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PHARMACOGENOMICS: A GLANCE ON REGULATORY FRAMEWORK AS PER EUROPE AND CANADA

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ABSTRACT

Pharmacogenomics aims to unravel the way that human genetic variation affects drug efficacy and toxicity; it is the study of how genes affect a person's response to drugs. In current times, though pharmacogenetics studies are being done extensively for research, its application for drug development needs to get started on a large scale. It raises significant regulatory complexities for the diagnostics arm of regulatory agencies. The attempt has been made to perform clinical studies where pharmacogenetics tests can be used for stratification of patients based on their genotype. As it contains genetic testing (E.g. DNA, RNA), complexity of genetic arrangements makes it difficult to find correct gene that affect the drug response. Currently EMA and Health Canada are recommending the use of pharmacogenomics in drug development. The purpose of the regulations is to provide advice on general principles of study design, data collection, data analysis in clinical trials, pharmacogenomics testing, labelling and data submission

INTRODUCTION:

"Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup." Genomics is playing a major role in identifying information from the human body and applying it to current drug therapy. It has produced a new era of individualized drug therapy for patients to achieve higher efficacy and safety. Due to the enhanced development of today's technologies, the long-term benefits of pharmacotherapy management are becoming closer to implement in clinical practice.

Many drugs that are currently available are "one size fits all," but they don't work the same way for everyone.

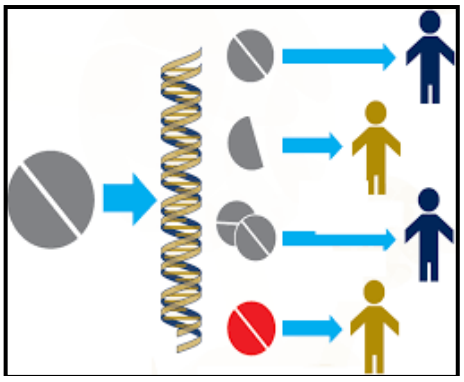

Fig. 1: Pharmacogenomics Concept

Currently, doctors base the majority of their drug prescriptions on clinical factors, such as a patient's age, weight, sex, and liver and kidney function. For a small subset of drugs, researchers have identified genetic variations that influence how people pharmacogenomic information to select the best medication and identify people who need an unusually high or low dose.

New methods to determine correct dose of drug –

The methods are based on a person's genetics that how the body processes the drug and the time it takes to metabolize. As it has already been proved that age, lifestyle and individual health also affect the response of patient towards drugs but understanding the genetic makeup of patient can improve the response and techniques such as DNA analysis have added new dimension to pharmacogenomics.Thus, pharmacogenomics can play a major role in the treatment of patient, with minimized side effects. The original concept of one drug for all approach which has been in use for past century, is based on statistical approach in which the patients are classified in broader classes, mainly as per age. But the pharmacogenomics classifies the patients into smaller groups based on the phenotypic and genotypic content.

Need for Pharmacogenomics:

Pharmacogenetics is a broad area of research. The effects of polymorphism of genes for enzymes like cytochrome P450 can be applied in drug delivery, development and the clinical application of drugs. The cost effective methods of genotyping can be used by the physicians in patient treatment. Currently, genotyping is not a clinically established technique, but now its status is likely to be changed. Although pharmacogenomics and tailored treatment shows increased efficacy and safety of treatment, it also includes ethical, social and race as important issues which need to be analyzed, in line with FDA guidelines on pharmacogenomics. With the use of new high-throughput screening methods and data-mining approaches, pharmacogenomics results can be improved.Pharmacogenomics into clinical practice has the potential to improve efficacy and reduce toxicity, by choosing "the right drug for the right patient in the right disease at the right dose".Pharmacogenomics raises significant regulatory complexities for the diagnostics arm of regulatory agencies. Firstly, there is the technical complexity of the tests and the need for standardization of platform technologies such as microarrays, and then there is the challenge of validating the results of tests that may analyses a vast number of biomarkers simultaneously. As it contains genetic testing (E.g. DNA, RNA), complexity of genetic arrangements makes it difficult to find correct gene that affect the drug response. Certain ethical issues also comes regarding handling of genetic samples and disclosing their data. Also depending on genetic information it is complicated process for physicians to write correct prescription. This also comes with another issue towards the pharmaceuticals as they need to re-label the drug product for which the pharmacogenomics data is found or available.Certainly this new developments will bring fresh challenges, and complexity towards regulatory as stringent regulations also needs to rationalise the frame work for pharmacogenomics regulations. Regulatory agencies are keen to achieve a harmonized approach to this area and have made some progress in this regard.Currently FDA is not only recommending the use of pharmacogenomics in drug development but beginning to explore how they can forge a common approach. The development of transnational policies and regulatory standards and processes may assist regulators in guiding and promoting

