Regulatory Pathways to Qualify Genomic Biomarkers: What Do We Need?

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Disclaimer

Views expressed today are my own, and do not necessarily represent those of PhRMA nor of Millennium Pharmaceuticals.

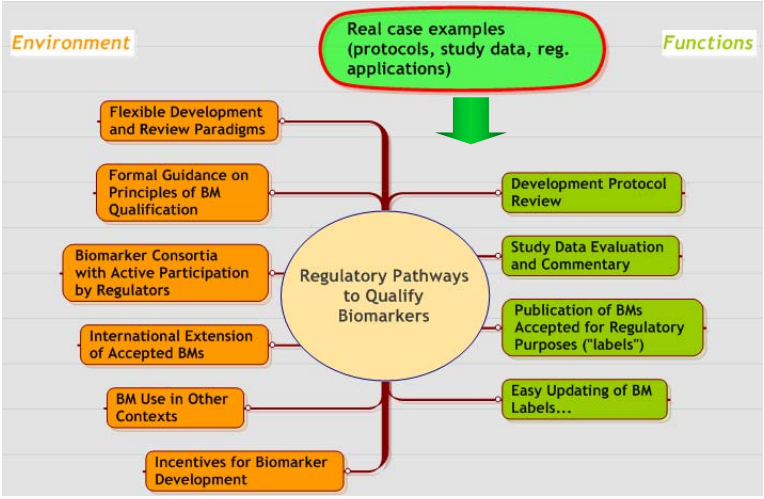
There is nothing more difficult to take in hand, more perilous to conduct, or more uncertain in its success, than to take the lead in the introduction of a new order of things.

Niccolo Machiavelli, 1469 - 1527

Vision

- Regulatory paradigms that allow full exploitation of the potential of genomic biomarkers to improve the efficiency of drug development and increase patient benefit from new therapies/diagnostics
- An integrated set of tools/enablers that support the development and use of biomarkers in drug development and regulatory decision-making
  - Facilitates use of biomarkers when this promotes development efficiency and patient access
  - Supports original objective of Critical Path
- Helpful if the parts can be seen as a gestalt to be achieved over several years

Needs Assessment



Functional Needs

- Needs for specific, objective interactions between sponsors and regulators in order to move candidate BMs to "qualified" status

Functions

- Development Protocol Review
  - Issue - Sponsors often need some confirmation that proposed experimental design will satisfy regulators before investing in BM development
  - No commitment on either side
  - Current possibilities
    - Pre-IND/pre-IDE meeting
    - VGDS – “safe harbour”
- Issues
  - Adequate resources in regulatory authorities
    - Expertise
    - Reasonable timelines

Functions

- Study Data Evaluation and Commentary
  - Issue – Process must be able to cater for different types of submissions
    - Data may be
      - part of a formal drug submission (NDA/BLA)
      - “free standing” (single study report outwith an application)
      - considered with information from other studies unrelated to development of a drug
        - a “dossier” or meta-analysis rather than a single study report

Functions

- Study Data Evaluation and Commentary
  - Available processes
    - VGDS (exploratory data)
    - Review Division meeting (e.g., end of Ph. 2a)
    - At present, no process to obtain definitive regulatory fitness-for-purpose other than by formal drug submission
  - Guidance should clearly detail
    - Policy framework for regulatory acceptance of BMs
      - Quantitative risk models
      - Need a means to accelerate the promotion of "probable" to "known" valid BMs
    - Review processes/expert consults
      - Can review be concluded outwith drug review?
      - ?User fees, etc?
    - Data to be submitted and report formats
    - ? List of BMs in use?
    - Other expectations

Functions

- Publication of BM "Labels"
  - Basic information about purposes for which use of BM is "accepted"
    - Would allow qualification of BM as "probable" or "known" valid
    - Could indicate basis for current acceptance
    - Issues
      - IP
      - Regulatory policy/practice

