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Don’t Wait Until It’s Too Late: Target Product Profiles and Avoiding Common Clinical Trial Mistakes

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Any reference to persons or companies living or dead is entirely coincidental.

What is a Target Product Profile (TPP)? and Why is it important?

- TPPs are used to develop a product based on desired characteristics.
- TPPs will eventually be used in the development of the “label” and the indication, which is your license to advertise and be reimbursed.
- The TPPs are living documents and should be started prior to the pre-clinical phase of R&D.
- They contain the go/no go criteria for moving a product forward.
- Required elements are indication, dosing frequency, route of administration, efficacy, tolerability (safety), and convenience (if applicable).
- They are also beneficial when pitching to VC community.

Product TPP for Asthma

Variable	Minimal	Optimal
Priority Attributes		
Efficacy	FEV1 >10% improvement	FEV1 >25% improvement
Receptor Binding	Single receptor	Multiple Receptor (Selectivity)
Tolerance/Safety	Non-inferior to SOC	Superior to current SOC
Convenience	Non-inferior to SOC	Superior to current SOC
Dosing Frequency	≥2 times daily	Once Daily
Route of Administration	Oral	Inhaled

FEV, forced expiratory volume exhaled in the first second; SOC, standard of care

Product TPP for Pulmonary Arterial Hypertension (PAH)

Variable	Minimal	Optimal
Priority Attributes		
Efficacy	>10% improvement in 6-minute walk distance	>25% improvement in 6-minute walk distance, Improved time to clinical worsening
Population	Adults only	Adults, children, women of child-bearing potential
Tolerance/Safety	Non-inferior to SOC	Superior to current SOC
Dosing Frequency	2-3 Times Daily	Once Daily
Route of Administration	IV, Oral	Inhaled

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Clinical Trial Design Considerations

Trial Considerations

Monotherapy	
Pros	Cons
True comparison with placebo; ideal for testing new agent with efficacy similar to, but fewer and/or less severe side effects than, SOC	Will not evaluate DDI or side effect profile with SOC
Allows inclusion of patients intolerant of SOC	Placebo effect is often present
Justified only in short-duration evaluations	Patients receiving SOC will be excluded from participation
	Delay in starting SOC for newly diagnosed patients
	Will require a stronger rationale to exclude SOC as the duration of the study increases

Add-on to SOC	
Pros	Cons
No ethical concerns about lack of SOC	Potential improvements in the safety and tolerability profile of the new agent may not be discernible over those of the current SOC
Permits evaluation of DDI and side effects	
Permits evaluation of potential additive or synergistic efficacy effects	

Noninferiority/Superiority to SOC	
Pros	Cons
A head-to-head comparison with SOC is ideal to understand efficacy	For superiority: narrow window for improvement vs. SOC
Avoids ethical concerns of a placebo-only arm	For non-inferiority: margins and size

SOC, standard of care; DDI, drug-drug interactions

Issues Encountered at Phase Ia (First in Human)

- Formulation issues (including bioavailability across oral, IV or lack thereof)
- Product stability
- Narrow therapeutic index
- Immunogenicity including cytokine storm/release syndrome (more common with proteins, can be fatal and almost sunk a large CRO)
- Single ascending dose and multiple ascending dose (with food effect, if oral)
- PK (C_{max}, T_{max}, AUC, $T_{½}$)

Biologics Anaphylaxis

- Biologic drugs are often dosed with antihistamines to reduce risk of allergic reaction.
- A patient in hospital had anaphylaxis post dose requiring epinephrine. The vial of biologic was returned to the mfr. for analysis. Once the vial was inspected for authenticity and confirmed authentic, a vial of the same lot held in storage was pulled.
- The vials were sent to the analytical chemists for analysis. The vial from the hospital subsequently showed high levels of clumping, e.g. trimers, aggregates, while the stored vial did not.

Biologics Anaphylaxis (Cont.)

- Once the analyses were conducted, the hospital pharmacists and nurses were asked the procedure for sending vials of biologics to the wards. It turned out that the hospital's pneumatic system was used.
- The g forces that the vials encountered on the way up and on the way down were high enough to cause the proteins to clump which caused the anaphylactic reaction.
- From then on, biologics were hand carried by technicians from the pharmacy to the wards.