the adoption of pharmacogenomics. Along with the FDA another leading regulatory authorities of Europe, and Canada are also looking forward in the development of pharmacogenomics field which keeps enormous rooms of growth as regulatory agencies to see pharmacogenomics as a promising opportunity to improve the safety and efficacy of medicines. As an emerging area of clinical science it will require regulatory flexibility and a willingness to grow with industry.

Regulatory aspects of Pharmacogenomics as per EUROPE [4, 5]:

The European Medicines Agency (EMA) guidance describe some principles for the influence of pharmacogenetics on drug pharmacokinetics, encompassing considerations and requirements for the design and conduct of investigations during drug development. For those cases where pharmacogenetics is envisioned to play a major role in the benefit-risk of a medicinal product because of its impact on pharmacokinetics, guidance is given regarding studies required and recommended at different phases of drug development to ensure satisfactory efficacy and safety in genetic subpopulations that have variable systemic exposure of active substances also the guidance has been provided for Voluntary Genomics Data Submission and labelling of Pharmacogenomics information. The intention of the guidance provided is to increase the usefulness of the information gathered from genomic studies and facilitate the implementation of pharmacogenomics (PGx) into drug development and patient treatment for the benefit of all stakeholders.

Regulations for Clinical Studies:

***In vitro* studies prior to human exposure:**

Human in vitro metabolism studies are to be conducted prior to phase I. Such studies preferably includes identification of the enzymes catalysing the in vitro metabolism and also the identification and characterization of metabolites formed through candidate major metabolic pathways, enabling early pharmacological activity screening of these metabolites. In case of an active parent drug, in the in vitro context for metabolising enzymes the following arbitrary rule is proposed: A pathway can be considered 'important' when based on in vitro data >50% of the drug is predicted to be cleared via a single polymorphic enzyme. Such a 50% reduction of clearance would give rise to a doubled exposure, which in an early PK study would be equal to increasing the dose to the next level. Mentioned in Fig. 2

Phase I (Exploratory) First time in Man Studies:

The possibility of **genetic influence** on the **drug's pharmacokinetics** should be considered early in the Phase I program.

When the *in vitro* data indicate that a relevant involvement of a known functionally polymorphic enzyme cannot be excluded, it is advised to genotype the first time in man study population for the relevant genes in order to avoid safety issues. In Phase I, the relative contribution of the identified polymorphic enzyme on the *in vivo* pharmacokinetics of a drug or active metabolite is estimated.If a marked effect of polymorphism is confirmed *in vivo*, it is recommended, where relevant, to expand the clinical Phase I program and also evaluate relevant interactions.

Phase II (Dose Finding, Exploratory):

Phase I studies indicate that pharmacogenetics influences the pharmacokinetics of a drug to a possible clinically relevant extent, this should be reflected in the design of the Phase II studies. In case no genotype/phenotype-based dosing is applied to normalise drug, the exposure level obtained in the genotypically-defined subpopulation should be studied in the Phase II study.

This can be done either by including a sufficient number of the **genotypically-defined group of patients**, or by **adjusting the dose** yielding the target

exposure in patients. The ultimate aim of the Phase II investigations should be to **optimise dose(s)** selection and **design** of the Phase III studies. Mentioned in Fig. 3.