Functions

- Updating of BM Labels
  - New uses for existing BMs
  - Graduation from “probable” to “known” valid
  - Identification of new surrogate EPs
  - Approved diagnostic tests based on particular BMs
- Flow of new info could be significant
  - Assumes no/few IP issues
  - cf genetic sequence databases

Environmental Needs

- Factors, not directly implicated in the qualification process, which will promote the qualification of BMs for decision-making

Biomarkers in Decision-Making

- BM uses
  - Safety BMs
  - Subsetting of patients, dosing
  - Diagnostics
  - Clinical endpoints
- Definition of "fit for purpose"
  - Surrogate endpoints - Prentice criteria*?
    - Statistical perfection, but seldom achieved
    - Other bases possible
      - Utility functions
      - Adaptive designs

R.L. Prentice, *Statistics in Medicine* 8, no. 4 (1989): 431–440.

Fit-for-Purpose Qualification

- Fit-for-purpose biomarker qualification - a graded evidentiary process linking a biomarker with biology and clinical endpoints and dependent on the intended application
- Classification of BMs according to
  - weight of available evidence
    - FDA classification
  - conformance to theoretical criteria (SEPs)
    - E.g., Fleming classification*

*Fleming, T.R. (2005) *Health Affairs*, 24, 67-78

Fitness for Purpose – Conceptual Classification

	Regulatory Purpose	Full Approval	Accel. Approval	CT Inc/Exc	Safety	Fast Track
Degree of Qualification						
FDA Definition	*Fleming Definition*					
	True efficacy measure (1)					
Known valid BM	Valid SEP (2)					
Known valid BM	Non-valid SEP (3)					
Prob. valid BM	Correlation (4)					

Regulatory Policy Issues

- Two premises
  1. For definitive information on patient benefit, there is no substitute for adequately powered RCTs
     - But these trials generally take years, during which time patients are denied general access to the potential therapy

Regulatory Policy Issues

2. Major promise of genomics is to allow dissection of treatment responses in subpops
   - Realistically, this can often only happen on a limited scale pre-approval
     - Numbers of each subpopulation that can be recruited are often too small, bearing in mind
       - Often low frequency of critical variants
       - Often modest differences between groups
         - Don't know *a priori* which differences are significant
       - Complex interactions affecting expression
     - Cf industry commentary on drug/diagnostic co-development paper

Can We Square the Circle?

- Two review models
  - Full approval – "approval as an event"
  - Conditional approval – "approval as a process"
- Full review model is often inimical to satisfactory investigation of patient benefit or exploitation of (genomic) biomarkers
- Need more process flexibility for data generation and review to improve detailed basis for, and conclusiveness of, decisions
  - Incentives for "evidence development" (cf CMS)
- Efficient use of biomarkers will depend upon objective quantification and balancing of risks by both sponsors and regulators

Review Designs

- Full approval model
  - Assume only endpoint achievement = patient benefit
  - Based on single corpus of data
  - Often inefficient
    - Sponsors continue to study drugs post approval, but these studies seldom focus on fine (re-)evaluation of risk:benefit or adjustment of prescribing to improve patient outcomes

Review Designs

- BM strategies
  - Make more use of BMs to decide go/no go for Phase 3 (e.g., Fleming)
    - BM data presented at EOP2 could be incorporated into SPAs
  - Greater use of BMs to select subpops in Phase 3
    - May win faster approval, but sponsors concerned
      - Fractionation of markets
      - Acceptability of BMs/this approach – regulatory risk
      - Need to co-develop diagnostic?

