# **Breakout Session Overview –** Dose translation from preclinical models to clinical doses

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Unmet Regulatory Needs and/or Question of Interest Statements:

- Compounds test; Biomarkers, endpoints in hindsight typically, doing so in vitro requires high throughput to enable dose responses; need to have confidence in BM's
- Identifying right doses for combinations, can clinical trial simulation tools be used with preclinical studies (allow more room to fail); Reg affairs to recommend use to predict application. Dose translation from preclinical models to clinical doses to preclinical
- COU related to regulatory purpose, efficacy vs safety; what needs to be done to extrapolate efficacy vs safety; haow can models be used to select appropriate/predict what dose would work in humans, (in vitro to in vivo)
- Developing standards similar to in vivo models (i.e. NOAEL , HNSTD with dose responses, applying factors to extrapolate to humans for translation (e.g. neutrophil example)
- Pharmacometric models to predict clinical doses
- FDA provided guidance when no pharmacologically relevant model. 10% rec activation or 50% receptor inhibition – Does this scientific approach still apply to in vitro MPS models
- Extrapolation of in vitro models and human data, models may Building confidence in ry, and how much heterogeneity is needed to be able to apply QSP modeling? Even if have the throughput – How are these models validated without going through hugh hurdles, is there some standards that can be employed

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Opportunities:

- Multi-site benchmarking, consortia based activities
- Clinical data are considered ranges, generation of large data sets to enable development of ranges, tested again lg biobanks, human as well as preclinical
- Using data animal and non-animal together to help build confidence, the target would be key
- Greater sharing of data, shared validation data sets, similar definitions, across precompetitive consortia
- Measurement of dose concentration in models, to help extrapolate data within and across labs and publishing and sharing.

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Gaps and Challenges:

- ..Correlation and measurement of drug concentrations in systems, not easy to do, should this be a standard to measure to understand exposure dynamics and dose response data (e.g. cMax in systems)
- Lack of consistent data structure in reporting of data, incomplete meta data, consistency in terminology e.g., imaging data that would correlate with other endpoints
- What are we benchmarking against?
- Translation of in vivo to in vitro biomarkers
- Modeling - how much standardization needed, how to incorporate various data types to get good outputs ve generating confusion and less than optimal data.
- Models that incorporation of metabolism (gaps and challenge), depends on COU and questions that need to be answered; what metabolites are getting generated and having a functional output
- Defining the models, understands trends and if fit for purpose or COU needed models
- Differences in clinical vs phenotypic endpoints, conversion between these.
- Demonstration of what an efficacious vs safe dose range when extrapolating to the clinic