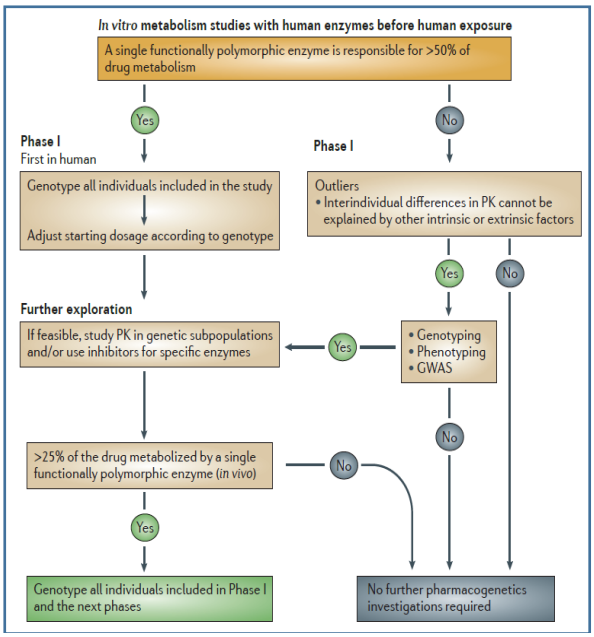

Fig 2: Decision making tree for in vitro studies prior to human exposure and Phase I studies

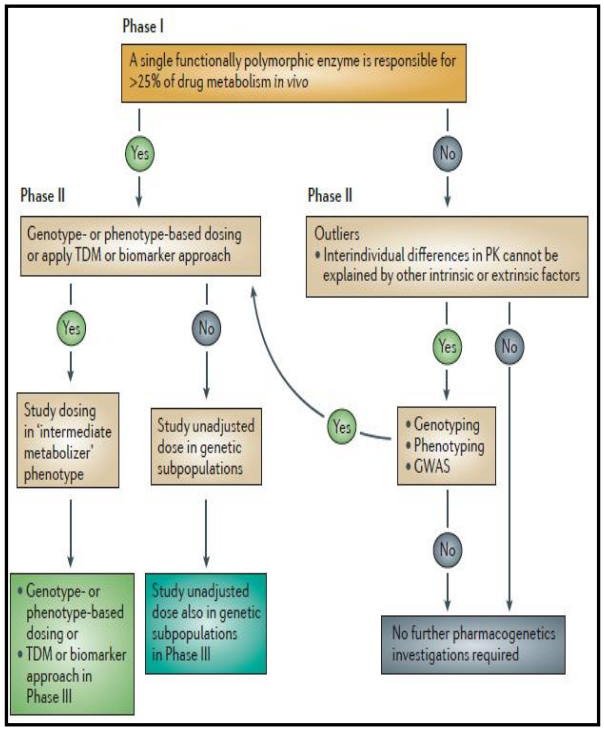

Figure 3: Decision making tree for Phase I and Phase II studies

Phase III (Confirmatory): Factors describing when pharmacogenetics studies are considered in Phase III studies:
If all previously acquired data suggest-

- No genotype specific treatment is under consideration, a goal of the Phase III study should be to confirm this presumed lack of clinical significance.
- A genotype based dosing regimen was developed in Phase I and Phase II studies then sparse sampling with population in the Phase III studies to confirm the dose normalization is done.
- The difference in exposure is likely to be clinically relevant but owing to the available marketed formulations it is not possible to adjust the doses. Then patients at risk should be excluded from trials.
- If suitable markers exist, The Phase III study should confirm that there are no efficacy and/or safety concerns for the genetically defined subpopulation.
- There is a significant difference in drug distribution in the genetically defined subpopulation, genotyping in all patients included in phase III studies is required.

Phase IV (Post Marketing): At the time of marketing authorization, information on the safety of a drug is relatively limited owing to factors including the low numbers of subjects in clinical trials. Furthermore, rare but serious ADRs may be identified late in development, or may only be discovered and characterized after marketing authorization and increased population exposure.

Requirements of DNA Banking: In all clinical phases of development, prospective banking of DNA for genotyping is highly recommended.

Regulations for Data Submission [6]:

The FDA and the EMEA issued Guidance for Industry: Pharmacogenomic Data Submissions and Guideline on Pharmacogenetics Briefing Meetings, respectively. Both documents encourage the voluntary submission of genomic data by the sponsors to the Agencies.

