drugs.

So... what changes
Well, what will be different?

The difference, as I said, is that we've acquired a legislative mandate, an obligation to think hard and think collectively about what we will do to encourage and facilitate development of these treatment, to write new guidance as needed, to report on results and more generally, to pin down and define concepts and plans that can otherwise be vague, imprecise and very variable from drug to drug and division to division. We will be sharing and discussing experiences, having regulatory briefings and advisory committee discussions on these complex concepts, e.g., what exactly is "broad flexibility" in applying statutory standards without undermining them; what makes a phase 2 study good enough to support approval and can such a study (provide) definitive evidence and still get some dose-response information. Etc.

Breakthrough Therapy - 1

Many others will be talking about the Breakthrough provision of FDASIA but a few points (note that we are working on guidance in this area so I can't say too much, except that we are listening closely:

Like all of the programs directed at drugs of special importance, FDASIA's Breakthrough designation is for drugs that may treat a serious or life-threatening condition and could represent substantial improvement over available therapy. Such drugs would of course be eligible for priority review accelerated approval, and, it seems likely anything else that Fast Track allows (rolling review).

Many of the things are already possible, as I've described and much more of what we can do to facilitate development is included in Fast Track. A difference is that BT requires that "preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints."

Breakthrough Therapy - 2

There is a lot of possible judgment in all this, words like “substantial,” “clinically significant,” “may demonstrate,” and we will need to address this.

Are those demands compatible with an effect on a surrogate, with accelerated approval? It seems near certain they will be.

And what will we actually do. We will meet, of course, and try to design definitive early trials, which of course we do now.

But what I think will change most is efforts to bring collective wisdom to these efforts, to share experiences, to use imaginative trial designs and analyses. We do that already, I think, but perhaps not as much as we could and should.



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