**BIOPHARMA Due Diligence Process**

**Cassava Sciences Failure as Primary Example**

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**Market**

* 1) With respect to the stock market, the 5% of the medicines you know will work are very much valued as if they will work. The market is often efficient. The same generally applies to the medicines that you know do not work. **(If** **you know it will work so does the rest of the market 90% of the time and the same applies if you know it will not, occasionally in the case of SAVA the market has not yet realized that it won’t work)**
* 2) Reference holders list to understand broader market sentiment and attain an understanding of how the street values the company
  + 2,1) Establish an understanding where the market cap is coming from, is it from retail investors hoping for a lottery ticket or is it from investors experienced in the sector
* 3) Reference options market premiums to determine market sentiment on plausibility of outcome either positive or negative
* 4) How many drugs are in the company’s portfolio, did they create the drugs or did they purchase the patent right, this can give insight into experience and likely hood of success or failure
* 5) The results of FDA approval or rejection result in binary events however in anticipation of these events there can be massive fluctuation in share price, hedge accordingly

**Judgement**

* 1) Do not let anything cloud your judgement, emotion should play ZERO part in determining the outcome, having a loved one effect by the disease is irrelevant to determining success or failure of research. Hope for success should be as irrelevant as hope for failure.
* 2) Clinical trials don’t have a chance of working, they either do or do not, there is no randomness.
  + 2,1) Clinical trials, done correctly, are deterministic. The outcome is preordained by the laws of physics: the chemistry of the drug, the biology of the patient, the medicine’s interference with the disease pathology. The carefully designed statistics allow us to blend away individual differences, the minute randomness that exists.
  + 2,2) If there is a potent effect: it will be seen.

**Start from the beginning**

* 1) Who invented it? What schools did they go to
* 2) Why, is it because of the potential for a winning lottery ticket or is it because it’s a viable method
* 3) What else have they working on? Was it a success or failure
* 4) What was their approach and has this approach been tried before, what were the results of similar approaches
* 5) Has their chemistry work been published in any reputable medical paper
  + 5,1) Has any published work been retracted by publishing body, is that work related to currently pursued medical research
* 6) Establish a timeline of past research and results if available
  + 6,1) Example: Dr Wang
    - 2000) While at JNJ for <1y researched if Amyloid-β binds Alpha-7
    - 2005) Oxytrex fails (Opioid)
    - 2008) Oxytrex MOA (mechanism of action) published by Wang & Burns: Filamin A binding changes MOR (Class of Opioid receptor) orientation
    - 2009) Wang published Amyloid-β-Alpha-7 interrupted by GSK drug (proven wrong)
    - 2010) Patent for simufilam filed as pain reliever which bind filamin A, again binding changes MOR orientation
    - 2012) Wang publishes small molecule inhibits Amyloid-β42/alpha7 formation via filamin
    - 2015-2016) Several alpha7 agonists fail in Alzheimer’s
* 7) Has the company published the science behind their drug discovery in any Med/Chem journals, it is often a point of pride for a scientist to publish science (duh)
  + 7,1) If the company has published preclinical data or human clinical data ensure they include the chemistry behind it
  + 7,2) Does the company have an in-house medicinal chemist
* 8) Are any of the employees under indictment (as ridiculous as it seems this was the case with SAVA), including former employees? Does the company have any accusations of fraud either from the federal government or from former employees? If so, are these indictments related to the company (and its research) or are they simply misfortunate and entirely unrelated circumstances?