It emphasize that voluntary submissions are used to help the Agencies gain an understanding of genomic data.

Stand-alone VGDS: A voluntary GDS that is not associated with an existing application. Such voluntary submissions will be handled as submissions to a new pre-IND application.

Stand-alone VGDSs (not submitted to an existing application):

Upon receipt of any submission accompanied by the VGDS cover sheet, the Central Document Room staff will:

- Stamp the submission with the receipt date.
- Establish a pre-IND number for the submission.
- Perform data entry in the corporate database for document tracking.
- Identify the submission by putting it in the IPRG jacket.
- Deliver the submission, using a courier, to the IPRG for review

Associate VGDS: A voluntary genomic data submission that is submitted to an existing application. Such VGDSs will be submitted to the existing application, but will not be used by FDA in the process of regulatory decision making regarding the existing application. Associated VGDSs (submitted to a previously established application):Upon receipt of any submission accompanied by the VGDS cover sheet, the Central Document Room staff will:

- Stamp the submission with the receipt date.
- Perform data entry in the corporate database for document tracking.
- Identify the VGDS by putting it in the IPRG jacket.
- Deliver the VGDS, using a courier, for review to the IPRG.
- The IPRG will maintain a log of VGDS sent to the IPRG for review.

Inclusion of information and recommendation in the product labelling [7, 8]:

Inclusion and positioning of genomic information in the product labelling in addition, the seriousness of the adverse reactions, the underlying disease, therapeutic alternatives, dose dependency, idiosyncratic effects, and potential interactions with other medicinal products, need to be considered.

Labelling should consider public health impact on the overall population and subsequently in specific genomic subpopulations.

Evidence based recommendations and/or information in the labelling regarding pharmacogenomic testing can be classified as:Pharmacogenomics testing mandatory

1. Pharmacogenomics testing recommended
2. Provide information

Information added as per the guideline of the summary of product characteristics (SMPC):

The Summary of Product Characteristics (SmPC) or the label sets out key elements of drug benefits and risks relevant to the clinical use of the product defined during the medicine regulatory assessment process. Current SmPCs often contain pharmacogenomic data available at time of the initial registration of the medicinal product. However, for adequate pharmacogenomic information to be maintained or improved, it is essential that relevant pharmacogenomic data gathered in the post-registration phase is used to update the SmPC as and when necessary during the life cycle of a product.

Regulatory aspects of Pharmacogenomics as per CANADA

Introduction [9]: Health Canada, the federal regulatory authority that evaluates the safety, efficacy, and quality of health products available in Canada, recognizes that the application of pharmacogenomics (PGx) is increasingly becoming an integral

part of the drug discovery and development processes. In Canada, pharmaceutical drugs are regulated by the Therapeutic Products Directorate (TPD) and biologic drugs are regulated by the Biologics and Genetic Therapies Directorate (BGTD) in accordance with the *Food and Drugs Act* and the *Food and Drug Regulations*. *In vitro* diagnostic devices (IVDD) are regulated by TPD's Medical Devices Bureau (MDB) in accordance with the *Food and Drugs Act* and the *Medical Devices Regulations*. This section provides guidance to sponsors on how the *Food and Drugs Act* and its associated regulations apply to the submission of PGx information to Health Canada.Many sponsors are considering integrating PGx into the drug discovery and development processes, and there are increasing efforts by regulators to determine the most appropriate means of using PGx information within the context of pre-market and post-market drug evaluation and regulatory decision-making.

Pharmacogenomics Studies: Testing in clinical trials, including PGx testing should be done without compromising the wellbeing of patients. When a drug is studied in one geographical area and/or specific subgroup(s), the intrinsic (e.g. PGx) and extrinsic (e.g. diet) factors that could impact on the extrapolation of data to other geographical area(s) and/or specific subgroup(s) should be considered.

One of the major impacts expected is that pharmacogenomics will change the way in which clinical drug trials are conducted and thereby change the drug development process. Pharmacogenomics is believed to have the potential to affect every stage of drug development, from the Preclinical Phase to Phase IV.

