Is a specific BP study required or can these measurements be incorporated into another study?

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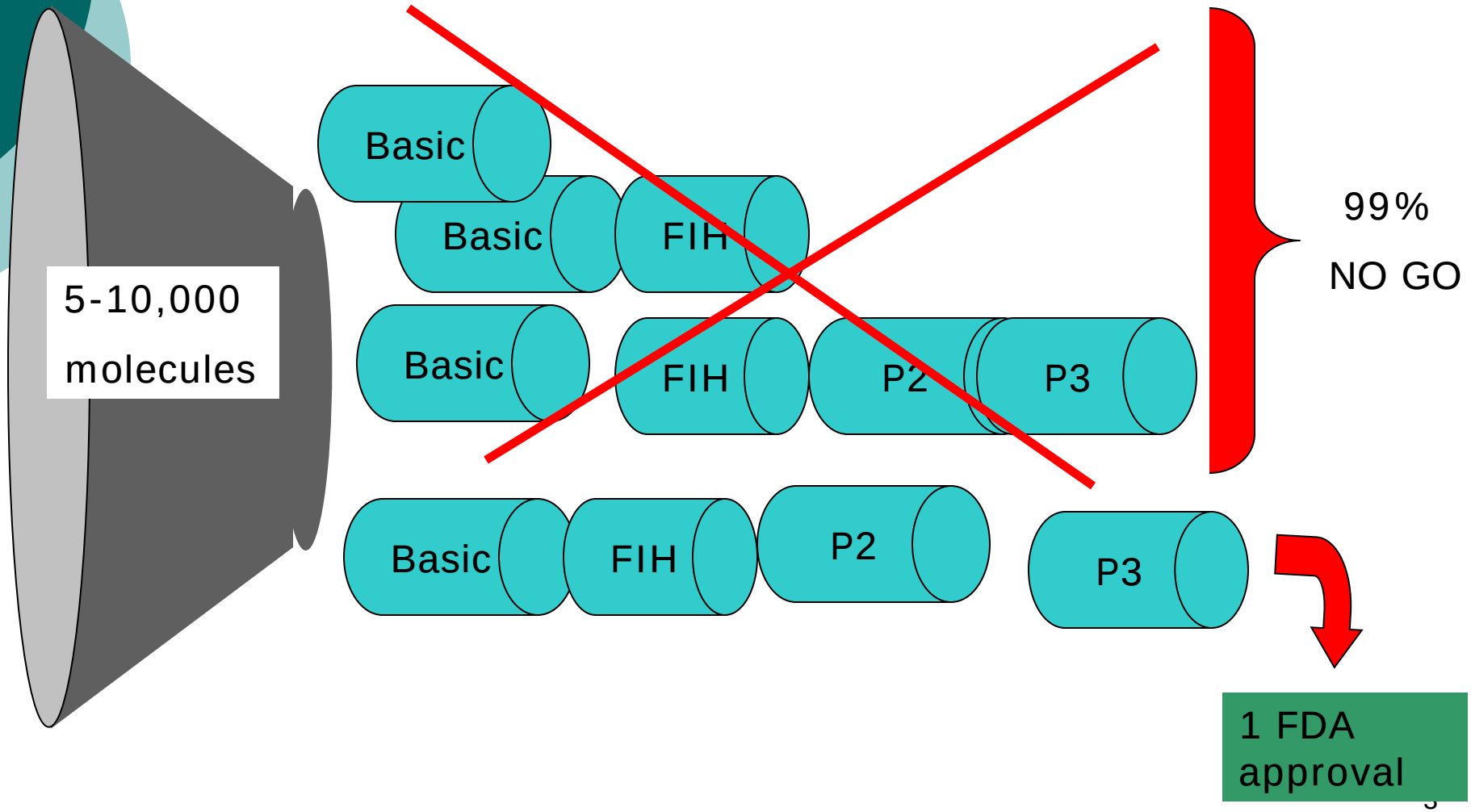
Outline

- QT vs BP as a risk factor
- Assessment of BP in Phase 1-2 studies
- Improvements in BP measurements in clinical trials
- Dedicated BP studies

Drug development is inherently a highly selective process…..