Issues Encountered at Phase Ib

- Drug-drug interactions
- Endpoints [PD, Validated Biomarker, Safety, Survival (oncology, rare disease)]
- Animal model not representative of human disease and cannot predict immunogenicity in humans
- Expanded access protocol (rare disease or PHE)
- Illegal administration of trial drug to patients not enrolled in the trial

- In exceptional circumstances, skip Phase II
  - 1b Study Power assessment
    - Not likely adequately powered for subgroups
  - Model informed drug development (work with FDA)
  - FDA approval before proceeding

Phase II Clinical Trial Planning

Considerations

- **Clinical Study design**:
  - population (inclusion and exclusion)
  - size
  - location
  - duration (preclinical coverage)
  - Phase 2A (proof of concept) and Phase 2B (dose-ranging)
  - arms
  - interim analysis
- **Pediatric Plan**: initial Pediatric Study Plan (iPSP) to FDA by EOP2 (EMA Paediatric Investigation Plan (PIP) by EOP1); prospect of direct benefit (efficacy) before pediatric dosing
- **CMC: bridging** (formulation, manufacturing site, manufacturing processes) and how much can you get done in Phase 2?

Phase II Clinical Trial Planning

Considerations

- **Clinical Outcomes Assessments (COA) and biomarkers:** Have you **validated** them? In the disease and population targeted ("**fit for purpose**")?
- **Regulatory strategy:** Anticipated/necessary **FDA** interactions. (Type C Clinical, CMC and COA +) EOP2. Indication-specific Guidance and Phase 3 endpoints.
- **Target Product Label:** By EOP2, you should create a TPL from the TPP
- **Clinical Trial Diversity Plan:** due by EOP2

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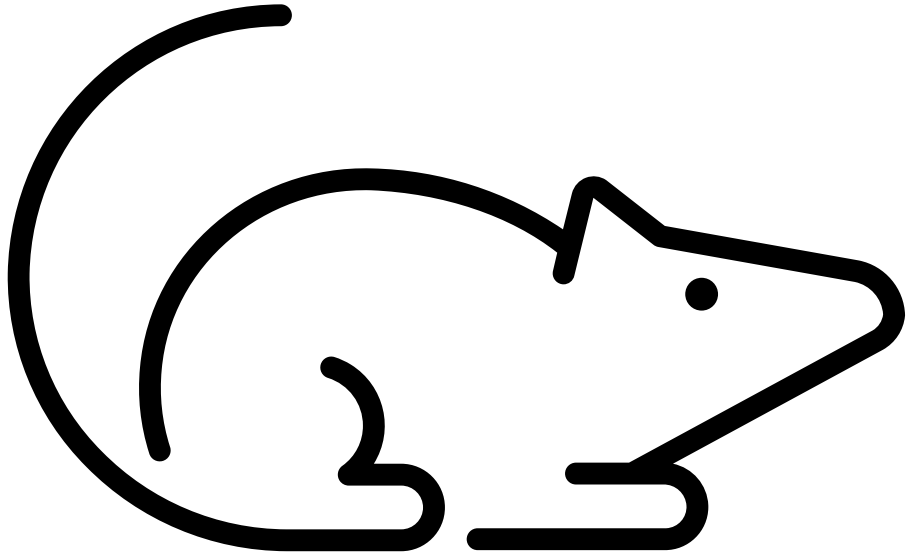
Clinical Trial Pitfalls: "All successful clinical trials are alike; each unsuccessful clinical trial is unsuccessful in its own way"

(apologies to Tolstoy)

“Don’t wait until it’s too late”: Phase 2 Pitfall Example

- Failure to test drug in a validated animal disease model
- **Why?**
  - Phase 2 is typically the time to apply for Orphan Drug (ODD) and Fast Track Designations
  - Usually not enough clinical efficacy evidence, so animal efficacy is key
  - *Example:* Company couldn’t get ODD or Fast Track because their preclinical efficacy studies in an animal model of human disease were conducted using a back-up compound



