AMPS-QT

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AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

Editorial

Exactly one year has passed since we hosted in these pages a contribution by Christine E. Garnett about the FDA plans to expand the ECG Warehouse to include continuous recordings. We have been heavily involved since then, side by side with Mortara Instrument, in supporting the FDA with this project and we figured it was important at this time to offer our readers a snapshot of the situation.

We spoke with Norman Stockbridge, MD, PhD, Director of the Division of Cardiovascular and Renal Products within the FDA Center for Drug Evaluation and Research, about his assessment of the situation, and we are positive our readers will value, as usual, his input in this matter. To add to the picture we received, and gladly publish, Mortara's view on the status of the holter warehouse project, and to complete it we offer our own assessment in an essay by Fabio Badilini. In conclusion, and to put it concisely, in a NASA-like lingo one could say "we are GO for launch", so don't miss it!

Introduction:

Fabio Badilini, PhD, FACC, AMPS llc

The ECG warehouse, initiated more than 10 years ago, has been successfully used to submit millions of digital ECGs and has significantly contributed to improve the reviewing process by the regulatory agency.

The warehouse was designed to host resting ECGs, i.e. 10-seconds of the 12-lead ECG signal, with the inclusion of the so-called median beats, i.e. the mathematically derived representation of the 10-seconds in a single cardiac complex. The standard also included the possibility of adding annotations, i.e. those measurements a core-lab had produced on the specific ECG.

A specific XML-based format, the HL7 annotated ECG (aECG) approved under the umbrella of HL7, had been specifically designed for the ECG warehouse; today, the HL7-XML aECG is a widely accepted standard which is used way beyond the context of pharmaceutical research.

The success of the ECG warehouse initiative has triggered the need to extend the capability to submit ECGs of longer duration, and in particular to submit a full Holter record. This to expand the possibility for the regulatory bodies to provide a more complete reviewing process, either for ICH E14 studies based on Holter extractions but in particular to support a platform for the FDA to inspect in detail all new methods and approaches to assess drug-induced effects on the ECG based on continuous ECG data. The extended warehouse, still designed by Mortara Instrument, is today a reality.

Q&A with Norman Stockbridge on the extended aECG format

AMPS-QT: ***What's happening?***

NS: You might think that after about a decade of Thorough QT studies, there wouldn't be all that much going on, but in fact this is a very dynamic period.

We are following with great interest the progress of the joint IQ Consortium and CSRC team's efforts to explore if the robust QTc assessment can detect QTc prolongation at the threshold of regulatory interest in a prospective clinical Phase 1 study, with the goal of obviating a dedicated clinical study. FDA has recommended to IQ/CSRC team some modest QT prolonging drugs to test to show that the QTc assessment in Phase 1 has adequate assay sensitivity. I am optimistic that they can do this, but I am worried that the impact on the early phase study may not be trivial and that the number of false positives may not be trivial, either.

Further downstream, we are exploring the possibility of shifting the proarrhythmic risk assessment from being largely based on human QT to one based largely on non-clinical assessment. I and others are concerned that some

of the drugs we have labeled as modest QT prolongers and given precautionary advice probably pose no threat at all, because they may involve self-limited effects on minor potassium currents. I also worry that engineering hERG effects out of drugs may have lost from the pipeline drug candidates with compensatory effects on inward currents (think amiodarone, ranolazine, and verapamil), or bought other off-target effects. We are planning to have a public meeting mid-year to discuss this topic.

Nearer term, and probably of more immediate interest to your readership, Mortara has recently renovated the ECG Warehouse to house long Holter ECG data. The new tools for viewing those data are now in place. AMPS has been very helpful in supplying test datasets and shaking bugs out of the new data standard.

I see two main purposes in this evolution.
First, clearly many companies are using Holter recorders to collect the data in TQT studies. The ability to pick short runs of stable heart rate around nominal sample points is a great advantage (though why people avoid QT-RR hysteresis in this manner rather than correcting for it remains an abiding mystery to me), but we reviewers of these data would like to have some insight into the nature of that selection process and what impact it has on study results.