Understanding BP behavior of drugs in important

- Assess benefit risk in patients by allowing:
  - Precise mean and outlier estimate in BP
  - Using BP as a component of risk prediction
  - No consistent relationship between BP rises seen in NHV and patients
- Inform product labeling and patient management with BP lowering agents if needed
- Phase 3 data obtained in intended population is preferred basis for labeling BP effects

QT signal ≠ BP signal

	QT Signal	BP Signal
CV risk exists	Yes. TdP	Yes
Signal obtainable in typical phase 1/2	No	Yes
CV risk translatable from Phase 1 to Phase 3	Yes	Maybe
Timeline for risk	Short	Long
Risk can be mitigated	No	Yes
Treatment can be monitored	Maybe	Yes
Implications of + study	Definable	Harder to define

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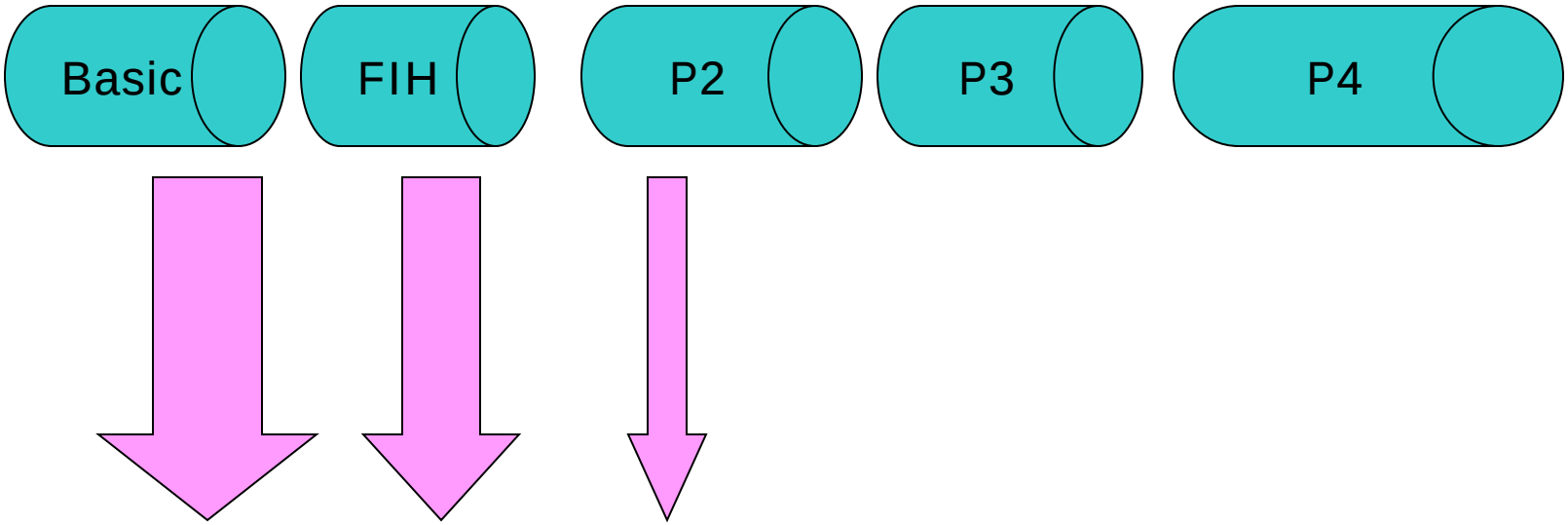
BP signals usually a concern early



Most signals around BP arise early and fewer new signals emerge as development proceeds. Few drugs get approved without a good understanding of their BP effects.