“Don’t wait until it’s too late”: Phase 2 Pitfall Example

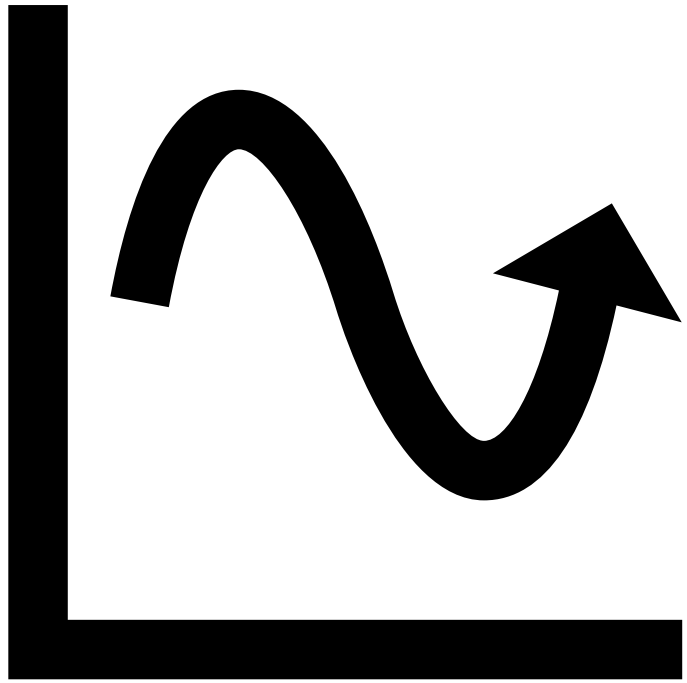
- Ignoring that a Phase 2b trial might be needed as **supportive evidence** in a marketing application and should be powered and conducted like a **pivotal trial**
  - *Example*: A company’s drug had 1 successful and 1 failed phase 3 trial; their phase 2b trial was successful but underpowered and used an unvalidated pharmacodynamic biomarker as an endpoint. The 2b trial data could not be used as **supportive evidence**.
  - **How did this happen?**
  - Company was overconfident that they would “win” in phase 3 and didn’t think they would need to rely on the Phase 2 results.

“Don’t wait until it’s too late”: Phase 2 Pitfall Examples

Failure to set CMC specifications before/during Phase 2

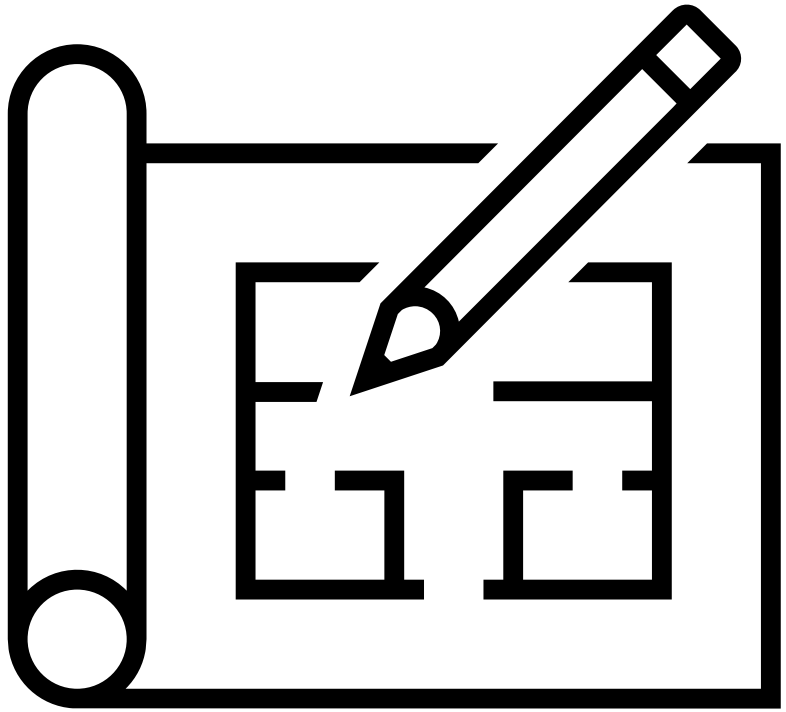
- *Example*: Company had a difficult tech transfer and an innovative botanical drug; the drug concentration varied by a factor of 3 going into Phase 2 studies. The company thought it was too early to set tighter specs. FDA disagreed and put them on **CMC Clinical Hold.**

- **Why did this happen?**
  - Company was afraid to talk to FDA. They thought “what they don’t know won’t hurt us.”
  - CMC group hadn’t discussed drug classification with FDA –they thought it was just a botanical, but it turned out FDA considered it both a botanical and a biologic.