The second reason for interest in Holter data has nothing much to do with TQT studies. We have struggled with assessment of ECG effects in antiarrhythmic drug trials. In recent years, we have shipped in hardware and software to review ECG data or shipped out a reviewer to go to a core lab to conduct part of the review.

AMPS-QT: ***How do you see the acceptance of the new Holter data format in the industry?***
NS: We are moving towards HL7 adoption of a standard, but we are not there yet. In the interim, perhaps AMPS and Mortara could help others prepare for this and even get their data uploaded for review.

As you know, the backbone of the ECG message is not much affected, and the new format accommodates a wide range of binary waveform data formats, so this transition should be less painful than the one people faced when we first started accepting digital ECG data. Nevertheless, once the HL7 process executes, we will give people some time to adapt before making submission of the Holter data an expected part of TQT study review.
And, of course, people who only collect 10-second data will be free to continue to do that and to use the existing HL7 message.

The Extended Standard

The current aECG
A 10-second, 12-lead ECG, sampled at 1000 Hz contains 120,000 samples and a set of annotations. ECG waveforms are encoded in the XML as a listing of sample values separated by white spaces. A single digit value and a space takes 2 characters (bytes) to encode, and a negative 3-digit value takes 5 characters (bytes) to encode.
An example of waveform encoding is shown below (ECG samples highlighted in yellow):

```
<component>
 <sequence classCode="OBS">
  <code code="MDC_ECG_LEAD_I" etc. />
  <value xsi:type="SLIST_PQ">
        <origin value="0" unit="uV"/>
        <scale value="3.75" unit="uV"/>
        <digits>-5 -5 -3 -1 -3 -4 -4 -4</digits>
  </value>
 </sequence>
</component>
```

A single annotation takes a few lines of XML encoding, which can correspond to about 3000 characters (bytes). An example of a QRS onset/offset annotation is shown below:

```
<component>
 <annotation classCode="OBS">
  <code code="MDC_ECG_WAVC"/>
  <value xsi:type="CE" code="MDC_ECG_WAVC_QRSWAVE"/>
  <support typeCode="SPRT">
   <supportingROI classCode="ROIBND">
    <code code="ROIPS" />
    <component>
     <boundary classCode="OBS">
      <code code="TIME_ABSOLUTE" />
      <value xsi:type="IVL_TS">
       <low value="20090505111144.188"/>
       <high value="20090505111144.282"/>
      </value>
     </boundary>
    </component>
   </supportingROI>
  </support>
 </annotation>
</component>
```

In addition to waveforms and annotations, an aECG XML file can/should also include patient demographic, study information, and a bunch of structural XML data.
The overall size of a digital 1000Hz aECG XML file can be estimated up to 0.7/0.8 MB, which can be broken down as follows:

- Waveforms (rhythm and median) : ~500 kb/file
- Annotations: ~60 kb/file for ~20 annotations
- Demographic and study information: ~15 kb/file
- Structural XML: ~15 kb/file

Although inefficient when compared to binary storage of ECG information, these XML files do not tax modern computers, networks, and software architecture.

The problem of Holter records

Some studies use Holter or telemetry ECG recording devices to capture continuously the ECG signal, with length of the processed data varying between 24 and 48 hours.

Considering an extreme scenario of an ECG with 12-lead, 1000Hz, 48 hour recording ECG, the total amount of digital data to store adds up to more the 2 billion ECG samples:

$$1000\left(\frac{samples}{sec}\right) * 3600\left(\frac{secs}{hour}\right) * 48\,(hours) * 12\,(leads) = 2{,}073{,}600{,}000\,(samples)$$

Which, using current aECG XML standard, will take about 9 GB of disk space. Typical XML software parsers read the entire XML structure into memory before making the individual pieces of information available to the hosting application. Although a few of today's computers may have enough processing power and memory to parse a 9 GB file in the current aECG XML format, it is unreasonable to expect all ECG labs and drug Sponsors to employ such computers for managing their ECG studies.

