

New strategies to support cardiac safety development .

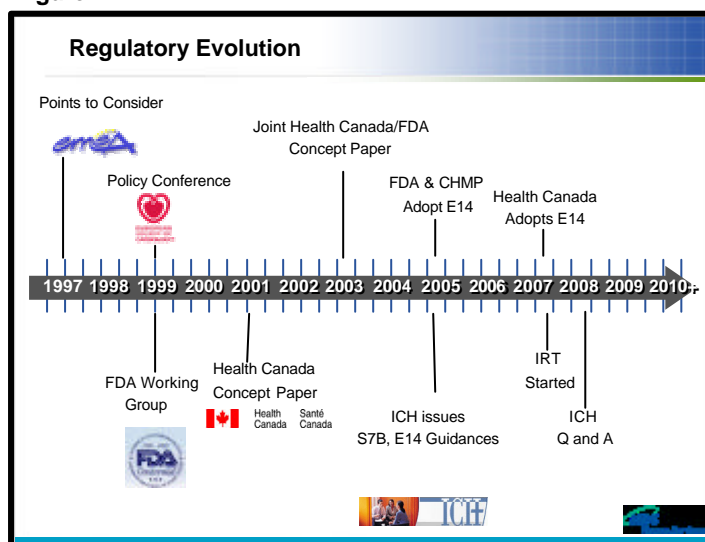
Introduction

“Its cardiac safety but not as we know it”. It is not difficult to imagine that many experts within the cardiac safety community, in their formative years, were first drawn to science watching the fictional exploits of Captain James Tiberius Kirk and his colleagues. Whilst it would be unfair to suggest that the scientific profession is full of “trekkies”, in the real World where science fact meets business opportunity, a number of companies, who provide cardiac safety services, are boldly going on.....

Regulation is good Business

Since the CPMP published their “Points to Consider” document in 1997 the sector, driven by regulatory pronouncements (figure 1), has changed beyond recognition. The centralised ECG market, prior to the publication of the Health Canada draft guidelines in early 2001 was estimated to be around \$70m¹. However, by 2006 this figure had grown to an estimated \$330m².

Figure 1



Re-printed Courtesy MDS Pharma Services

The key to this growth was the regulatory requirement for Thorough QT/QTc studies (TQT studies). These studies, conducted in a Phase 1 environment, required intensive ECG collection to characterise the QT liability of a compound.

The main beneficiaries of the new regulatory requirement were ECG core laboratories whose expertise at collecting and overreading ECGs was highly sought after. More importantly the costs for digitally collecting and manually overreading ECGs in a TQT study could be over \$1m per study.

The TQT Study Strategy

As the regulatory requirement for Phase 1 TQT studies progressed from the consultation period to being adopted as E14 and S7B guidelines by the International Conference of Harmonisation (ICH) steering committee, core laboratories developed a simple but effective strategy or business model. This strategy combined scientific expertise (i.e. the ability to design or advise on how to design a TQT study that meets the current regulatory requirements) and operational capability (to digitally collect and manually overread ECGs in vast numbers (up to 40,000 per Phase 1 TQT study).

TQT studies were seen as highly profitable and became the focus of attention for the larger established ECG core labs, as well as the developing smaller or start up core labs. Subsequent research by Macto Consulting² identified twenty companies who provided centralised ECG services during this period, five of whom could be classified as start up businesses.

The Changing Environment

Armed with a greater understanding of the scientific issues associated with trying to determine QT liability and a profound awareness that the increased cost of performing expensive TQT studies is having a dramatic effect on its R & D budget, pharmaceutical and biotechnology companies are challenging the regulators.

2 Inside Views – The Industry View

- QTc prolongation is not the ideal biomarker to assess QT liability
- Submission of automated algorithms rather than expensive manual overreads.

In addition, a number of ECG core laboratories, which are outlined below, are also responding to the challenge.

MDS Pharma Services Inc

As one of the leading ECG Core labs, MDS Pharma Services Centralised Cardiac Services division has been looking at alternative strategies to help their customers manage the assessment of QT liability for their drugs more efficiently.

According to Dr William Wheeler, a Board-Certified Cardiologist and recognised industry expert, and Global Medical Director, at MDS Centralised Cardiac Services, there can be a “tick box” approach to assessing QT liability rather than a more formal and strategic scientific approach to assessing QT risk. This approach involves, looking at each stage of clinical development, asking questions about the drug and the results of the QT information available to date. Finally, when would be the right time to conduct a thorough QT/QTc study.

Robust QT Study

MDS Centralised Cardiac Services' approach to assessing QT liability involves recommending what they term as 'robust' QT studies.

Robust QT studies are not part of the regulatory requirement but represent a strategic approach that allows companies to have a better understanding of the QT liability their drug.