Prior data may focus attention early on BP

- Another molecule in same MOA with liability eg Torcetrapib
- Target is in similar or related pathway
- Off target effects suggest a BP signal
- Preclinical safety studies to enable first human studies show a CV or BP effect

Phase 1 studies are already designed to detect modest BP signals

- Critical to have optimal BP measurement since sample sizes are small in Phase 1.
- Appropriate analysis strategy
- Automated identical devices- validated and remove observer bias
- Hourly triplicate readings with a automated device
- Simultaneous PK readings
- Physical activity is minimized to reduce variability
- Phase 1 studies have 2-4 fold higher doses than anticipated clinical dose
- Thorough QT study can serve as a context to assess BP carefully (see Miragebron)

Detection of blood pressure signals in early development

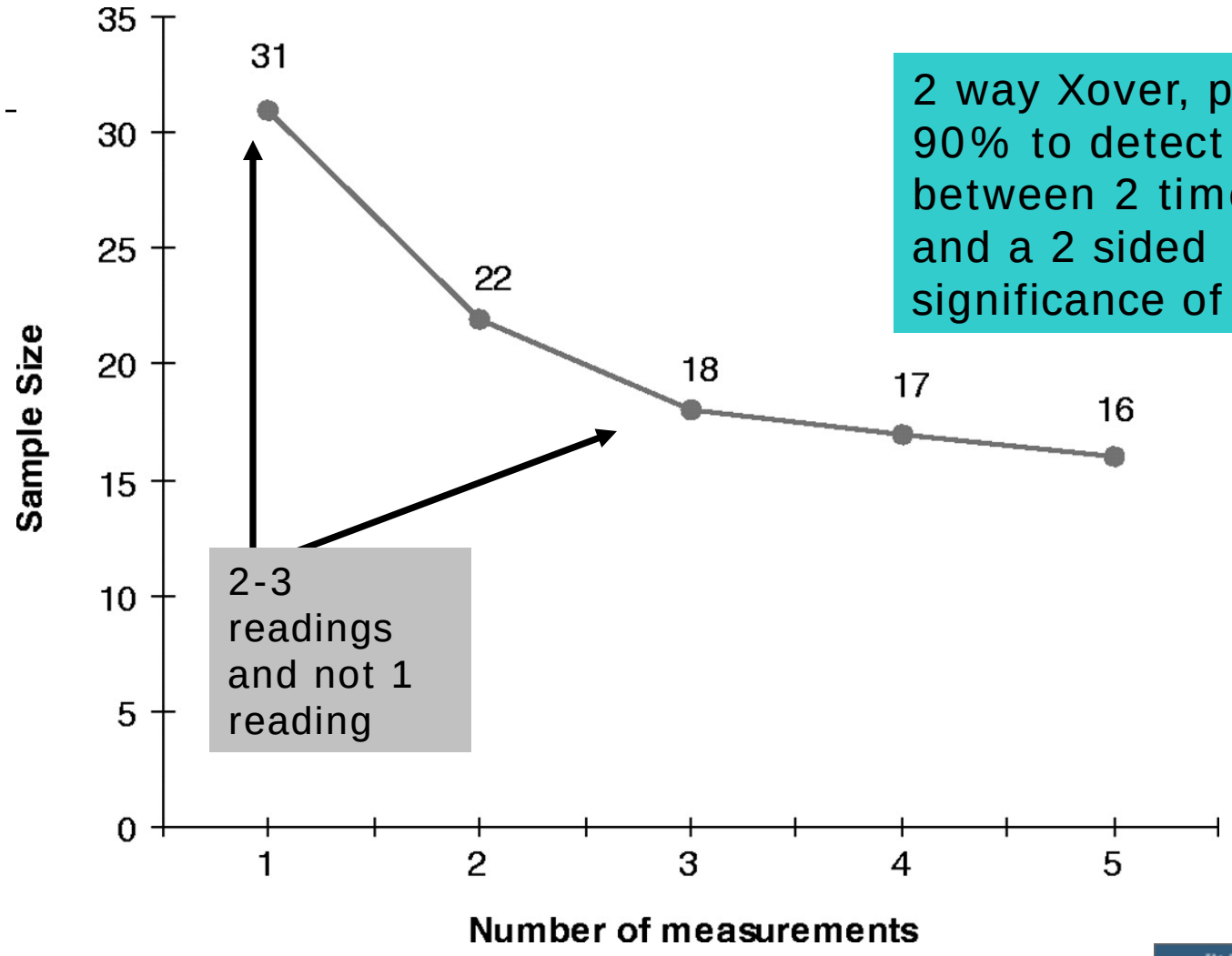
- Blood pressure signals can easily be detected in early phase studies in healthy volunteers
- Historically, these signals have been detected using standard manual or automated cuff measurements
- With more advanced monitoring techniques, more precision and sensitivity can be expected
- Preclinical and early clinical blood pressure signals can and should be confirmed and more fully characterized in later phase studies