**Chemistry and Biology**

**Definitions**

* **Crystal Structure** – specific arrangement of atoms within a single crystalline material
* **Co Crystal** – crystalline structure made up of two or more different molecules, held together by non-covalent bonds, in a defined stoichiometric ratio within the same crystal lattice.
* **“Crystal clear” evidence** –in the context of binding this often refers to a high-confidence demonstration of molecular interactions between two entities, typically validated through X-ray crystallography or cryo-electron microscopy and done by peer review, Evidence is considered "crystal clear" when multiple methods converge on the same conclusion, and results can be reproduced independently.
* **“SAR”**- “structure-activity relationship”. Without SAR, you cannot design a medicine, because you are “flying blind” as to what you are designing and optimizing.
* **Ligand** - A ligand is a substance that binds to a biomolecule, such as a protein
* **Shape Complimentary** - the concept that two molecules, like a protein and a small molecule, fit together well because their shapes perfectly match like a lock and key, allowing for optimal interaction and binding
* 1) When looking at a drug we want to know exactly what the “binding event” looks like
* 2) To work, a putative (generally thought to exist or be true) drug must make some molecular interaction with one or more targets in the patient
* 3) targets should be related to the patient’s illness
* 4) when drugs form bonds with their targets (usually proteins), they tend to (not always) form a hydrogen bond network.
  + 4,1) This hydrogen bond network typically disrupts the function of a protein by blocking the ability for another molecule (sometimes a protein) to have its own binding event.
* 5) It is critical to understand the protein target thoroughly
  + 5,1) The way to understand protein function is via deletion in organisms, we can induce them in animals and expect similar results in humans.
    - 5,1,1) Example with simufilam. Filamin A is an X-linked intracellular protein whose primary role is to bind actin. Actin is one of the most common proteins in the human body, underlying the cellular cytoskeleton. If we knock out filamin or mutate then it has adverse impacts. This could make “binding” filamin A, dangerous. By interrupting any of the large number of natural functions of filamin A, a filamin A binder may cause toxicity. However, if it is not causing toxicity then we must question if it is a filamin A binder!
* 6) Is there literature or are there databases that confirm or deny if it could be a viable pathway, in essence does research from the pharmaceutical industry suggest that the proposed method is viable
* 7) Is the method of action based on an FDA approved approach or is it based on a hypothetical
  + 7,1) If based on a hypothetical, is it new or did the hypothesis come from a failed trial
* 8) Is the molecule the right size for the target
  + 8,1) If it is a small molecule targeting another small molecule (enzyme, a GPCR/receptor pocket), does it have the right hydrogen bond doners and acceptors for Lipinski-like “desirable” pharmaceutical properties.
    - 8,1,1) Hydrogen bonding is a key factor in the way many drugs interact with their targets, especially small molecules that target other small molecules
    - 8,1,2) hydrogen bonding is crucial.
    - 8,1,3) Small molecules often interact with a specific binding pocket on their target, the presence of the correct hydrogen bond donors and acceptors enables strong, selective interactions.
  + 8,2) If it is a large molecule such as monoclonal antibodies, proteins, or RNA-based drugs, the specific requirement for hydrogen bond donors and acceptors is less prominent compared to small molecule drugs
    - larger molecules typically rely on a wider range of interactions
    - Hydrogen bonds still play a role in stabilizing the structure and binding affinity, but they aren't the only or most critical force in every case.
* 9) Can the drug bind to its target
  + 9,1) Is there “Crystal Clear” evidence of binding, and “SAR”
    - 9,1,1) typically a crystal structure or co-crystal
    - 9,1,2) Has the “SAR” been peer reviewed
  + 9,2) Is the alleged binding location viable
    - 9,2,1) Is anything else known to bind at the site
    - 9,2,2) Is the binding site a flat surface (this can hinder the ability to form high quality bonds)
    - 9,2,3) Is it shape complemtary
    - 9,2,4) Is the binding site solvent exposed
      * it can be difficult for bonds to form if a binding site is solvent exposed because the surrounding solvent molecules (typically water) can compete with the ligand for interactions with the binding site residues, potentially hindering the formation of strong, specific bonds with the target molecule.
* 10) Can the drug do what it says it can do, is it plausible for the drug in question to inhibit whatever it is trying to inhibit (enzymes, Protein to protein interaction, ect), activate or block receptor activity if that is the goal.

**Pharmacodynamic (PD) and Pharmacokinetics (PK) and Clinical data**

**Definitions**

* **Pharmacodynamics** – (what a drug does to the body) Biochemical, physiologic, and molecular **effects of drugs on the body** and involves receptor binding (including receptor sensitivity), post receptor effects, and chemical interactions
* **Pharmacokinetics** – (what the body does to a drug) refers to the **movement of drug into, through, and out of the body**—the time course of its absorption, bioavailability, distribution, metabolism, and excretion.
* **“First Pass”** - Some of the drug gets broken down in the liver before it can reach its target in the body. This is called the "first pass," and it **reduces the amount of the drug that circulates in the body and that can achieve its intended effect**. Some drugs are significantly broken down by the liver. When taken orally, a large portion of the drug is metabolized before it can have its intended effect. This is why such drugs might require higher oral doses compared to other forms, like injections, which bypass the liver.
* **Efficacy**- efficacy refers to the ability of a product or treatment to provide a beneficial effect

**Cliff Note: P value (mentioned in 3,3) is absolutely critical in determining success, everything else is compounding data**

