**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 that 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, as in the case of SAVA the market had 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 of what factors the market cap is derived 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's rights, this can give insight into experience and likelyhood of success or failure
* 5) The outcome of the FDA's decision (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 affected by the disease is irrelevant in 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 interaction 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 from a drug or medical device: it will be reflected in the data. (providing the trial is well constructed)

**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 are their prior ventures and academic contributions? Were they successful or failures
* 4) What is their approach? has this been tried before? what were the results of similar approaches in the past?
* 5) Has their chemistry work been published in any reputable medical paper
* 5,1) Has any published work been retracted by a publishing body, is that work relevent 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 their scientific work (duh)
* 7,1) whether or not the company has published preclinical data, or human clinical data prior 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 within the patient.
* 3) target's should have a clear relevence to the disease pathology.
* 4) when drugs form bonds with their desired targets (for example a protein), 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 function? thoroughly
* 5,1) The way to understand protein's 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 effects. This could make “binding” filamin A, dangerous. By interrupting any of the numerous natural functions of filamin A, a filamin A substrate may cause toxicity. However, if it is not causing toxicity then we must question if it is a filamin A binder! (confusing, check this)

6) Is there any literature? or are there any databased fundementals that allude to the drug having a viable mechanism?. In essence does similar research avaliable suggest that the proposed method is valid and based on principles outlined in theory or similar studies?

* 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 novel? or did the hypothesis come from a failed trial?
* 8) Is the molecule an apropriate size for it's intended 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. (I'd check this section for validity, It seems somewhat questionable to me)
* 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 to it's intended target
* 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 for example 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 it's reported potency consistent with that of similar drugs
* Are the company's 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, is not a peptide or protein based drug and therefore can be ingested orally (due to it's small size)
* 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 Gastro-intenstinal tract (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 long enough for it to be absorbed, distributed and take effect
* 2,5) Where do the highest concentrations of the drug accumlate, and do these areas match the desired target area for this disease, 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 does 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 random 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 have led to many failures. The narrative typically applies as follows. If the subgroup chosen has a milder disease severity, the company might claim that the sicker patients were ‘too far gone’ for the drug to work. If the stronger subgroup had a higher severity, 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 be compared to rigorously 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. (unsure of this statements validity)

**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 this match with the areas affected by the disease? if the half life is short can we be sure there are lasting effects once the drug is no longer present in the patients system?
* 3) Is the molecular size consistent with that of similar drugs that perform similar functions?
* 4) Is the target site relevant to the disease? have other labs replicated similar work? or is the hypothesis based in theory or already disproven theories? (not always proteins)
* 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 (I would say: is it low enough to show valid statistical significance)
* 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 ( are the data sets valid for comparison)
* 8) Disregarding all the above-mentioned research, what is the success rate for similar attempts to treat this disease, how many drugs with a similar aproach to this have gotten FDA approval? (this isn’t necessarily determining of our drugs success, however should be taken into account, especially if the disease in question has been historically difficult to find effective treatments for) as (This could be indicitive of hurdles to solving a specific problem.) ( Does the drug in question address the main issues people have had in the past with creating an effective treatment for this particular disease?)