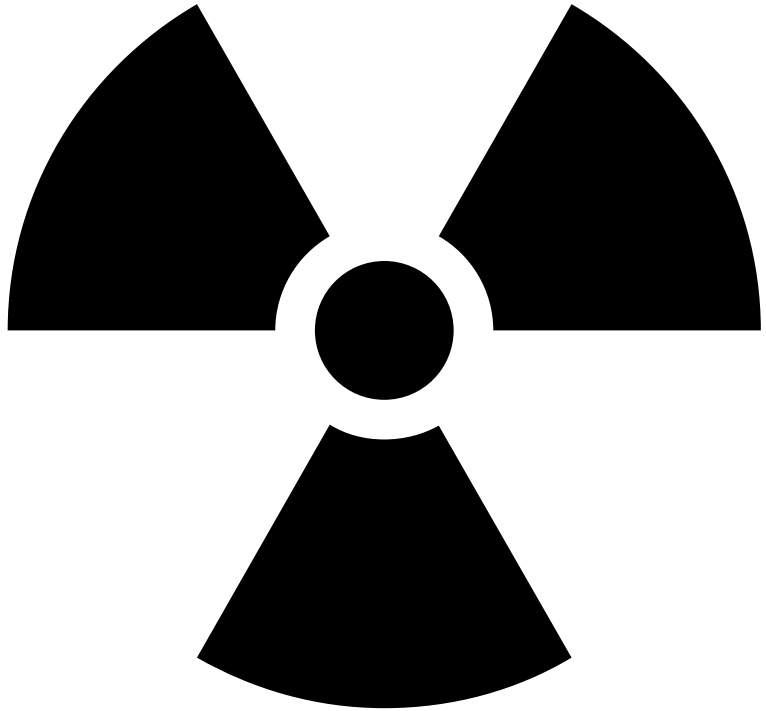
“Don’t wait until it’s too late”: Phase 2 Pitfall Examples

- Failure to have design controls for a digital device prior to Phase 2
  - **Why?**
  - You cannot validate a device/biomarker in Phase 3 if you want it as a primary or key secondary endpoint on the label
  - *Example:* Company had digital device that they were testing in Phase 2b without design controls or clinical and analytical validation plan agreed on by FDA – project was scrapped.
  - **How did this happen?**
  - Company wrongly thought that they could conduct studies under a Research Use Only (RUO) Investigational Drug Exemption and fly under FDA radar and still put the results on the label.
  - Very common mistake among academic researchers creating devices.



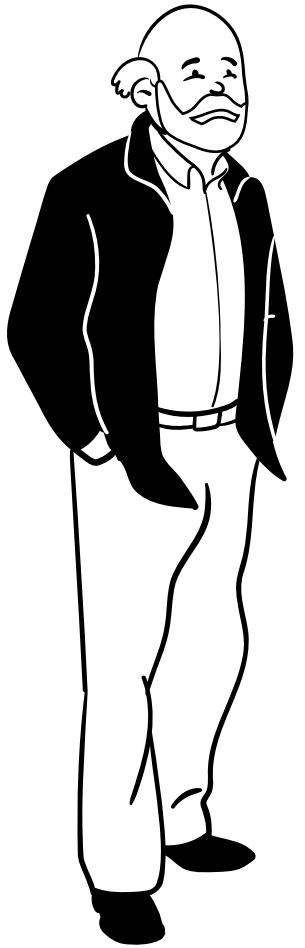
“Don’t wait until it’s too late”: Phase 2 Pitfall Examples

- Failure to accurately assess the risk of a device
  - *Example:* Company had digital device that did not pose any physical risk to the patient but was intended to diagnose a disease – they suggested to FDA that it was a Class I (low risk device). FDA said it was class III (highest risk)
  - **Why did this happen?**
  - Company did not consider misdiagnosis in their risk assessment.



