12 – Pharmacogenomics

Presentation to APEC Preliminary Workshop on Review of Drug Development in Clinical Trials

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Disclaimer: the information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop
Overview

- Introduction to Pharmacogenomics (PGx) and “Individualized Therapy”
- Examples of applications of PGx
- Regulations and Guidance
- PGx requirements for clinical trials
Because investigators have previously been unable to determine which participants will benefit from a drug, trials have had to be large enough to show statistically significant responses among all subjects.
- Failure rate in clinical trials is \( \sim 50\% = \frac{1}{2} \) cost of total development costs

- Typically efficacious in only 40 to 60 percent of patient population
- Ideally, physicians would test each patient BEFORE treatment to prevent from lack of efficacy and/or avoid adverse drug reactions

- Human Genome Sequence brought about increased understanding of tools to decipher DNA

- Costs of genomic sequencing and bioinformatic analysis are decreasing, while capabilities growing exponentially
Pharmacogenomics Concept

Genetic profile for non-responders or toxicity

Treat with alternative drug or dose

Genetic profile for favorable response

Treat with conventional drug or dose
Examples: Drug Metabolism

- CYP2C19 and CYP2D6 Variants – Poor vs extensive metabolizers
- N-acetyltransferase - slow and fast acetylators
- Deficiency of dihydropyrimidine dehydrogenase (DPD) activity - Capecitabine
- Glucose-phosphate dehydrogenase (G6PD) deficiency - Rasburicase
- Thiopurine methyltransferase deficiency or lower activity - Azathioprine
- Homozygous UGT1A*28 allele - Irinotecan
Examples: Drug Target

- C-KIT expression in GIST - *Imatinib*
- CCR5 - Chemokine C-C motif receptor on human T-cell - *Maraviroc*
- EGFR expression - *Erlotinib, Cetuximab*
- Her2/neu expression - *Trastuzumab*
- Philadelphia (Ph1) chromosome - *Busulfan*
Regulatory Guidance

- **FDA**: Guidance for Industry - Pharmacogenomic Data Submissions

- **EMEA**: Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling

- **ICH Topic E15**: Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories
  - To ensure consistency in the terminology used by the different regions

- **Japan**

- **Health Canada Guidance**: Submission of Pharmacogenomic Information
 Definitions

- **ICH E15**: The study of variations of DNA and RNA characteristics as related to drug response

- **HC Guidance**: Pharmacogenomics is the identification and study of genes and their corresponding products which influence individual variation in the efficacy and/or toxicity of therapeutic products, and the application of genomic information to help inform therapeutic product development and/or clinical application. This may include:
  - choosing the most appropriate therapeutic product for a patient;
  - selecting optimal dose; and/or
  - identifying those at risk for unexpected or more frequent adverse drug reactions
PGx and Division 5 of the Regulations

- C.05.005 (e):
  - (vi) any results of clinical pharmacokinetic studies of the drug,
  - (vii) any information regarding drug safety, pharmacodynamics, efficacy and dose responses of the drug that were obtained from previous clinical trials in humans
PGx Guidance

- Interpretation of C.05.005 (e)(vi)(vii):
  Any PGx results from clinical pharmacokinetic studies of the drug as well as any information regarding drug safety, pharmacodynamics, efficacy and dose responses of the drug that were obtained from previous clinical trials in humans shall be submitted as part of the CTA in accordance with C.05.005 (e) if the results support the safety and/or efficacy of the drug for which the application is being filed.
Considerations for Clinical Trials Involving PGx Testing

- PGx tests may be considered “medical devices”
- The main criteria for data requirements for the use of the medical device in a clinical trial application are:
  - Whether or not the test will be used to make patient management decisions in the trial (as opposed to use only in exploratory studies)
  - Stage of drug development
  - Whether or not the test is licensed
PGx for Patient Management

- Generally, the PGx test should be licensed or an Investigational Testing Application (ITA) is required in order for the PGx test to be used in a trial.

- For a PGx test that is licensed for sale in Canada, the sponsor should provide the name, description, and licence number of the device and whether the device will be used for its intended purpose.

- If PGx test is not licensed, and an ITA is required, then the sponsor should include all available data that supports the analytical validity of the test.

- Under consideration: On a case-by-case basis, the requirement for a license or ITA could be waived for early Phase I proof-of-concept trials until a later development phase; patient safety is always a deciding factor.
PGx for Exploratory Research

Authorization of the medical device is not required for PGx testing if:

- the test is not manufactured, sold or represented for *in vitro* diagnostic use; or
- the test is labelled “For Research Use Only” and is not otherwise labelled or otherwise represented for a specific diagnostic application.
Informed Consent (1)

■ Scenarios under which PGx information may be collected:
  ■ PGx testing carried out within the context of the main clinical trial
  ■ PGx testing as a sub-study that is not linked, but may be indirectly related to the main clinical trial
  ■ For future use (banking) in exploratory studies

■ Informed consent is very important in all scenarios
The informed consent form should explain:

- that PGx testing will be conducted and the purpose of such testing (i.e., how the PGx data will be used)
- the sample and data coding strategy, and the storage, destruction, and security measures used for sample and data preservation to ensure confidentiality to the extent possible
- That after anonimization, it is not possible to retrieve a subject’s sample
- the rights of the subject with regards to the PGx testing and the study overall

Constraints and conditions and any other general guidelines set by each local Research Ethics Board / Institutional Review Committees must be respected, in addition to any applicable Federal and/or Provincial legislation.
If Filing a CTA with PGx

- Sponsors are encouraged to request a consultation meeting with Health Canada prior to submitting a CTA that contains PGx information or that uses a PGx test, especially in circumstances where the PGx test will be used to determine subject eligibility, drug dosing, or some other risk management strategy.
Conclusion

- PGx is not a new topic but facilitated by new tools
- Several Guidance documents have been developed by different regions
- We are now seeing CTAs with a PGx component
- Co-approval of an ITA for the PGx test may be required
- Informed consent is one of the most important aspects of PGx testing
## References

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