Preclinical Studies [10]:

From an economic perspective, at the Preclinical Phase, it is expected that pharmacogenomics could be used in the selection of drug candidates that will enter clinical development, and which will be tested on humans in such a way that compounds responsible for variable drug response and toxicity may be eliminated.

Rodent models are particularly useful for genetic studies of different diseases because of advanced genome annotation, availability of genetic tools (e.g., whole-genome microarrays), and low housing costs. The rat, in particular, provides the additional advantage of a body size that facilitates surgical manipulation and yields sufficient joint tissue for molecular analyses.Rodent models have proven extremely useful in helping understand more about the genetic basis of many diseases in humans. A number of well-characterised rodent models have been proposed, consisting of inbred strains, selected lines, genetic knockouts, and transgenic animals.

Clinical Studies: As per this guidelines of Canada it requires sponsors, as part of a clinical trial application, to submit pharmacogenomics data that pertain to the pharmacodynamic aspects, pharmacokinetics, and toxicological effects of the investigational product or data that support its safety and/or efficacy, as well as data being used by the sponsor to support the design of the proposed clinical trial or to justify the proposed indication(s)/labelling. Moreover, the guidance distinguishes between pharmacogenomic testing using either a test already licensed for sale in Canada or already authorized for investigational testing, or using a test that is not presently licenced or authorized. In the latter case, the sponsor must obtain an authorization for investigational testing. The intent of these provisions is to minimize the risk of exposing research subjects to harm. Because pharmacogenomics research will depend on determining who is genetically susceptible to an adverse reaction or who may not be responsive to a drug, it may require looking a new at the question of risks, and whether it is ever acceptable to conduct clinical trials with subjects who

are more likely to be harmed or to experience no effect from a drug.

Accordingly, it can be anticipated that pharmacogenomics will have a profound effect on every stage of drug development, from Phase I to Phase IV. It will serve to reduce risk in Phase I by analyzing inter-individual and population differences in drug metabolism, to adjust dosages and correlate efficacy with genotype in Phase II, and to predict safety and efficacy in Phase III. Overall, these results will determine whether pharmaceutical companies are able to make genetically-related claims promoting use in a genetically defined subpopulation.

Pre-clinical and Clinical Drug Development:

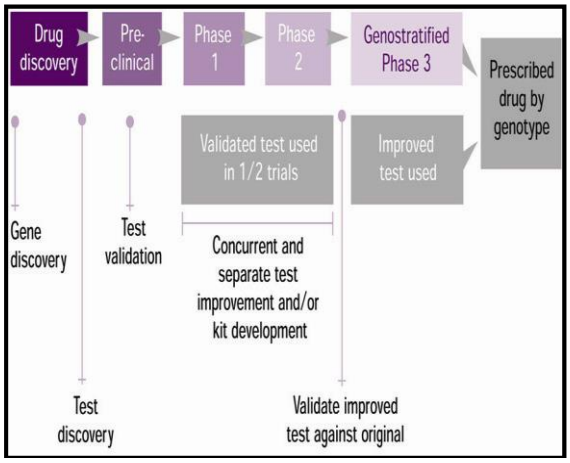

Fig4: Current and future uses of pharmacogenomics in pre-clinical and clinical drug development

It combines studying the effects of genes on enzymes and enzymatic systems to explain the impact they have on the ADME (Administration, Distribution, Metabolism and Excretion) of drugs and on clinical drug development. The two objectives of personalized medicine are to increase the efficacy of drugs and to reduce the incidence and severity of adverse effects by allowing pre-screening patients predisposed to toxicity before prescribing a drug. Initially, pharmacogenomics was used in Phase I clinical trials to explain variations in individuals' abilities to metabolize drugs. As researchers became more familiar with the advantages, it started using it in Phase II clinical trials. Eventually, they will use the knowledge acquired in Phase I and II clinical trials to design improved Phase III clinical trials, which will remain pivotal. This current situation as well as its evolution, both upstream and downstream, is well illustrated in below figure.