The solution: the extended aECG

The primary and most important enhancement of the extended aECG standard is to support the possibility to reference waveform data in external files. The previous aECG XML can still provide the structure and context to the data, but the actual sample values locations can be better encoded as arrays of numbers in external binary files.
An example of external waveform encoding is the following:

```
<component>
  <sequence classCode="OBS">
    <code code="MDC_ECG_LEAD_I" etc./>
    <value xsi:type="SLIST_PQ">
          <origin value="0" unit="uV"/>
          <scale value="3.75" unit="uV"/>
          <externalFile
            filePath="waveform_example.dat"
            fileType="LE_BINARY"
            itemType="INT"
            itemSize="2"
            ...
            ...
          />
    </value>
  </sequence>
</component>
```

The highlighted section shows the reference to the external file named *waveform_example.dat*, which is a binary array of 2-bytes integer values.
Annotations can also be located in an external file, which can be particularly useful in studies/situations where, for example, all the cardiac beats need to be annotated.

The following is an example of QRS onset/offset annotations encoded in an external file named *Annotations.dat*:

```
<component>
  <annotation classCode="OBS">
    <code code="MDC_ECG_WAVC"/>
    <value xsi:type="CE" code="MDC_ECG_WAVC_QRSWAVE"/>
    <support typeCode="SPRT">
      <supportingROI classCode="ROIBND">
          <code code="ROIPS"/>
          <component>
            <boundary classCode="OBS">
              <code code="TIME_ABSOLUTE"/>
              <value xsi:type="IVL_TS">
                    <low>
                      <externalFile
                      filePath="Annotations.dat"
                      fileType="LE_BINARY"
                      itemType="STRING"
                      itemSize="20"
                      recordSize="80" i
                      temOffsetIntoRecord="0"
                      recordCount="22"
                      nullValue=""
                      />
                    </low>
                    <high>
                      <externalFile
                      filePath="Annotations.dat"
                      fileType="LE_BINARY"
                      itemType="STRING"
                      itemSize="20"
                      recordSize="80"
                      itemOffsetIntoRecord="20"
                      recordCount="22"
                      nullValue=""
                      />
                    </high>
              </value>
            </boundary>
          </component>
      </supportingROI>
    </support>
  </annotation>
</component>
```

The external file mechanism proposed is extremely flexible and it includes various data types and encoding methods, from binary files to CSV text files, Little/Big Endian, compressed or not, interleaved versus sequential data within a single file or separate files for each item, etc. This allows support of many (if not most) existing Holter and annotation file types, including ISHNE waveform files.

In summary, an Holter aECG object can consist of a number of separate files:

- an XML file encoded in aECG HL7 format (approximately 30 KB);
- one (or more) external file/s with ECG waveforms;
- optionally, one (or more) external file/s with ECG annotations.

External referencing is particularly suited for large amount of data (such as waveform or the annotation for the entire record) whereas the "old" aECG HL7 format can still be used for including small amount of data.

ECG Workflows

We now show three potential workflow scenarios and where AMPS technology comes into place.

Scenario 1: ICH-E14 compliant workflow - 10s ECG extractions from Holter/telemetry (Figure A)
This is what is happening today. The extracted ECGs are submitted to the (un-extended) FDA Warehouse as single aECG files containing both ECG waveforms and annotations. The workflow is the following:

- Holter record acquisition
- Holter Beat detection/labeling Review
- Holter extractions generation
- Manual extraction using Holter proprietary software
- Optimized extraction, using Antares tool
- ECG Extractions over-reading by cardiologist, using CalECG tool
- HL7 generation of each 10s ECG extraction and FDA Warehouse submission

