CMC Due Diligence for CGT Products: Asking the Right Questions

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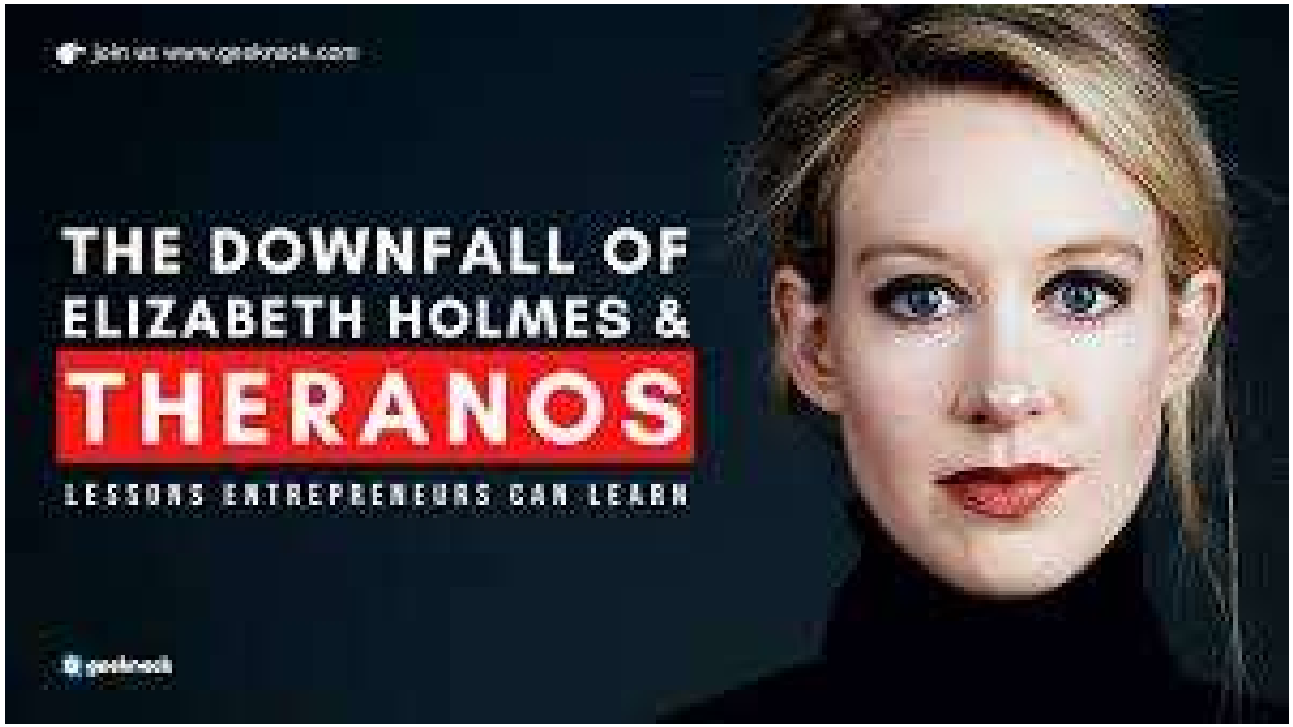
THE DOWNFALL OF
ELIZABETH HOLMES &
THERANOS
LESSONS ENTREPRENEURS CAN LEARN

Q. Where to begin due diligence?

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A. Focus on four key areas:

1. Product definition and characterization
2. Manufacturing
3. Quality Assurance
4. Regulatory

Product Definition and Characterization

1. How is the product defined?

Product Definition and Characterization

1. How is the product defined?
   - Review QTPP (if any)
   - Is there a phase-appropriate understanding of CQAs?
   - Hypothesized mechanism of action?
   - Specifications? In-process and release testing tables.
     - Startup: Plans for further analytical development, refinement of specifications
     - Later-stage: Specifications finalized

Product Definition and Characterization

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2. Is analytical method development phase-appropriate?

Product Definition and Characterization

1. How is the product defined?
2. Are analytical methods relevant, well-controlled, and phase-appropriate?
   - Analytical method SOPs, method qualification reports, test results
     - Phase I-II: Assays qualified
     - Phase III: Assays validated
   - Stability-indicating assays
   - Is there a phase-appropriate stability testing plan?

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2. Are analytical methods relevant, well-controlled, and phase-appropriate?
3. Is potency testing phase-appropriate?
   - Phase I-II: Potency testing development plan, development reports
   - End of Phase III/BLA: Potency testing validated

Manufacturing

1. What is the manufacturing process?

Manufacturing

1. Is the manufacturing process defined and phase-appropriate?
   - Use of closed-systems and (semi-)automated process technology?
   - Process flow diagram(s), batch records, and SOPs
   - Process run data
   - Manufacturing process risk analysis report
   - Process development reports and plans. Comparability reports and plans.
   - Process qualification report. Process validation plan.
   - Phase-appropriate understanding of CPPs? Process control system.
   - ***How often does the process fail?***
   - ***Has there been a successful tech transfer of the manufacturing process?***

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2. What materials are used?