Submission of Pharmacogenomics Information:

Pre submission consultation meeting:

Sponsors are encouraged to request consultation meetings with the relevant Directorates prior to submitting CTA or NDS that contain PGx information or that use a PGx test. These consultations will enable sponsors and Health Canada to share information and knowledge pertaining to the integration of PGx in the drug development and approval process and will help familiarize Health Canada staff with industry activities related to PGx.

Information Requirements for Clinical Trial Applications [11]:

In accordance with guidance, sponsors are required to submit PGx data that pertain to thePharmacological or pharmacodynamic aspects, pharmacokinetics, and toxicological effects of the drug if the PGx data is relevant to, or supports the use of the investigational product in the proposed clinical trial.

- 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 guidance if the results support the safety and/or efficacy of the drug for which the application is being filed.

- If PGx data are being used by the sponsor to support the design of the proposed clinical trial or animal study, to justify testing in humans, or to support the proposed indication(s)/labelling of the drug, it shall be submitted as part of the CTA.

Request for a Pre-Clinical Trial Application (CTA) Consultation Meeting:

Requests for a pre-CTA consultation meeting should be submitted in writing by the sponsor to the appropriate Directorate. Requests should be submitted in the form of a cover letter proposing four dates and times suitable for a pre-CTA consultation meeting. The cover letter should be accompanied by the following information:A brief synopsis of the proposed study;A list of preliminary questions to be addressed by the Directorate during the meeting; andSufficient information for Health Canada to assess the utility of the meeting and identify the appropriate staff necessary to discuss the proposed issues. This will assist in ensuring efficient use of Health Canada resources.

Pre-Clinical Trial Application (CTA) Information Package:

The Information Package, which should be submitted in accordance with current electronic specifications, should contain:

a) Proposed agenda, any prepared slides including a finalized list of questions, and a complete list of attendees

b) A brief summary of all data including:

- A tabular listing of completed nonclinical and clinical studies,
- An outline of the observed toxicological manifestations and a discussion of their impact on the use of the drug in humans,
- An outline of the observed adverse events and a discussion of potential safety problems;

c) A proposed global clinical plan for the current stage of drug development including regulatory status in other countries;

d) Details of the proposed clinical trials to be conducted in Canada, within the scope of the intended CTA, including:

- A statement of trial design,
- Parameters, values, ranges or limits for indication(s) and clinical use(s), patient study population(s) and routes of administration,
- Parameters, values, ranges or limits for dosage form(s), dosage regimen(s) and formulation(s),
- Proposed procedures and/or criteria for patient monitoring, clinical efficacy and safety assessments, alternative treatments, premature patient discontinuation and other considerations, as appropriate;

e) A summary of significant Quality (Chemistry and Manufacturing) aspects of the drug, if applicable;

- A summary of the method of manufacture for both drug substance and dosage form,
- Relevant flow charts,
- A listing of quality control procedures and specifications,
- A summary of product characteristics, and
- A listing of all production site(s) - **only for biologics and radiopharmaceuticals**.

As per guidance, Health Canada reserves the right to request any additional information that is required to assess the safety and risks of the drug intended for use in the proposed clinical trial, and which could include PGx information. Additional information would be requested in accordance with Health Canada's *Management of Drug Submissions Guidance Document*.

Clinical Trial Applications (CTAs): The sponsor must file a CTA **prior** to the initiation of the trial [C.05.005]. CTAs are required for human clinical trials using drugs not authorized for sale in Canada, including clinical trials in Phases I through III of drug development and comparative

bioavailability studies; as well as trials involving marketed drugs, where the proposed use of the drug is outside the parameters of the NOC or DIN, e.g., one or more of the following is different:

a) Indication(s) and clinical use;
b) Target patient populations(s);
c) Route(s) of administration; or
d) Dosage regimen(s).