Scenario 2: - ICH-E14 compliant workflow - full Holter submission with AMPS Pollux (Figure B)
This is similar to scenario 1 where an extended aECG object is generated at the end of the process, i.e. without the need for Core lab to modify the existing workflow, and thus allowing adaptation to the extended standard with minimal impact. The updated workflow is as follows:

- Holter record acquisition
- Holter Beat detection/labeling Review
- Holter extractions generation
- Manual extraction using Holter proprietary software
- Optimized extraction, using Antares
- ECG Extractions over-reading by cardiologist, using CalECG tool
- Holter aECG generation, merging Holter record with Holter Beat annotation and 10s annotated ECG extractions.
- FDA Warehouse submission

AMPS has recently developed Pollux, a tool that performs exactly this, i.e. at the end of the process of an extraction-based study, it brings together all the pieces (continuous data in ISHNE format, ECG extractions and related annotations) and generate all the necessary records (one extended aECG per Holter) to be submitted.

Scenario 3: future workflows - full Holter submission - (Figure C)
Ideally, studies involving continuous ECG should process the data and generate all the necessary aECG objects in a single step, thus avoiding the need to go back and forth. This ideal workflow should be as follows:

- Holter record acquisition
- Holter Beat detection/labeling Review
- Holter annotation and submission to FDA Warehouse

While being the ideal way to go, this scenario will require significant amount of work as it would imply in most cases a complete new design of Core lab workflow. Nonetheless, we expect this scenario to be the future and the correct way to implement and submit new methods of analysis. In this regard, AMPS is currently working on a new version of WinAtrec, the platform that embodies the Holter-bin and the beat-to-beat approach.