“Don’t wait until it’s too late”: Phase 2 Pitfall Examples

- Failure to oversee data quality and integrity
  - *Example:*
    - Company had a primary histologic endpoint.
    - Slides were read by a famous overseas pathologist.
    - He bragged about the high, inter-reader reliability scores of pathologists on his team who were “independently” reading slides.
    - Turns out the “expert” was re-reading his colleagues’ scores and changing any that he didn’t agree with.
  - **Why did this happen?**
  - Inadequate sponsor oversight and inadequate understanding of data integrity
  - Failure to understand consensus read
  - Trusting “experts” blindly
  - Not obtaining FDA input on histologic methods



Phase III Clinical Trial Planning

- **Clinical Study design**:
- **Trial population** –Needs to be as representative as possible of disease population but not too sick to achieve efficacy or safety results (stratification by risk category)
- **Trial size** – Minimum of 1500 patients total exposed to study drug and 100 exposed for one year for drugs that treat common illnesses (ICH E1A)
- **Trial location** – Phase 3 trials are typically multi-site; if some sites are overseas, you need to understand the countries' regulations and ensure that FDA will accept the data
- **Duration** – Most Phase 3 trials are one year or longer
- **Interim analysis** – You will spend α on an interim analysis –Your final results will need to be more significant than $p<0.05$ (2-sided)

“Don’t wait until it’s too late”: Phase 3 Pitfall Example

- Ignoring the concept of clinical meaningfulness
  - **Why?**
  - Clinical meaningfulness can be difficult to grasp because it involves psychometric analyses that are scrutinized by the Clinical Outcomes Assessment (COA) group at FDA.
  - *Example*: A company’s drug achieved statistically significant efficacy results in Phase 3. The FDA did not consider the results clinically meaningful based on Phase 2 patient interviews. The company received a Complete Response (CR) letter.
  - **How did this happen?**
  - Company had not done enough COA work during Phase 2 to determine the clinical meaningfulness of their drug.

“Don’t wait until it’s too late”: Phase 3 Pitfall Example

- Insufficient Vendor Oversight and Ignoring 21 CFR Part 11 (Quality)
  - **Why?**
  - Companies assume large CROs do adequate sub-vendor oversight
  - *Example*: A company’s primary Phase 3 endpoint included an MRI score. CRO contracted a radiology vendor to read MRIs. Three months before BLA submission, an unblinding episode was discovered that involved readings of MRIs on 35 patients and lack of audit trail.
  - **How did this happen?**
  - Company had not conducted regular vendor audits because they thought the CRO had done it. When an audit was finally conducted by the sponsor and the CRO, the vendor failed. Company elected not to inform FDA (“what they don’t know can’t hurt us”). The drug failed on efficacy even before the FDA had a chance to perform a clinical data audit.

In Summary

- Sometimes **clinical trial failures** are unavoidable, but many are **avoidable**
- They **cost millions and even billions of R&D dollars** and can crush good preclinical development
- **Common causes** are:
  - Not talking to the FDA early and often
  - Not conducting animal studies in a disease model with lead compound
  - Not validating biomarkers, devices and endpoints in Phase 2
  - Not bridging CMC changes in Phase 2
  - Not considering the patient voice early (clinical meaningfulness, clinical trial diversity, PROs)
  - Inadequate oversight of vendors and experts
  - Inaccurate data (lack of data integrity)
  - Conducting too many interim analyses
  - Not having a good TPP

  - **You can avoid these mistakes and succeed!!**

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Q&A

Audience Poll

- What are some types of Phase 2 trials (select one or more)?

- A) Proof of Concept Trial
- B) Dose Ranging Trial
- C) Single Ascending Dose Trial
- D) Confirmatory Trial

Audience Poll (Answer)

- What are some types of Phase 2 trials (select one or more)?

- A) Proof of Concept Trial (Phase 2a)
- B) Dose Ranging Trial (Phase 2b)
- C) Single Ascending Dose Trial (Phase 1)
- D) Confirmatory Trial (Phase 3)

Audience Poll

- When is the best time to validate Patient Report Outcomes instruments and biomarkers that will be used as pivotal trial endpoints?
- A) By the end of Phase 2
- B) By the end of Phase 3
- C) Post-marketing
- D) Before pre-clinical work is conducted

Audience Poll (Answer)

- When is the best time to validate Patient Report Outcomes instruments and biomarkers that will be used as pivotal trial endpoints?