Review Designs

- Conditional approval model
  - Extension of gradualist paradigm beyond cancer/AIDS/etc
  - EU Conditional approval – Reg. 726/2004, Art. 14(7)
    - No automatic link with "accelerated assessment"
    - Amongst potential uses – confirmation of effects in subgroups of wider indication that was basis for CA ("selective approval")
  - Sec. 115 of FDAMA, 1997
    - Allows approval based on use of biomarker(s) and single pivotal study

Review Designs

  - E.g., "Twin Track"approach*
    - Track 1 – short-term evidence of benefit (biomarkers, short-term outcomes, absence of unmanageable ADEs)
      - Results in conditional approval – uncertainty reflected in labeling, promotion
      - Rapid patient access with prescribing/monitoring conditions and obligation to continue development
    - Track 2 – long-term evidence of the range of outcomes embracing studies of subpops, comorbidities and comparator drugs
      - Allows qualification of new BMs and creation of diagnostics, as necessary
      - Would lead to broader labeling

*Califf, R. M. (2004) *Health Affairs* **23**, 77-87
Also Avorn, J. (2005) *New England Journal of Medicine* **353**, 969-972

Review Designs

- Key Questions
  - Is the design supported by the ethical construct?
  - Does it actually improve the efficiency of development, regulation and drug use?*
- Review process could be chosen to make the best use of the available information to evaluate the product's contribution to patient benefit and to encourage development of further evidence

*Katz, R. (2004) *J. Am. Soc. Exp. NeuroTher.* **1**, 189-195.

Consortia

- Biomarker consortia
  - Can expedite aggregation of data
  - Spread costs/risks
  - Adapt competitive mindset
    - Data sharing/IP
- Involvement of regulators important
  - BM selection for qualification
  - Protocol review
  - Can still maintain independence in data review and policy formation
- Several consortia under discussion/ forming

Other Contexts

- Contexts
  - Medical practice
  - EBM – reimbursement
    - CMS coverage with evidence development (CED)
      - Potential for CED to support development of BMs prospectively or retrospectively

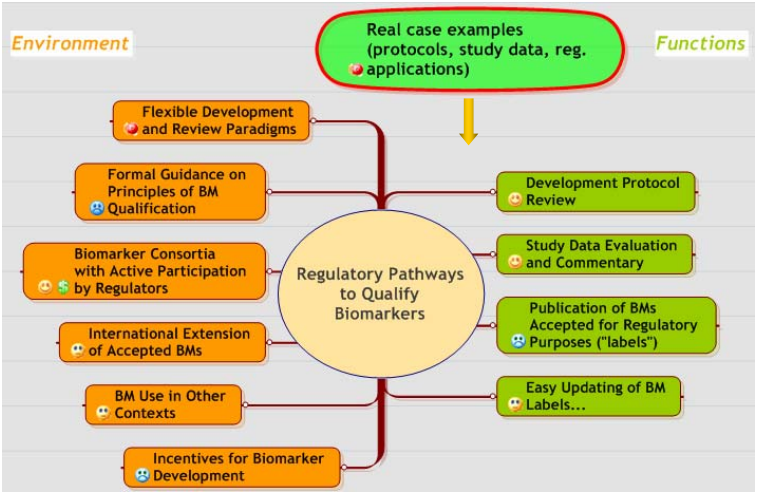
International Extension of BM Acceptance

- Issue - Investment in BM qualification will be significantly compromised unless there is prompt international utility
- Processes
  - Joint scientific advice (US/EU – pilot scheme)
  - Joint VGDS/Briefing meetings (US/EU)
  - ICH
    - Pharmacogenomics discussion group forming
      - Still a long way from agreeing BMs
- Do not have to have explicit acceptance in every case
  - Different regulators will converge separately on some BMs

Incentives for Biomarker Development

- Operational incentives exist, but also perceived risks
  - E.g., SEPs → Accelerated approval
- Most regulatory incentives not specifically focused on genomics
  - E.g., data exclusivity, Hatch-Waxman, etc
  - Orphan category for subpops?

Regulatory Pathways to Biomarkers – Current Situation



Conclusions

- Progress depends upon
  - Keeping the focus on the vision
  - Becoming more insightful about risk
    - Evaluate risk accurately and holistically
      - Must have robust risk models
  - Continuing the debate on possible future states
    - Need powerful "joined-up" processes
      - Structured to provide incentives to use biomarkers to develop database for each drug
  - Increasing the numbers of real cases passing through the emerging system

Medicine is a science of uncertainty and an art of probability.

Sir William Osler, Canadian physician, 1849-1919

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