Manufacturing

1. What is the manufacturing process?
2. What materials are used?
   - Ancillary materials (reagents)
     – Quality? Phase-appropriate qualification (materials and suppliers)
     – Sole-supplier materials? Primary animal-origin materials? Human-origin material? Novel excipient(s)?
     – Raw materials risk assessment and mitigation plan? (Phase II or later)
     – Risk mitigations in place?

Manufacturing

1. What is the manufacturing process?
2. What materials are used?
   - Cells, tissues, viral vectors
     – Source(s), control, testing, GTP compliance
     – Vector manufacturer qualified? May need site visit.

Manufacturing

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2. What materials are used?
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Manufacturing

1. What is the manufacturing process?
2. What materials are used?
3. Is the manufacturing facility suitable?
   - Is manufacturing in-house or contracted out? (If CDMO is used, pay a visit)
   - Equipment
   - Staffing – levels, training, management expertise
   - Quality systems – GMP/GTP infrastructure

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3. Is the manufacturing facility suitable?
4. What are the projected costs?
   - Product yield?
   - Cost per dose?
   - Scalability? (scale-out/scale-up)

Quality System

1. Is the quality system robust and effective?

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   - Critically important for any due diligence project – ***work with an experienced quality consultant***
   - Is QA independent? Is the quality system phase-appropriate?
   - Does the operation function per the quality manual? SOPs followed? Sign-offs?
   - Does QA interact with other teams well?

   - Academic research labs -- no formal quality systems, but DD should still assess basic quality practices, reliability of data

Regulatory

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Regulatory

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   - Investigate regulatory aspects ***early*** in due diligence
   - Regulatory submissions -- briefing documents, INDs
   - Regulatory meetings – meeting minutes, follow-up interactions
   - Regulatory correspondence

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- Academic or Phase I/II startup: limited or unavailable data
  - "Can you put the data in my hands?"
  - Golden glow of illustrious founders

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- Inadequate evaluation of comparability; challenges not fully recognized
- Academic or Phase I/II startup: limited or unavailable data
- Pharma companies, for acquisition by Big(ger) Pharma
  - Assumption that CMC and regulatory must be satisfactory. Minimal due diligence on technical and regulatory aspects.

Sources of Information

- **Product TPP, QTPP**
- Organizational chart, table of SOPs, **quality manual**
- **Regulatory submissions, meeting minutes, correspondence**
- Scientific Foundation
  - **Recent grant proposals and reviewer comments**
  - **Scientific/technical publications**
- Manufacturing
  - **Process descriptions, flow diagrams. batch record template(s)** and examples, batch record audit report. Process qualification and validation – description, SOP, reports.
  - Example PD plan, **PD reports**, **technology transfer report(s)**
  - **Process control program**
- Testing
  - **In-house analytical methods**, equipment, IQs, OQs, PQs performed, **outlier and trend analysis**. Example analytical method SOP, development report, validation report, outsourced testing, **proficiency survey reports**
- Materials
  - Materials management system description and SOP. **Raw materials qualification plan**, reports
  - Receiving inspection, sampling, testing and disposition of raw materials SOPs
- Facility
  - **Manufacturing facility description(s) and layout(s), facility validation report.** Certifications, accreditations, and licenses. Regulatory and accreditation inspection documents.
  - **Briefing document(s) and minutes of facility-related regulatory interactions**
- QA
  - **CAPA plan, CAPA/deviation/nonconformance/complaint SOPs and reports**
  - Validation master plan
  - **Establishing specifications SOP**
  - CoA generation, product release SOPs
  - Vendor qualification plan and reports, management and monitoring SOPs, tables of suppliers and contract service providers, quality agreements in place, example supplier quality agreement, purchasing controls
  - SOPs for staff training, proficiency testing SOPs, training matrices by function
  - List of manufacturing and facilities equipment, IQs, OQs, PQs performed. Equipment management, qualification, calibration and maintenance SOPs
  - Risk management SOP. Internal audit SOP(s) and log. Handling and investigation of OOS results SOP(s)
  - Sampling plan SOP
  - Labeling control program SOP(s). Data integrity program SOP. Software validation program, validation examples - analytical and manufacturing software
  - Cleaning, EM, PM SOPs, EM reports, cleaning records, trend data. Personnel aseptic technique/gowning qualifications
  - SOPs for line clearance/product changeover
  - Change control SOP(s)
- CDMO
  - Template facilities section for client's regulatory submissions.
  - Descriptions of manufacturing platforms, analytical systems.
  - Project management practices and policies. Redacted project proposals, descriptions of recent projects.
  - Numbers and types of CGT products developed and manufactured, and stage of development.