Clinical Trial Application (CTA) Format:

The CTA is composed of three parts (modules) in accordance with the CTD format:Module 1 - contains administrative and clinical information about the proposed trial;Module 2 - contains Quality (Chemistry and Manufacturing) summaries about the drug product(s) to be used in the proposed trial; and

Module 3 - contains additional supporting Quality information.The CTA should be submitted on electronic media, accompanied by a hard copy cover letter, and be organized in accordance with the current electronic specifications: *Guidance Document: Preparation of Drug Regulatory Activities in the "Non-eCTDElectronic-Only" Format.*

Clinical Trial Applications Involving Pharmacogenomic Testing:

At the clinical trial stage, PGx testing used for diagnostic purposes or patient management can be achieved in two ways:

(i) Use of a PGx test that is licenced for sale in Canada;(ii) Use of a PGx test that is authorized for investigational testing

1. **PGx test that is licenced for sale in Canada**

   If a sponsor of a clinical trial intends to collect data using a PGx test that is already licenced for sale in Canada, the sponsor should include in their CTA the name, description, and licence number of the IVDD and whether the device will be used for its intended purpose.

2. **PGx test that requires authorization for investigational testing**

   If a sponsor of a clinical trial intends to collect PGx data using an IVDD that is not licenced or is not already authorized for investigational testing by Health Canada, the manufacturer/device sponsor shall obtain an authorization for investigational testing from MDB.

Information Requirements for New Drug Submissions (NDS), Supplemental New Drug Submissions (SNDS), Abbreviated New Drug Submissions (ANDS) [12]: The requirements for the sale of new drugs in Canada and prohibits the sale of new drugs unless the manufacturer has filed a submission that is satisfactory to the Minister. Guidance outline the requirements for submission of a New Drug Submission (NDS), Abbreviated NDS(AND), and Supplemental New Drug Submission (SNDS) respectively.Submissions should be filed in accordance with the Health Canada guidance document, *Preparation of New DrugSubmissions in the CTD Format*.There are no restrictions on the information that may be added to or removed from the original NDS, SNDS, ANDS In order to comply with the above-mentioned sections, sponsors shall submit PGx data if it provides evidence of the safety and/or clinical effectiveness of the new drug in the context of its proposed indications. Similarly, if PGx data is being used to support the proposed dosage of the drug, the claims to be made for the drug, or the contra-indications and adverse reactions of the drug, the data shall be submitted by the sponsor.

NDS, SNDS, or ANDS involving Pharmacogenomic Tests: If the sponsor used a PGx test that is already licenced in Canada, the sponsor should indicate in their submission, the name, description, and licence number of the IVDD that was used.In Canada, all devices intended to be used for PGx testing are classified as Class III medical devices and require a pre-

market scientific assessment of the safety and effectiveness by the MDB. Since these devices may have profound impact on the safety and effectiveness of the drug for which the assay/test is performed, data for pre-market review will be required.

Labelling Considerations: The Canadian guidance on the submission of pharmacogenomic information specifically addresses labelling. It recommends the inclusion of pharmacogenomic information when identified subgroups of patients are likely to experience higher or lower clinical efficacy in order to properly define those subgroups, as well as when there is sufficient evidence to support special dosage considerations for specific subgroups.

Preparation of New DrugSubmissions in the CTD Format.

NDS	SNDS	ANDS
New Drug Submission	Supplemental New Drug Submission	Abbreviated NDS
If the product has been identified as a New Drug, the submission should be refiled as an NDS, or ANDS	Any additional information to NDS should be submitted as SNDS	If the product has been identified as a New Drug, the submission should be refiled as an NDS, or ANDS
If, during the review of a CTA, NDS, ANDS, SNDS a sponsor's name is changed or the sponsor wishes to change a product name, the information may be submitted.		
1. Priority - NAS, Clinical or Non Clinical /Chemistry &Manufacturing data, Clinical or Non Clinical Only 2. NOC/c - NAS, Clin or Non Clin /C&M, Clin or Non Clin Only 3. NAS (New Active Substance) 4. Clin or Non Clin Data/C&M 5. Clin or Non Clin Only 6. Comp/C&M 7. C&M/Labelling 8. Published Data 9. Labelling Only 10 Administrative (X-ref.,product or manufacturer name changes) 11. Disinfectants (submitted as 4-10 class-type)	1. Priority - Clinical or Non Clinical /Chemistry &Manufacturing data, Clinical or Non Clinical Only 2. NOC/c - Clin or Non Clin/C&M, Clin or Non Clin Only 3. Clin or Non Clin/C&M 4. Comp/C&M 5. Clin or Non Clin Only 6. C&M/Labelling 7. Published Data 8. Rx to OTC - No New Indication 9. Labelling only 10. Administrative (X-ref., product or manufacturer name changes) 11. Disinfectants (submitted as 3, 4, 5, 6, 7, 9, 10 class-type)	1. Comp/C&M 2. C&M/Labelling 3. Published Data 4. Labelling Only 5. Administrative (X-ref., product or manufacturer name changes)

