Regulatory Issues Affecting Commercialization

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Alliance for Regenerative Medicine

+ *The Alliance addresses the collective challenges of the regenerative medicine industry by harnessing the resources of our broad and diverse membership.*

Mission:

Advance regenerative medicine by representing and supporting the community of companies, academic research institutions, patient advocacy groups, foundations, and other organizations before the Congress, federal agencies and the general public.

History: Founded in 2009, 80+ members and growing

ARM Members:

- Companies – J&J, Pfizer, Roche, GE, BD, Lonza, Celgene, StemCells Inc., Organogenesis, ABH, Mesoblast, Athersys, Cytori, Sangamo, Aldagen, Geron, EMD Millipore…
- Research Institutions – WFIRM, UPMC/McGowan, CIRM…
- Foundations – NYSCF, JDRF…
- Investors – Kleiner Perkins, Safeguard Scientific…
- Patient Advocacy Groups – Parkinson's Action Network, GPI, ALS Assn…

ALLIANCE for Regenerative Medicine

Committee Structure

+ *The Alliance utilizes five committees that provide expertise and leadership on key issues.*

Communications and Education Committee
CHAIR: Dean Tozer, Senior Vice President, Advanced BioHealing

The Communication and Education Committee has primary responsibility for overseeing the Alliance's communications activities, including interaction with the media and public education.

Membership Committee
CHAIR: Keith Murphy, CEO, Organovo

The Membership Committee manages the membership recruitment activities of the Alliance. It assists staff with recruitment of new members, encourages member participation in recruitment activities, and directs the fulfillment of member programs.

Government Relations and Policy Committee
CHAIR: Susan Solomon, President, New York Stem Cell Foundation

This committee is responsible for formal interaction with Congress, congressional staff, and federal agencies including testifying, attending meetings, and other activities as appropriate. The Committee guides the development of an advocacy agenda and executes the lobbying strategy for the Alliance on Capitol Hill. It focuses on both authorization programs and appropriations related to regenerative medicine. The Committee also advocates for programs to fund regenerative medicine research at NIH, DoD, and elsewhere.

Regulatory and Reimbursement Committee
CHAIR: Ed Field, President and COO, Aldagen

The Regulatory Committee oversees development and implementation of the regulatory agenda for the Alliance. This includes prioritization of regulatory objectives with key agencies such as the FDA, the CMS, and the PTO. The Regulatory Committee is responsible for interaction with regulatory agencies at public hearings, meetings, roundtables, PDUFA negotiations, submission of comments to the regulatory docket, and other forums for public discussion.

Science and Technology Committee
CHAIR: Alan Trounson, President, CIRM; Doug Doerfler, President and CEO, MaxCyte

The S&T Committee serves as a forum for Alliance members to exchange ideas, information, and data on different science and technology issues within the regenerative medicine field. One of the principal responsibilities of the Committee is to consider issues relating to process and research standards in the context of regulatory science that could be adopted by the industry after consultation with other interested and qualified organizations and the appropriate federal agencies.

ARM Regulatory Agenda

- A predictable and efficient review and approval process that enables approval of safe and effective products as quickly as possible
  - Modify existing rules? New rules?
- Increased coordination between FDA and NIH
  - FDA-NIH Leadership Council focus on RM
- Improving the science base at the agency
- Development of cross-cutting standards and tools to evaluate RM products
- Improved communication between industry and agency, especially outside the context of specific product
- Ensure coordination between FDA review divisions
- Create a framework/environment to help all product developers and move products to patients as soon as possible

Key Regulatory Activities

- **Interaction with FDA:**
- **Meeting with FDA Commissioner Hamburg, 2010**
  - ARM tells FDA we want collaborative relationship
  - FDA tells ARM they're looking for regen med "umbrella group"; asks for ARM's help re regulatory research and key scientific questions that are obstacles to regulatory approval (cell characterization, animal models, etc.). Need for standards.
  - ARM cell potency project/Joint workshops with NIST (to be discussed below)
  - Plans to develop other RM industry priority standards issues for collaboration
- **Future meeting with FDA**
  - Follow up to Commissioner meeting
  - First in a series of regular meetings to discuss RM issues
  - Agenda being developed

Key Regulatory Issues

Additional Regulatory Activities:

- Engage NIH-FDA Joint Leadership Council
- Meeting at White House OSTP
- Submissions to FDA public docket re: FDA's Device Innovation Initiative; Regulatory Reform; etc.
- Nomination for industry representative to FDA's Cellular, Tissue, and Gene Therapies Advisory Committee
- Support increased FDA appropriations

Key Regulatory Activities

Standards:

- ARM undertook an international standards inventory and gap analysis resulting in the creation of working groups and a series of workshops to pursue issues in cell potency assay development and validation
  - Part I – Inventory: Completed a comprehensive identification of all "standards" efforts either completed or underway relevant to the field of RM (Completed 2010)
  - Part II – Gap Analysis: Developed a gap analysis of existing and planned standards efforts to identify issues and key therapeutic or technology categories not covered (Completed 2010)
  - Part III – Working Groups – NIST Project: Organized 4 working groups among cell therapy and tool/device/service companies to pursue joint issues in cell potency assay development and validation.
    - Project entails developing a registry of cell potency assays used by RM companies and efforts to validate them; 2) identifying and/or developing appropriate reference standards for assay development; and 3) developing, validating, and analyzing new potency assays to address regulatory requirements for RM product approvals
    - Held meeting at NIST in July
    - Need to develop standards/criteria that pass regulatory muster

Key Regulatory Issues

Use of Animal Studies:

- Issue arose during ARM-Hamburg meeting

- Some cell therapy testing would need to be performed either in immunosuppressed or immunodeficient animals to determine cell fate and long term outcomes.
  - Few animal models, especially models with disease specific manifestations relevant to either reliably predict the mechanism of action of the cell or to adequately test possible treatments for diseases with complex traits where multiple genetic and environmental factors contribute to pathophysiology.

