BIOPHARMA Due Diligence Process/Checklist

$SAVA Failure as Primary Example

Contents

1 Market

1. Market efficiency in drug valuation:
   - Top 5% of known-effective medicines priced accordingly
   - Similarly for known-ineffective drugs (SAVA case shows occasional lag in market realization)
2. Holder analysis:
   - Determine market cap drivers: retail "lottery ticket" investors vs. experienced sector investors
3. Options market analysis:
   - Premiums as sentiment indicators for binary outcomes
4. Pipeline assessment:
   - Portfolio size and origin (internal development vs. patent acquisition)
5. FDA event dynamics:
   - Binary approval/rejection outcomes with pre-event volatility
   - Hedging strategies recommended

2 Judgement

1. Emotional discipline:

- Eliminate personal bias (e.g., affected family members)
- Hope is irrelevant to scientific assessment

2. Clinical trial determinism:
   - Outcomes governed by physics/biology, not chance
   - Proper trials reveal true efficacy (no "maybe" outcomes)
   - Statistical design accounts for individual variability

3 Starting from the Beginning

1. Inventor background:
   - Academic pedigree verification
2. Motivation analysis:
   - Scientific merit vs. financial lottery potential
3. Track record:
   - Previous project successes/failures
4. Approach novelty:
   - Historical precedent for methodology
5. Publication history:
   - Peer-reviewed chemistry work
   - Retraction history (especially if relevant to current research)
6. Historical timeline (Dr. Wang case study):
   1. 2000: Amyloid-/Alpha-7 research at J&J
   2. 2005: Oxytrex failure (opioid)
   3. 2008: Filamin A/MOR mechanism publication
   4. 2009: Retracted GSK drug claim
   5. 2010: Simufilam patent filing (pain)
   6. 2012: Amyloid-42/alpha7 inhibition claim
   7. 2015-16: Alpha7 agonist failures in Alzheimer's
7. Scientific transparency:
   - Journal publications (including chemistry details)
   - In-house medicinal chemistry capability
8. Legal scrutiny:
   - Active indictments (SAVA example)
   - Fraud allegations (company-related vs. unrelated)

4 Chemistry and Biology

Key Definitions

Crystal Structure Atomic arrangement in crystalline material

Co Crystal Multi-molecule crystalline structure with non-covalent bonds

Crystal Clear Evidence High-confidence binding validation (X-ray/cryo-EM + peer review)

SAR Structure-Activity Relationship (essential for rational drug design)

Ligand Target-binding molecule

Shape Complementarity Molecular lock-and-key fit principle

1. Binding event characterization
2. Molecular interaction requirements
3. Target-disease relevance
4. Hydrogen bond networks:
   - Typical protein binding mechanism
   - Functional disruption via competitive binding
5. Target validation:
   - Knockout studies (Filamin A case study)
   - Actin cytoskeleton implications
   - Toxicity/binding paradox
6. Pathway viability:
   - Literature consensus assessment
7. MoA basis:
   - FDA-approved vs. hypothetical mechanisms
   - Failure-derived hypotheses
8. Molecular sizing:
   - Small molecules:
     * Hydrogen bonding requirements (Lipinski rules)
     * Binding pocket compatibility
   - Large molecules:
     * Reduced hydrogen bonding emphasis
     * Multi-interaction dependence
9. Binding verification:
   - Crystallographic evidence
   - Peer-reviewed SAR
   - Binding site characteristics:

    - Known ligand precedent
    - Surface topology
    - Solvent exposure effects

10. Functional plausibility:
    - Inhibition/activation mechanics

5 Pharmacodynamics (PD) and Pharmacokinetics (PK) and Clinical Data

Definitions

Pharmacodynamics Drug's biological effects (receptor binding, downstream effects)

Pharmacokinetics ADME properties (absorption, distribution, metabolism, excretion)

First Pass Hepatic pre-systemic metabolism

Efficacy Treatment's beneficial effect capacity

1. PD assessment:
    - Dose-response curve validation
    - Patent consistency check
2. PK optimization:
    - Administration route compatibility (Simufilam oral case)
    - Solubility/metabolic resistance
    - GI stability and first-pass effects
    - Half-life adequacy
    - Tissue distribution alignment
3. Trial evaluation:
    - Phase II:
        - Efficacy signals vs. placebo
    - Phase IIb:
        - Go/no-go for Phase III investment
        - Blinded vs. open-label designs
    - Statistical rigor:
        - p-value threshold (< 0.05)
        - ADAS-Cog benchmarks (Alzheimer's)
    - Data transparency:
        - Subgroup analysis pitfalls
        - Post-hoc rationalization risks

- Publication status:
  - Peer-reviewed journal validation
- Comparison validity:
  - Controlled vs. open-label data
  - Cross-trial reliability

6 Final Checklist

1. High-affinity binding with crystallographic validation
2. Optimal PK profile (half-life, distribution)
3. Molecular size appropriateness
4. Target-disease relevance and reproducibility
5. Phase data showing statistical significance ($p < 0.05$)
6. Comparison methodology validity
7. Historical success rates for disease target