It also calls for specific instructions when the optimal use of a drug can be determined through pharmacogenomics testing. Sponsors shall comply with all of the applicable labelling requirements in the *Food and Drugs Act* and *Regulations*. Sponsors should refer to the *Guidance for Industry: Product Monograph* for guidance on the development of a product monograph. When developing the product monograph and labelling, sponsors should consider whether there is evidence to support the inclusion of PGx information. For example,

- When PGx data demonstrate that subgroups of patients experience higher or lower clinical efficacy, specific labelling may be warranted to identify and define

the population subgroup(s) that may derive the greatest benefit;When PGx data demonstrate that subgroups of patients may be at increased or decreased risk for ADR(s), specific labelling may be warranted to identify and define the specific subgroup(s);

- When there is sufficient evidence to support special dosage considerations for specific population subgroup(s), these should be defined (for example, when there is evidence to support dosage reductions for particular patient subgroups to avoid ADRs);When testing is recommended or required in order to optimize the use of the drug (e.g. if testing is recommended prior to selecting or prescribing treatment).When the medical and technical aspects of the submission have been evaluated, staff from the relevant review division will be available to discuss the development of an appropriate product monograph with the sponsor.

Phenytoin [13]: The FDA labeling recommendations for carbamazepine were followed by the inclusion of similar information in the warning section of the product labeling for phenytoin highlighting the risk of severe and potentially fatal SJS or TEN. The FDA recommends genetic testing for the presence of the HLA-B*1502 allele in patients of Asian ancestry who are being considered for therapy with phenytoin. Testing recommendations for phenytoin are based on literature describing SJS and TEN, as well as the presence of an aromatic ring which has a similar structure to carbamazepine. However, the genetic association of HLA-B*1502 and SJS or TEN development may be more complex in the case of phenytoin. A case-control association study identified that additional variants (HLA-B*1301, Cw*0801, and DRB1*1602) may also be associated with development of phenytoin induced SJS and TEN.33 Sensitivity and specificity values for HLA-B*1502 testing from a meta-analysis of studies published as of 2012 were 36.6% and 87.2%, respectively, perhaps indicative of additional factors influencing phenytoin-associated risk for SJS and TEN.34 In addition to the recommendation for HLA-B*1502-positive subjects, the Dutch Pharmacogenetics Working Group provides dose recommendations for carriers of CYP2C9 variants in patients treated with phenytoin, which is a major substrate for this metabolic pathway. This recommendation outlines a 25% dose reduction for CYP2C9*1/*2 or *1/*3 and a 50% dose reduction for *2/*2, *2/*3, or*3/*3 carriers. However, this recommendation is not reflected in the latest phenytoin drug label.

CONCLUSION:

Now a day's regulatory authorities are becoming more active for PGx studies as the pharmacogenomics is becoming integral part of drug discovery and development process, they had provided guidance to sponsor on how and when to submit PGx information to regulatory authorities. As next-generation gene sequencing technology advances quickly, previous technical challenges for performing pharmacogenomic studies or practices in this have been mostly resolved by the help of the guidance provided by Europe and Canada. Though there are specific regulations available for PGx studies to be performed in Europe while not in Canada, Where as Canada is having regulations mainly focusing on PGx testing and NDS, SNDS and ANDS submission whereas Europe has only Volunteer Genomics Data Submission procedure while both the countries are focusing on labelling part as well. Despite of regulations available in Canada there are many areas pertaining to clinical trial is left unexplored to be developed in the field of Pharmacogenomics to be regulated so that it will provide clear glance in this area.

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