- A) By the end of Phase 2
- B) By the end of Phase 3 (too late)
- C) Post-marketing (way too late)
- D) Before pre-clinical work is conducted (likely too early)

Audience Poll

- You have a patient reported outcome instrument that you are using in Phase 2 clinical trials for Disease B. It has previously been validated with publications in Disease A.

- You should:
- A) Attempt to validate it during Phase 2 trials of Disease B
- B) Not worry about validating it since it has already been validated for Disease A
- C) Wait until Phase 3 to validate it
- D) Schedule a meeting with COA Division of FDA before the end of phase 2

Audience Poll (Answer)

- You have a patient reported outcome instrument that you are using in Phase 2 clinical trials for Disease B. It has previously been validated with publications in Disease A.

- You should:
- A) Attempt to validate it during Phase 2 trials of Disease B
- B) Not worry about validating it since it has already been validated for Disease A (not validated for B, thus, not fit for purpose)
- C) Wait until Phase 3 to validate it (too late)
- D) Schedule a meeting with COA Division of FDA before the end of phase 2

Audience Poll

You find a major quality issue during a routine inspection in Phase 3 that could compromise the data integrity of your primary endpoint. Do you?

- A. Conduct an internal investigation immediately, inform FDA, and commit to developing and sharing a CAPA (corrective plan) with them
- B. Wait to talk to the FDA until and if they discover the issue themselves during an audit.
- C. Isolate the data from patient samples affected by the quality error and either live with smaller n or enroll more patients. Perform sensitivity analyses with and without the affected samples.
- D. Submit the NDA, hope you get an approval, then hope FDA never discovers it.

Audience Poll (Answer)

- You find a major quality finding during a routine inspection during Phase 3 that could compromise the data integrity of your primary endpoint. Do you?
- A. Conduct an internal investigation immediately, inform FDA, and commit to developing and sharing a CAPA (corrective plan) with them.
- B. Wait to talk to the FDA until and if they discover the issue themselves during an audit. (Really bad)
- C. Isolate the data from patient samples affected by the quality error and either live with smaller n or enroll more patients. Perform sensitivity analyses with and without the affected samples.
- D. Submit the NDA, hope you get an approval, then hope FDA never discovers it. (Not advisable)

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Back-up Slides

Phase I Clinical Trial Planning

- Considerations
  - SOC, where?
  - Dose (NOAEL x safety factor)
  - Therapeutic index
  - Arms
  - Route of administration
  - NHVs vs PTs
  - Enrollment criteria
  - Endpoints
  - PD
  - Efficacy determination (likely underpowered)
  - Rare/orphan disease
  - Safety
  - AEs
  - Rescue meds
  - Staggered start
  - FDA consultations
  - Stopping rules
  - Drug induced liver injury
  - Immunogenicity
  - Named insured