- Stem cell based, disease-in-a-dish models could reflect pathology better than current animal models in some cases.

- Work with FDA to identify other mechanisms for testing for IND “approvals” that are less reliant on animal models

Key Regulatory Issues

Improved Communication:

- FDA regulations say that the agency will meet in person or via telephone call with sponsors (21 CFR 314)
- ARM members' experience is there are flaws in the current review process; leads to delay or even clinical hold
- FDA should adopt a more consultative role with sponsors and provide "informal" advice and guidance regarding the development pathway.
  - Sponsors/FDA would be in closer communication and have a clearer understanding of data requirements and other key aspects of study.
- FDA should allow sponsors to engage regularly with all relevant agency staff during "informal" pre, pre-IND meetings. FDA should also adopt regulations/practices that increase communication -- more informal or formal meeting opportunities -- during the entire development process.
- This should not -- and would not -- lower the standards for approval.
- Particularly for novel products and technologies -- such as in RM -- more frequent discussions with reviewers throughout product development and review will ease uncertainty and provide clarification of agency views of key issues

Key Regulatory Issues

Patient Involvement in the Approval Process:

- Patients should have greater involvement in the drug review/approval process than simply being clinical trial participants or serving on FDA Advisory Committees.
  - Perhaps having a role in the evaluation of clinical data from studies and associated risk/benefit decisions by drug sponsors and the FDA.

- Patient Representative program ensures patients are on advisory committees and gives patient advocates representing serious and life-threatening illnesses an opportunity to participate in the FDA drug review regulatory process.
  - Evaluation of this project?

- Consider expanding and strengthening this program.
  - Patients will help sponsors and the FDA identify new innovation pathways and build public trust
  - Help identify the appropriate risk/benefit balance; patient involvement was critical during the HIV/AIDS crisis in the late 1990s and led to fundamental changes at FDA and rapid approval of therapies.

Key Regulatory Issues

Innovative Regulatory Approaches:

- Recent proposal: a priority review program for pioneering medical devices designed to facilitate the development and regulatory evaluation of innovative medical devices.
  - CDRH will engage product developers earlier in the process on issues (identifying clinical endpoints and data requirements, engage experts and provide guidance prior to the regulatory submission).
- FDA's proposal includes:
  - Creation of new Center Science Council (CSC) comprised of senior managers and reviewers to monitor the device development and review processes;
  - Early identification of needed expertise, including the agency's commitment to seek expertise outside CDRH;
  - Assignment of a "Case Manager" to coordinate Center actions for review of their device submissions, ensuring timely information exchange, etc.;
  - Development of an Innovation Pathway Memorandum to describe a proposed roadmap and timeline for device development, clinical assessment, and regulatory review;
  - Frequent communication with the sponsor; and
  - Established timeframes for regulatory review - reviewers would have 150 days to complete their review.
- These features will facilitate the scientific and regulatory evaluation of transformative innovative products in a timely manner and they should be adopted agency-wide.

Key Regulatory Issues

FDA-CMS Parallel Review:

- Proposal for parallel review published in the **Federal Register** on September 17, 2010
- ARM supports the objective -- reduce the time between FDA and obtaining third-party payment.
- But: it could stymie commercialization efforts because:
  - The process will insert reimbursement and coverage issues into the FDA review and approval process, causing delays; and
  - The implications of the proposal are broad and unknown, thereby creating uncertainty for product developers seeking marketing approval as well as reimbursement for their products.
  - Sponsors can already meet with CMS prior to completion of FDA review
- FDA's process is designed to be completely separate from coverage and payment; governed by different statutes with different standards and objectives. CMS and FDA have completely different missions.
- Details unclear; but agencies will develop guidance and implement a pilot program

Key Activities – Legislation Affecting Regulatory Issues

Regenerative Medicine Promotion Act of 2011

- National strategy
- GAO report of current federal research and regulatory activities
- Creation of Coordinating Council – federal agencies with input from the private sector and patients to determine obstacles to commercialization, propose solutions, set goals, priorities and performance metrics.
- NIH grants for collaborative research; support IND filings within 4 years
- Authorization for FDA regulatory sciences research
  - Public-private partnerships
  - Research done within the agency and outside the agency

PDUFA Reauthorization

- Performance goals/increased user fees
- Support to aid rare disease drug development
- FDA has published the agreement with industry – Congress to draft legislation this fall
  - Will likely include other FDA-related provisions (supply chain safety, etc.)

Conclusion

FDA Regulatory Authority:

- Many challenges for RM drug developers
- Need to be organized and advocate
- Collaborative relationship with FDA is best way forward – work together on removing obstacles to commercialization
- FDA and other federal agencies and Congress will be making decisions that will affect the industry
- Many opportunities for industry to affect change

Find Out More

For more information, visit us at www.alliancerm.org.

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