* 1) Does it have good pharmacodynamics (PD)
  + 1,1) Does it adhere to laws of dose response?
    - Example: very low doses of drugs have very low pharmacodynamics. A very small amount of drug behaves no differently from a moderate or a large dose of the drug. The effect is simply magnified. At a low enough dose, there is almost no effect at all, at some higher dose the effect begins to appear, and at an even higher dose the effect increases, eventually the effect plateaus and does not improve despite even higher dose
  + 1,2) Is its reported potency consistent with that of similar drugs
    - Are the companies claims consistent with their patent data
* 2) Does it have good pharmacokinetics (PK), is the molecule of choice compatible with method of administration
  + 2,1) E.G. Simufilam, it is not peptide or protein based and therefore can be ingested orally
  + 2,2) Is it soluble enough and metabolically resistant enough to be administered orally (if oral administration is the intended method),
  + 2,3) Can it make it through the GI (Is it going to be broken down by digestive enzymes or stomach acids) and “first pass” metabolism
  + 2,4) Is the half life of the drug enough for it to be absorbed, distributed and take effect
  + 2,5) Where are the highest concentrations found and do these areas match the areas affected by the disease it is targeting, where are the lowest concentrations found.
* 3) What do the trial results show
  + 3,1) Phase II trials are designed to give hints or directions of efficacy or dose response, most importantly do the results show significant improvement over placebo
  + 3,2) in Phase IIB, the goal is to determine hints of efficacy and consider whether the often multi-hundred-million-dollar investment in Phase III is prudent, do the results indicate that it works and should begin phase III
    - 3,2,1) Phase IIb studies often include direct head-to-head comparisons or placebo-controlled, blinded designs for their entire duration.
    - 3,2,2) Open-label studies are more exploratory and focus on long-term or additional outcomes.
    - 3,2,3) head-to-head studies are designed to establish comparative efficacy.
    - 3,2,4) It is more common for Phase IIa studies to be open-label and Phase IIb studies to include head-to-head comparisons
  + 3,3) How is success measured, what is the P value, and does it show statistical significance that can be attributed to the drug's actual effect rather than random variation. If the drug is designed to treat Alzheimer’s or dementia what do the ADAS Cog results show, does it match the average expected decline.
    - 3,3,1) a low p-value (typically below 0.05) suggests a higher confidence that the observed difference is not due to chance and the drug is likely effective
  + 3,4) Is the data being presented transparently or are only specific subgroup analyses being shown. By splitting data into two or more subgroups, one naturally creates a subgroup with superior performance
    - 3,4,1) Post-hoc observations in biopharma that has led to many failures. The narrative typically applies as follows. If the subgroup chosen has milder disease severity, the company claims that the sicker patients were ‘too far gone’ for the drug to work. If the stronger subgroup was more severe, the company claims the opposite: the drug only works on patients who are sick enough to benefit from the medicine. The history of medicine proves that neither is true
    - 3,4,2) . If the company truly believed that the result was far better in “mild” patients, it would have strictly enforced a “mild” requirement for its Phase III trials. “Is this what the company is requiring for phase III” is an important question to ask.
  + 3,5) Have the trial results been peer reviewed and published in reputable journals
  + 3,6) Is the data being compared correctly, open-label data must never compare it to rigorous controlled data (it is apples to oranges), can the data be relied upon for cross-trial comparisons?
    - 3,6,1) It would not be hard to instruct clinical trial sites of the importance of this Phase II data and tell them to err on the side of benefit. A control group removes this potential for bias, which is why it is used.

**Final checklist to determine functionality and probability of success**

* + 1) Is it a high affinity binder with crystal structure data that has been peer reviewed
  + 2) Does the PK look good, is the half life long enough, where is it distributed in the body does that match the area effected by the disease, if the half life is short can we be sure there are lasting effects once it is no longer present.
  + 3) Is the molecular size consistent with that of similar drugs that preform similar functions
  + 4) Is the target protein relevant to the disease, have other labs replicated this work or is the hypothesis based on disproven theories
  + 5) Does phase data show significant improvement, and statistically significant deviation from placebo
  + 6) What does P value show and most importantly is it less than 0.05
  + 7) Is the data being presented with an apples-to-apples comparison or apples to oranges; is an open label trial being compared to a placebo-controlled study
  + 8) Forgetting all the above-mentioned research, what are the chances it works, how many drugs targeting this disease have been failed vs how many have gotten FDA approval (this isn’t vital however should be considered especially if the disease in question has been particularly hard to find effective treatments for)