

IBCs in a Changing Research Landscape: *A Policy Conference*

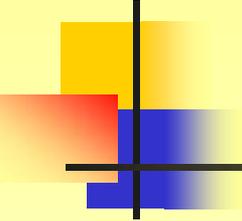
Industry: Roles and Responsibilities

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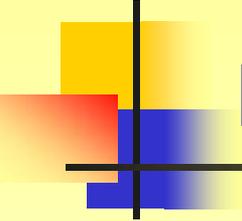
VICAL Incorporated





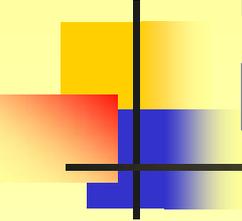
Progress

- Over 480 gene transfer trials are recorded on the OBA protocol list
 - 86% Phase I studies
 - 13% (64) of these in phase 2
 - 1% (3) of these trials in phase 3.



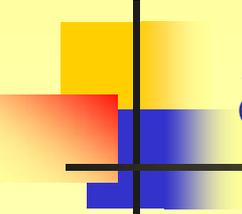
What has changed in the research landscape?

- Human gene transfer studies moved beyond Phase 1 research to late stage development
 - Phase 2, Phase 3.
 - Better characterized product
- Industry sponsors ~2/3 of human gene transfer clinical trials.
- Industry is a major partner in realizing and delivering potential benefits of gene-based medicines.



Human Gene Transfer Research: FDA findings of Good Clinical Practices

- During 2000, FDA inspections
 - 70 clinical study sites
 - Industry and Academic Sponsors
 - GCP compliance acceptable
 - GCP deviations not different from other bioresearch programs



Random Sampling of Phase 1 and 2 INDs, FDA March 2000

24 IND Sponsors of
Human Gene Transfer
Research

70 Clinical Investigators
Participating in these
INDs

Independent

70.8% (17/24)

27.1% (19/70)

Government (DHHS)

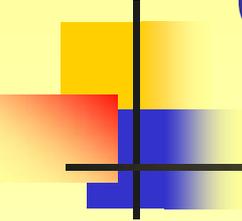
4.1% (1/24)

7.1% (5/70)

Industry

25% (6/24)

65.7% (46/70)

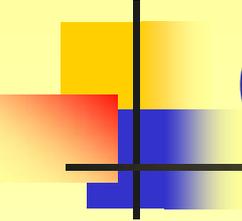


Gene Transfer Clinical Investigator Inspections A Comparison

FDA inspected 70 randomly selected clinical investigators for GCP compliance.

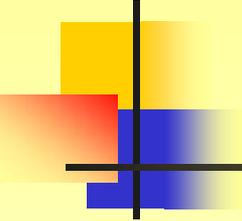
| | NAI | VAI | OAI |
|------------|-------|-------|-------|
| GT | 38% | 55.9% | 5.0% |
| 2000 total | 30.9% | 57.1% | 11.9% |
| 2000w/o GT | 21.4% | 60% | 18.5% |
| 1999 | 28.5% | 54.2% | 17.1% |
| 1998 | 34.9% | 53% | 12% |

Random surveillance inspections of Phase 1 and 2 gene therapy clinical trials indicates the trials were being properly conducted with fewer deviations than found in Phase 3 studies.



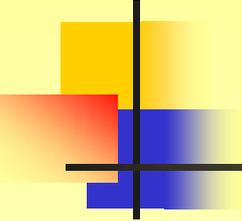
Industry in Development of Gene-Based Medicines

- Establish and Maintain Best Practices
 - Quality in Non-Clinical Research and Development
 - Quality in Manufacturing
 - Safety, Diligence and Quality in Clinical Research
 - Regulatory Compliance and Appropriate Reporting
- Realize and Deliver Potential Benefits
 - Facilitate the realization and delivery of potential benefits of gene-based medicines to Patients and Caregivers.



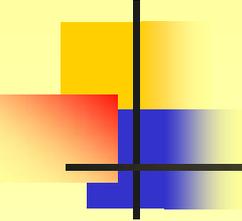
Sponsor/Manufacturer Interests

- Partnership in safe, prudent advancement of the field
- Contribute to oversight, self-monitoring
- Contribute to rule-making objectives and process
- Appropriate disclosure, recognize survival requirements of proprietary nature