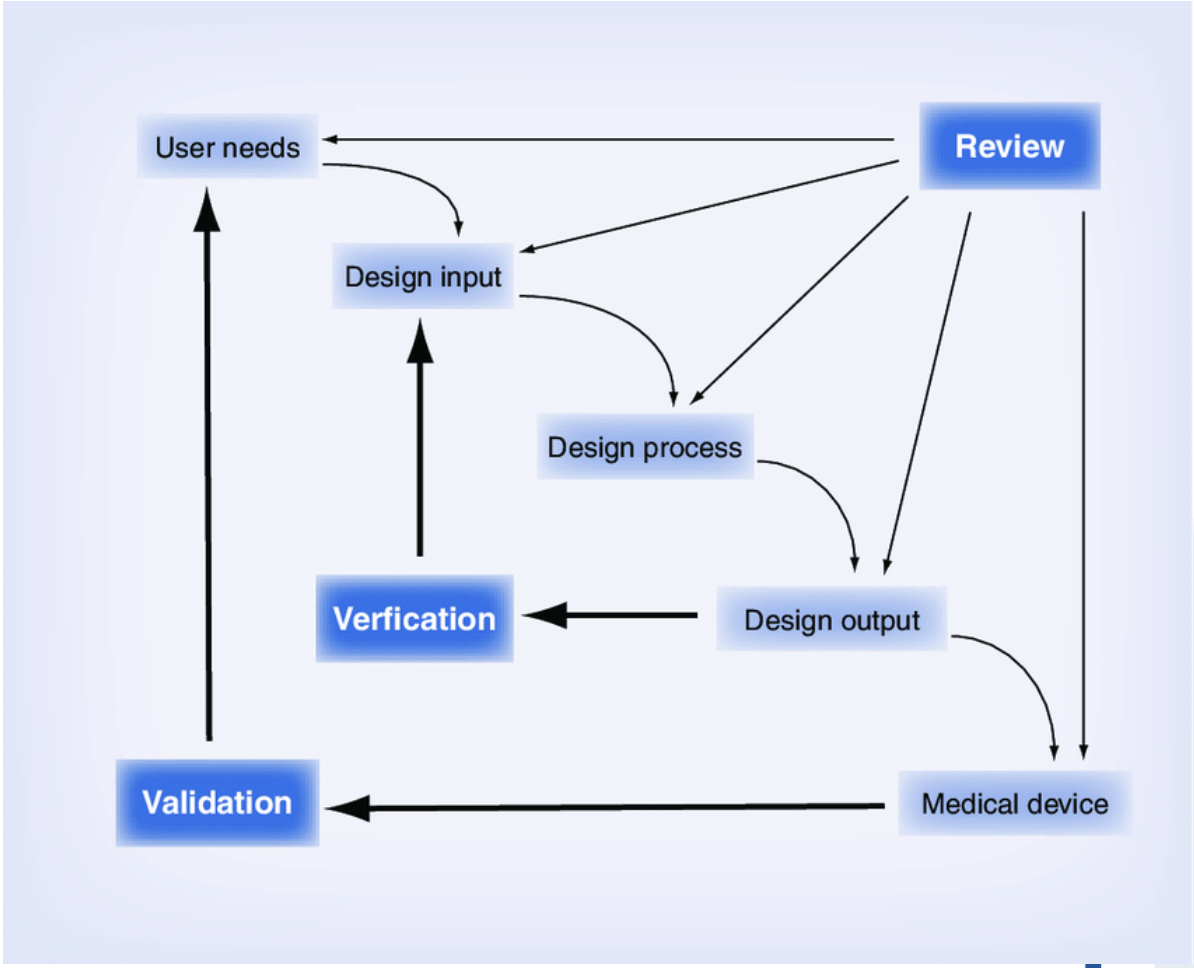
Phase III Clinical Trial Planning

Considerations

- **Marketing Application Submission**:
- What do you want on your label and can you support it with data?
- Are there major safety concerns that could result in black box warning, Risk Evaluation and Mitigation Strategy (REMS) and/or Post-Marketing Requirements (PMR)?
- Will there be an Advisory Committee – (yes, if new molecular entity with significant risk)? If so, you need to arrange for consultants to help you prepare starting one year in advance
- What will the launch price be in different markets?
- Have you talked to HTA's in EU and/or payers in US?
- Have you completed your pediatric study plans?

Design Controls (21 CFR 820.30) – 3rd most common cause of FDA violations

- FDA Guidance: "Design controls are a component of a comprehensive quality system that covers the life of a device. The assurance process is a total systems approach that extends from thedevelopment of device requirements through design, production, distribution, use, maintenance, and eventually, obsolescence." (Design Control Guidance For Medical Device Manufacturers | FDA)
- Design and development planning
- Design input (intended use and user needs)
- Design output (verification and validation)
- Design review
- Design transfer (into product specifications)
- Design changes
- Design history file



TPP for a Multi-parameter Cardiometabolic POC Device

- Example
- https://researchonline.lshtm.ac.uk/id/eprint/4663670/1/Development%20of%20a%20target%20product%20profile%20for%20a%20point-of-care%20cardiometabolic%20device.pdf

Study Design Considerations for New IPF Drugs

- Table 1
- https://www.atsjournals.org/doi/pdf/10.1164/rccm.201903-0592PP
- https://www.atsjournals.org/doi/full/10.1164/rccm.201903-0592PP