Assessing QT liability in SAD/MAD studies allows assessment at probably the highest exposures. Assessing QT development risk and more accurately predicting drug effects that allow more TQT study design. It is imperative that sufficient data be available on a compound prior to the TQT study.

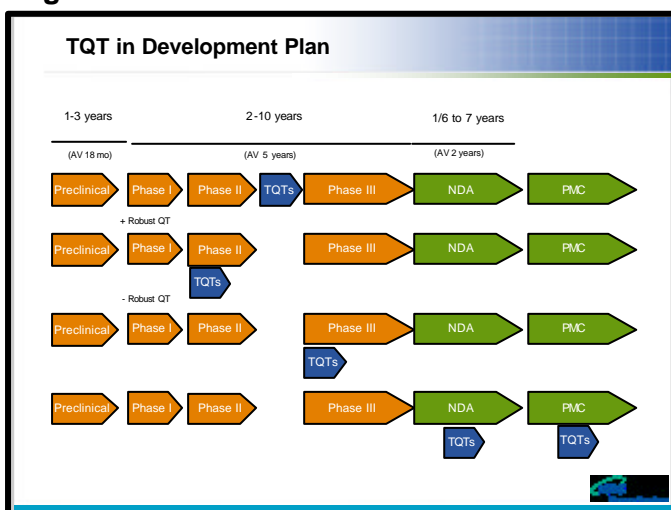
The MDS Robust QT strategy allows their clients greater scientific flexibility, so they have a greater understanding of their compounds' QT liability without the requirement to invest in a TQT study too early in the development cycle (figure 2). This multiphase QT strategy allows clients to reduce their investment risk and at the same time expedite drug development.

Medifacts International Inc

Medifacts International Inc. is a global provider of Cardiac Diagnostics Services (figure 3) to the Pharmaceutical, Biotechnology and Medical devices industry. The company has shown fantastic growth over the last few years and has benefitted, like its competitors, from the increased need for centralised ECG services as a result of the changes in the regulatory environment.

However, the Medifacts business model or strategy to support cardiac safety in drug development is based on providing a range of technology solutions in addition to expert scientific knowledge of cardiac safety and blood pressure. These technology solutions, allow clients to benefit by being able to collect a broader range of relevant clinical data (ECG, Holter, arrhythmia or BP) and bring efficiencies to the data centralisation process that can reduce overall study costs.

Figure 2



Re-printed Courtesy MDS
Pharma Services

Figure 3



Re-printed Courtesy Medifacts International

In addition to searching for technology solutions in the market place, Medifacts will, if necessary, invest in research and development to bring bespoke technologies to support their clients and their drug development plans.

The Medifacts technology based strategy allows clients to take advantage of their expertise across all phases of study development.

NewCardio Inc

NewCardio Inc is the newest company to provide services and technologies that support cardiac safety in drug development.

The NewCardio solution is based on vector cardiography, to provide real-time 3D analysis of the heart's electrical activity, to generate 3D visual representations (Figure 4).

Figure 4



Re-printed Courtesy NewCardio Inc

NewCardio's solution for understanding QT liability in drug development is based on QTinno™.

QTinno™ is a software tool that automates and analyses ECGs. QTinno™ uses what the company calls "Intelligent Automation" to analyse ECGs. Essentially QTinno measures the cardiac time intervals of all the available beats using its 3-Dimensional vector magnitude virtual ECG lead and then uses a curve fitting algorithm to identify the end of the T wave.

The NewCardio strategy is not based on becoming a full service core ECG lab but on the recognition that the intensive nature of the TQT study with manual or semi automated analysis is not only extremely expensive, but very time consuming and places a great strain on the core labs efficiency. The QTinno™ solution could therefore be an ideal supporting tool for core labs, providing, accuracy of measurement, reduced costs and time for analysis (QTinno™ can process 10,000 ECG in less than two hours).

Conclusion

TQT studies in their current design are expensive but a strategy based on the collection and analysis of these studies is problematic. Firstly, the Pharmaceutical and Biotechnology companies have a better understanding of cardiac safety and are therefore more reluctant to accept study designs for TQT studies that require 40,000 manually overread ECG. Secondly, it would appear that the regulators are more willing to accept the submission of fully automated ECG data for TQT studies.

Therefore companies such as those highlighted in this article that are providing alternative strategic solutions, could be in a better position to prepare for the long term. These companies appear to understand that the costs and the numbers of TQT studies (current design) will decline. This is an economic, scientific and regulatory reality and not the stuff of science fiction.

References

1. J Sulola and D Harvey, ECG Vendors Report (2005), Macto Consulting Limited
2. J Sulola, Market Intelligence Report, eVendorSearch (2006), Macto Consulting Limited