Precision in Phase 1 studies-

- Randomized, DB cross over 2 periods
- Washout was 1-7 days
- 10 healthy men and 10 healthy women, 18-50yrs
- Interventions: Phenylephrine in 3 increasing does, 0.2, 0.4 and 0.8 ug/kg/min. NS in 3 increasing infusion rates identical to PE.
- Order and method of BP were randomized.
- Manual readers blinded to automated readings
- BP measurement: Triplicates (Q2m) start at 20 minutes after start of infusion for each method. Each dose of infusion lasted about 35 minutes.

Terra SG, 2004.

Figure 1. Influence of repeated number of blood pressure measurements on sample size.



Terra S G et al. J Clin Pharmacol 2004;44:457-463

Figure 2. Mean blood pressure by phenylephrine dose and time (N = 20).

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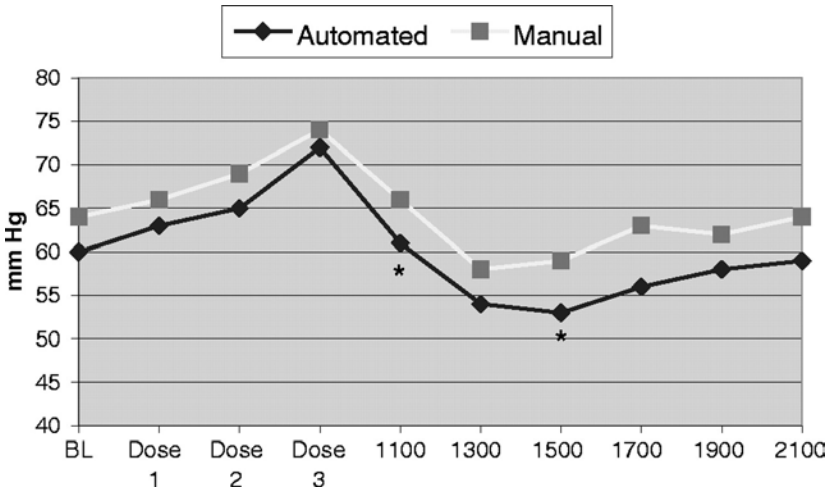

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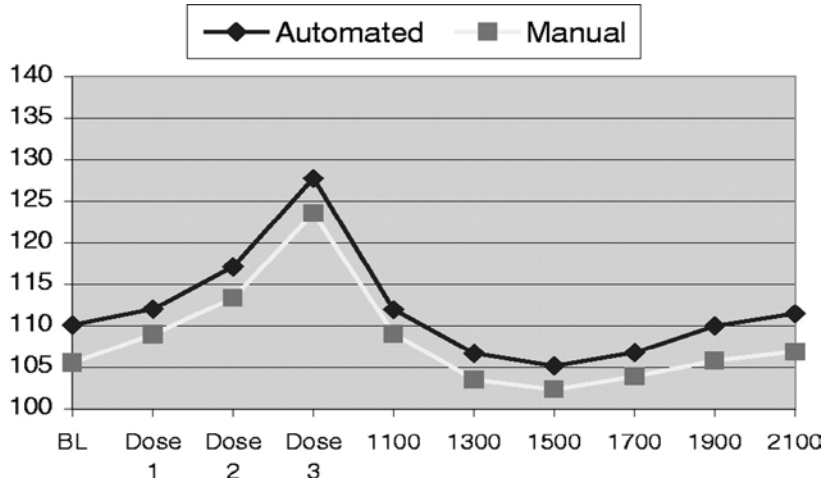

