INTRODUCTION
Advanced knowledge of the human genome has remodelled the pharmaceutical domain, triggering changes in treatment paradigms and patient expectations. Regulators are anticipated to facilitate adoption of innovative methodologies in practice.

Are regulatory developments, or the lack thereof, shaping the progress in the translation of predictive bench science to tailored bedside treatment?

AIMS
The research group within the Malta Medicines Authority and the Department of Pharmacy at the University of Malta, is conducting pharmacogenetic investigations such as genotyping and its correlation to drug blood levels for amitriptyline, as it relates to regulatory labelling. The level of harmonisation reached on the integration of pharmacogenetic implications in official sources of drug information is assessed.

METHOD
Guidelines from the European Medicines Agency (EMA) and the Food and Drug Administration (US-FDA) which represent current regulatory thinking on the application of pharmacogenetics and complement scientific discussions between innovators and regulatory bodies during drug development9, were analysed. Pharmacogenetic implications identified through observations along the life cycle of an established drug, which are possibly underserved by regulatory guidance, were evaluated.

The evolution of the FDA-approved drug label and the EU-Summary of Product Characteristics (SmPC) for amitriptyline were reviewed in light of evidence-based guidelines issued by the Clinical Pharmacogenetics Implementation Consortium (CPIC)7. The regulatory review process related to amitriptyline was assessed, considering the US approach towards inclusion of pharmacogenetic data in product literature compared to the level of harmonisation reached at EU-level.

In the EU, amitriptyline is authorised via national procedures with divergent decisions taken by Member States resulting in product information differences in the countries where it is marketed. In 2015, the Greek medicines regulator, referred the matter to the Committee for Medicinal Products for Human Use (CHMP) which in 2017 concluded that there is a need to harmonise the amitriptyline prescribing information.

RESULTS
Alternative drug or defined dose adjustments to amitriptyline therapy, based on patient genotype, are recommended by CPIC. The FDA-approved drug label for amitriptyline comments marginally on a potential 8-fold increase in amitriptyline plasma concentration for poor metabolisers. The prescribing information in the FDA-approved drug label does not quantify the recommended dose adjustments for CYP2D6 metabolisers and makes no direct reference to CYP2C19.

The harmonised EU-SmPC, as per the EU Commission implementing decision of May 20178, includes important pharmacogenetic considerations. Two new sections were added as warning on the co-administration of amitriptyline with Cytochrome P450 inhibitors of CYP2D6 and on the administration of amitriptyline to known poor metabolisers of CYP2D6 or CYP2C19, excerpt reproduced hereunder.

"Known poor metabolisers of CYP2D6 or CYP2C19
These patients may have higher plasma concentrations of amitriptyline and its active metabolite nortriptyline. Consider a 50% reduction of the recommended starting dose."

This revision represents a step forward with respect to actionable prescribing recommendations which can be applied in daily clinical practice. EU Member States shall implement the changes set out and take account of the said conclusions for the assessment of the efficacy and safety of amitriptyline products.

CONCLUSION
Scientific, financial, ethical and commercial hurdles, together with regulatory issues represent dynamic concerns in making precision medicine a working reality. The harmonised regulatory vision evolving for amitriptyline should be effectively replicated for newer drugs with pharmacogenetic links being identified early on in their development. In the realm of regulatory science, the route to personalised medicines necessitates the integration of genomic science in drug research, assessment and product information to translate into tangible clinical advances.

Acknowledgement
Research funded by the ENDEAVOUR Scholarships Scheme

REFERENCES