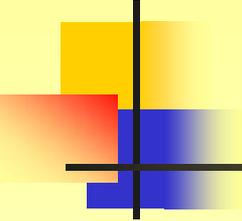
Industry Contributions

- Cooperative Development of Laws
 - FDAMA 1997, PDUFA 1992
- Cooperative Development of Regulations & Guidance
 - Designated products as “well-characterized”
 - Continuum of cGMP compliance throughout development
- Innovator of Best Practices
 - Current Good Manufacturing Practices
 - Practices driven by industry innovation
 - Quality standards driven by Industry-Regulatory partnerships



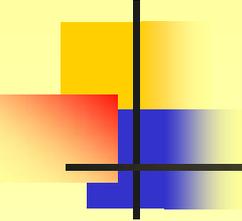
Major Partners

- Helping to Realize Potential Benefits of Gene-Based Medicines
 - Patients and Caregivers
 - Regulators and Government
 - Academia and Funding Institutions
 - Local Review Committees
 - Manufacturers and Clinical Research Organizations



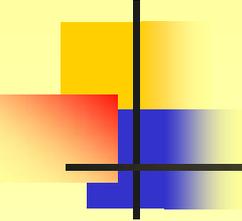
Roles of Industry: Sponsor

- Safety, Informed Consent, Public accountability
- Regulatory compliance and reporting
- Financial support, Public accountability



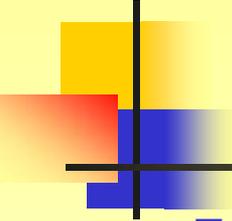
Roles of Industry: Developer

- Research, Manufacturing
- Quality Systems, Regulatory Affairs
- Clinical Program design and management



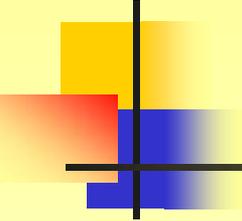
Sponsor/Manufacturer Interests

- Responsibility
 - Patient safety and well-being
 - Scientific Discovery
 - Advancement of product development
 - Quality Systems in Manufacturing and Clinical Research
 - Endurance versus competitive pressures and lengthy development costs



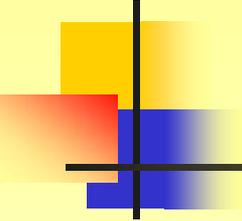
VICAL Inc. Development

- Research, Manufacturing & Clinical Development
- Designed and sponsored 23 human clinical research protocols during the last 7 years
 - BSL 1
 - Phase 1 trials, single trial sites
 - Phase 2 & 3 trials, multi-centered
 - Approx. 100 clinical study sites initiated.
- ~ 20% Non-Academic study sites
 - Expanding participation in clinical research



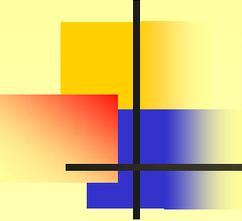
IBC Review in Vical Programs

- Vical IBC with BSO since 1993.
- Reviews internal research, manufacturing, study drug supply stream to study sites
- Outside members \geq Vical members.
- No Vical management members
- Outside community members include such as University BSO, Banker, EH&S Specialist



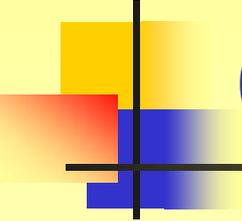
Local IBC Review in Vical Programs

- In academic centers, local IBCs review protocols and product information provided by Vical
- For non-academic sites without IBCs, often many months delay for site to set up meaningful local IBC.
- Delays challenge development opportunity
- Cancel clinical study plan at sites that will not establish local IBC.
- Local IBC in full compliance with NIH Guidelines



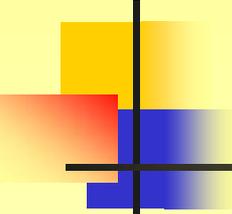
Establishing Local IBC's at Non-Academic Sites

- Core IBC from Vical IBC non-employees
- Vical request to establish local IBC
- Identify 3rd party organizer, volunteer
- Identify & train 2 local technical, medical reviewers, 1 site staff as contact
- Site management acknowledgement letter
- Register with OBA
- Telecon open meeting



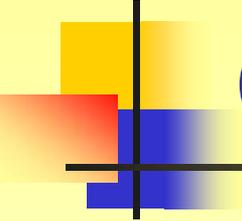
Question

- **What constitutes good oversight to ensure that IBCs associated with various types of clinical research sites fulfill the letter and intent of the *NIH Guidelines* ?**



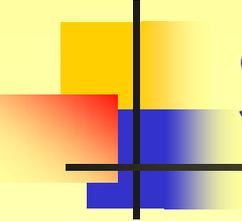
February 2, 2000 OBA Statement to Senate Subcommittee on Public Health

- The *NIH Guidelines* are intended to assist the
 - Principal Investigator
 - Institution
 - Institutional Biosafety Committee
 - Biological Safety Officer
 - Institutional Review Boardin determining safeguards that should be implemented.
- “...it is the **responsibility of the institution** and those associated with it to adhere to the intent of the *NIH Guidelines* as well as to its specifics.
- “**Each institution** (and the Institutional Biosafety Committee acting on its behalf) **is responsible** for ensuring that all recombinant DNA research conducted at or sponsored by that institution is conducted in accord with the *NIH Guidelines*.”