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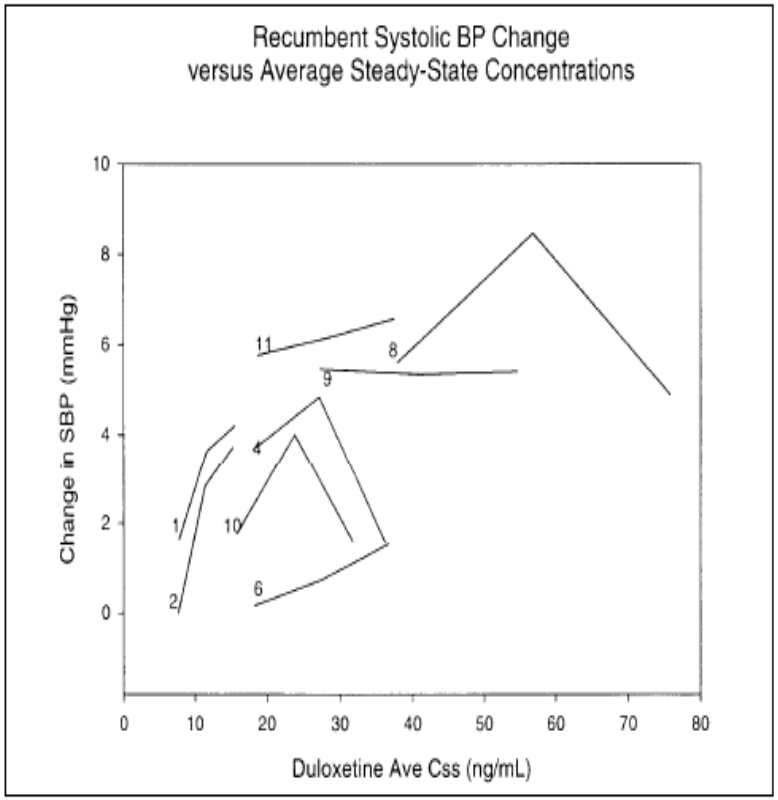
Case example: duloxetine



Vital sign measurement	Treatment (mg BID)	Mean	Mean change (from lead-in)
SBP (mmHg)	PBO lead-in	119.7	
	Duloxetine 20		3.0*
	Duloxetine 30		4.5*
	Duloxetine 40		3.7*
	PBO washout		1.3
DBP (mmHg)	PBO lead-in	67.7	
	Duloxetine 20		1.5*‡
	Duloxetine 30		1.7*‡
	Duloxetine 40		2.9*‡
	PBO washout		1.6*

Sharma et al JCP 2000

N = 12 healthy males; 8 active, 4 PBO

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Are there ways to improve BP monitoring and assessment in early drug development?

- Enhance BP monitoring standardization and frequency in areas outside of CV
- Standardize equipment and site training especially for multicenter multi country studies eg phase 2
- Time data to capture average BP effects rather than min or max
- Conduct PK BP modeling assessment in Phase 1

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Questions about dedicated BP studies?

- Dedicated BP studies may help to:
  - Quantify 24-h average BP
  - Assess nocturnal BP
  - Obtain BP during daily activities
- How will we use BP data from dedicated studies?
- How valuable is a dedicated BP study for drugs that will be used for a short period eg 2-4 weeks?
- What population will these studies be done?
- Do we include a positive control?

Is assay sensitivity required in Phase 1-2 studies ?

- Consistent predictable effect on BP in NHV is needed for an agent to be considered for assay sensitivity?
  - Very few studies have examined this
- Placebo effect may lower BP in some situations complicating BP assessment

Summary

- Current BP assessment in Phase 1-2 likely will capture most BP signals that are modest in size and confirmed in later patient trials
- PK BP modeling for all phase 1 data may assist in detecting BP signals.
- Further improvements especially in Non CV drugs can be made by standardization of measurement properties
- Since benefit risk is determined in patients intended for the drug, characterization of BP effects should be performed in patient populations.
- Dedicated BP study will not remove necessity to continue characterization of blood pressure throughout development process.

- backups

Relevance of mechanism to BP Signal

- A basic assessment of potential causative mechanism of raising should be conducted during development
- Drugs that affect BP through alterations in measureable neuro-hormones eg catecholamines would be of concern even if BP signal was relatively small.
- Drugs that raise BP through salt and water retention while treatable with diuretics would be of concern in patients at risk of or with a history of HF.
- Clues to mechanism may be obtained in phase 1/2 through careful AE assessment eg edema, renal function.