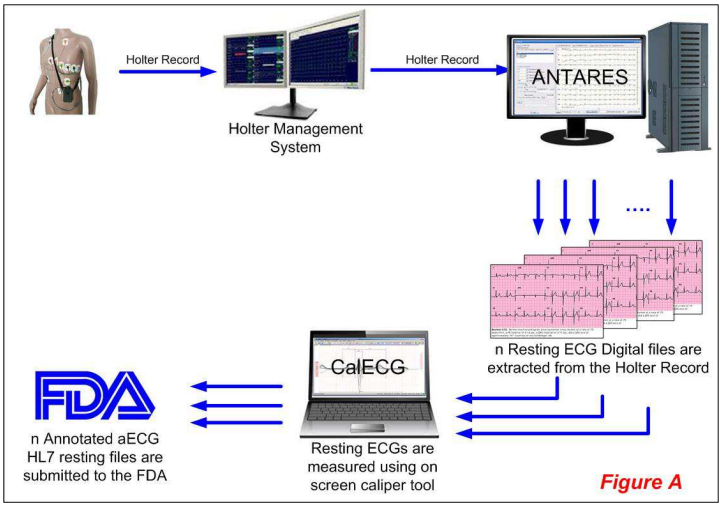

Figure A

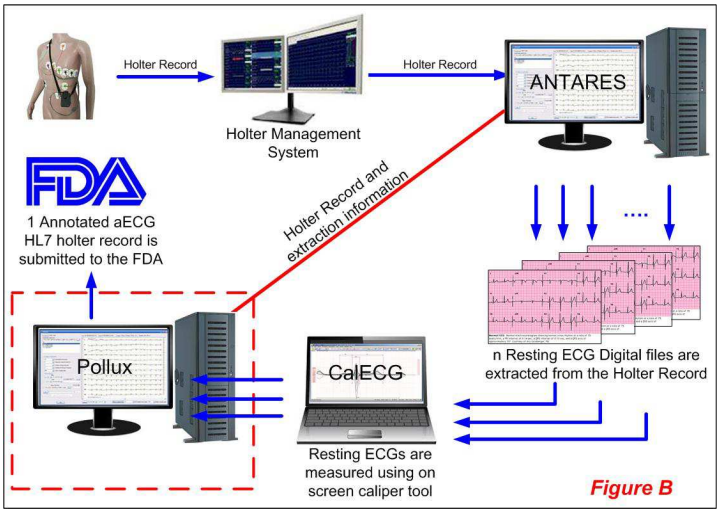

Figure B

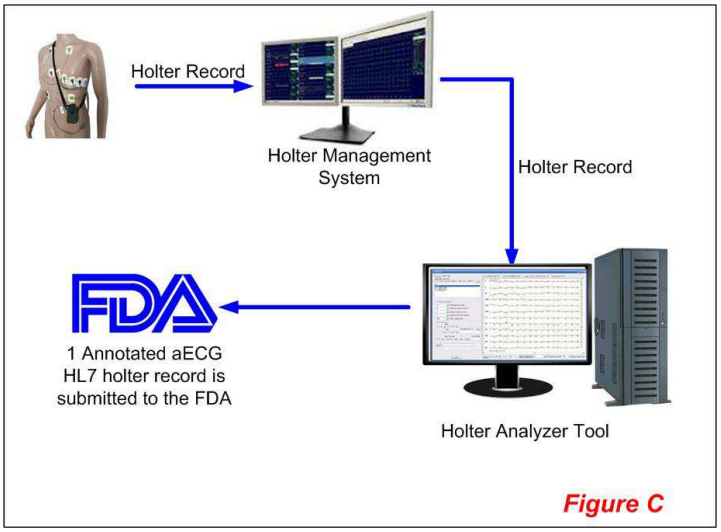

Figure C

Mortara's perspective

To wrap-up this overview, we asked Barry Brown from Mortara Instrument, Milwaukee, WI to provide for our readers a concise bullet-point summary of the project.

AMPS-QT*: How advanced is the testing of the new Warehouse Software?*

BB: In order to test the expanded warehouse we have asked AMPS to provide some Holter samples independently generated by their technology.

We have received a few data samples generated by Pollux (see the previous article in this magazine) and we were able to successfully import them, thus confirming compatibility with the latest ECG warehouse release.

AMPS-QT*: Did the new standard obtain formal approval?*

BB: HL7 has approved the "Annotated ECG v2" project and expects to formally approve it in 2015 after it goes through their standardization process.

AMPS-QT*: Is the new ECG warehouse ready?*

BB: The ECG Warehouse stands ready to receive data in the proposed format.

Products News

Latest Releases

In Q1 2013 we have released:

- Fat-QT v. 1.2.0, with v. 4.1.1 of BRAVO algorithm;
- TrialPerfect v. 2.9.0, with CalECG v 3.3.x and improved usability thanks to several new features.

Looking forward

We are in the latest stages of validation of:

- CalECG v. 3.5.0, with the latest BRAVO algorithm;
- Fat-QT v. 1.3.0, with the latest BRAVO algorithm;

Both products will be released in April 2013.

AMPS Notebook

Fabio Badilini will be attending the 38th **ISCE conference**, the meeting he chaired last year, that will be held in San Jose, CA from April 17th to 24th.

AMPS Recommends

Rather that focus on a new article, we take advantage of this special issue to reference the original paper that described the ISHNE format. This article, published in 1999, was led by our Chief Scientist Fabio Badilini and it is recognized as pioneering work. As of today, this

continuous ECG format is widely used, particularly after the advent of the Telemetric Holter warehouse (THEW) that adopted ISHNE as the standard to store their ECG records. AMPS Holter technology also uses ISHNE extensively and we expect to see many external aECG waveform files also being ISHNE.

Badilini F, The ISHNE Holter Standard Output File Format, ANE 3 (1998), 263-266.

The paper can be downloaded from the AMPS website.

AMPS People

On this issue of our bulletin, we introduce the latest AMPS acquisition: Federico Piantoni.
Federico obtained his Bachelor degree in Engineering from the University of Brescia in 2012, discussing the thesis titled: "Graphic representation of 1D and 2D data on portable devices".
Federico joined AMPS mid-January this year and he will mainly focus on developing Android and IOS based applications for portable and mobile devices.