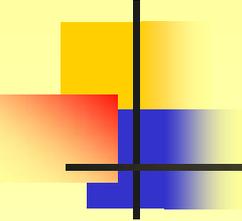
Institutional Biosafety Committee Oversight

- Role in Clinical Trial Oversight may vary according to institution activity
- Academic research setting
- Non-academic setting



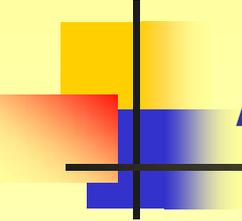
Initial vs Later IBC Review in Stages of Clinical Development

- Initial Stage
 - Phase 1
 - Confirms no subject enrolled before RAC process is complete
 - Possibly "Novel"
 - Initial review & containment levels
- Later Stages
 - Phase 2 or 3
 - Confirms no subject enrolled before RAC process is complete
 - Established use
 - Established review & containment levels



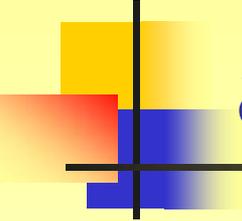
IBC at Phase 2 and 3

- Full product characterization
- BSL 1, 2: Issues of Handling Containment usually addressed by Phase 2
- Research product and use are typically exempted from full RAC review
- IBC for Phase 2 & 3 clinical research to ensure that Appendix M requirements are satisfied.
- Clinical monitors, local lab expert review support monitoring handling procedures.



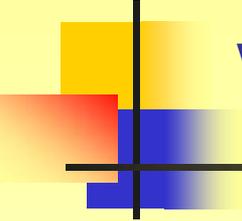
Key Roles of IBC for Non-Academic Clinical Trial Site

- Institutional authority over research
- Institutional authority over PI
- NIH Guidelines followed
- Local standards applied
- Local research practices reviewed



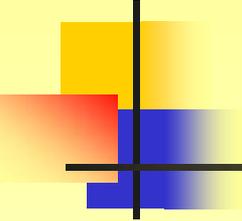
Issues in Phase 2, 3 may be addressed by local IBC

- Authority to effect response to recommendations by institution & PI
- Safety for clinical use, MSDS of Mfgr
 - Safety to handlers, caregivers, patients
- Long term effects and follow-up
- Reporting requirements
- Annual review



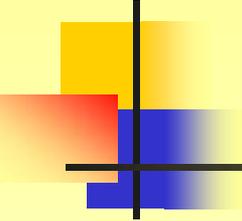
VICAL Approach to IBCs

- Clinical Research at Phase 3
 - Expanding role for non-academic centers
 - Limited Sponsor resources drives timely completion of clinical trials



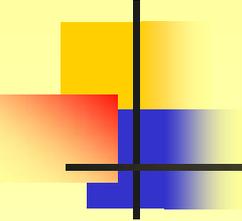
Local IBC for Novel Approaches

- New vectors/new gene delivery systems, new diseases, unique applications of gene transfer, and other issues considered to require public discussion.
- Scientific rationale, scientific context (relative to other RAC reviewed proposals), appropriate and sufficient preliminary *in vitro* and *in vivo* safety data, resolution of relevant social and ethical issues.
- NIH Guidelines, Appendix M



Remote or Central IBC

- Multi-site Phase 2 and Phase 3 Development Track protocols in non-academic centers may benefit from remote or central IBC review.
- Optimized review process
- Greater expertise
- Avoid unproductive delay



Proposal

- Novel new human gene transfer protocol that is determined to be “novel” may trigger a requirement for absolutely local IBC review, academic centers.
- Centralized or Remote IBC review may be acceptable where novelty is not found, nor full RAC review is warranted, BSL-1, 2, academic or non-academic centers.

When might Remote IBC review be most appropriate?

| BSL-1,2 | Non-clinical Research | Mfg | Phase 1 | Phase 2 Phase 3 |
|--------------------|-----------------------|-------|-----------------|--------------------|
| Novel Approach | Local | Local | Local | Remote OK |
| Non-novel Approach | Local | Local | Local or Remote | Remote OK |
| | | | | |