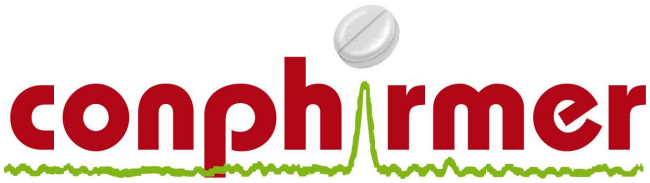
FRONT PAGE

PROJECT FINAL REPORT



Grant Agreement number: 261670

Project acronym: CONPHIRMER

Project title: Counterfeit Pharmaceuticals Interception using Radiofrequency Methods in Realtime

Funding Scheme: CP

Period covered: from 01/07/2011 to 31/12/2014

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Project website Error! Bookmark not defined. **address: www.conphirmer.eu**

[1] Usually the contact person of the coordinator as specified in Art. 8.1. of the Grant Agreement.

4.1 Final publishable summary report

Executive Summary

CONPHIRMER is a collaborative project (CP) funded by the European Commission under the Security theme of the Seventh Framework Programme (FP7). The project started on 1 July 2011 and lasted 42 months. The project coordinator is King's College London (KCL, UK). The other beneficiaries are Franco-German Research Institute, St Louis (ISL, France), Institute of Mathematics, Physics and Mechanics (IMFM, Slovenia), Post-graduate School of the Josef Stefan Institute (MPS, Slovenia), Lund University (LUND, Sweden), Ministry of Finance – Customs Service (PCS, Poland), Stelar s.r.l. (STELAR, Italy), London South Bank University (LSBU, UK) and Bagtronics Ltd (BAG, UK). A further beneficiary, Rapiscan Systems Ltd (RSL, UK) dropped out in early 2012, replaced by STELAR, LSBU and BAG.

The URL of the project is: http://www.conphirmer.eu

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The CONPHIRMER consortium has come together to put into the hands of customs officers and other agents of law enforcement a portable and easy-to-use sensor for telling genuine medicines from fakes without having to remove the medicines from their packaging. With this device agencies charged with tackling the growing menace of the trafficking in counterfeit medicines will be able to screen packaged pharmaceuticals at EU borders and airports quickly and accurately using a non-invasive and non-destructive technology that uses only harmless radio waves. The proposal is for a three-year programme leading to the trialling of a prototype, portable scanner that will draw on the expertise of seven organisations in five states, including two recent additions to the EU family, Poland and Slovenia. The technology employed will be based on quadrupole resonance (QR), a radiofrequency (RF) spectroscopic technique that has already been developed and deployed for the detection of concealed explosives. The completed prototype will not require operators to have special technical knowledge to deploy it, allowing training in its use to be completed quickly; and it will utilise only easy to source RF and electrical parts. It will also offer a clear advantage over optical-based technologies in that RF can penetrate even multiple layers of packaging material, allowing for scans to be carried out without the need to remove pharmaceutical products from their packaging.

Project Context and Objectives

In 2014, the United Nations Human Rights Council adopted a resolution recognizing access to safe medicines as a human right. The global nature of the trade in counterfeit medicines is illustrated in the map, below, reproduced from an article in the New York Times in December 2007, which shows the route that a counterfeit medicine took from its point of manufacture in China to its point of sale in the USA.

Figure. The Global Nature of the Trade in Counterfeit Medicines (picture courtesy of CTV/the New York Times).

The danger to public health arises from a rise in infectious diseases with the potential for drug resistance, from the risk of poisoning from toxic materials present in counterfeit formulations and from the channeling of profits from this illicit trade into other criminal and terrorism-related activities. A rapid, widely-deployed, field-based detection system that will allow conclusive identification and classification of counterfeit drugs whilst not delaying the distribution of verified medicines should offer a valuable tool in the control of counterfeit medicines. By aiding in the detection of counterfeit or fake or substandard medicines, this technology can help combat a major threat to public health and considerably reduce the risk of a medical pandemic by intercepting counterfeit or substandard medicines before they reach the patient.

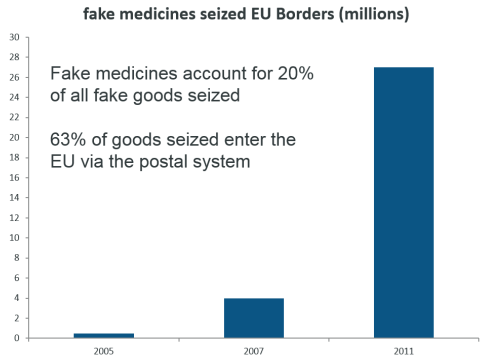


Figure: The rise of the seizure of fake medicines at EU borders (figures: EU press release April 2014)

If we consider the EU, there has been a dramatic increase in the seizure of fake medicines in recent years (figures from an EU press release April 2014), as illustrated in the chart on the next page.

The CONPHIRMER consortium has come together to put into the hands of customs officers and other agents of law enforcement a portable and easy-to-use sensor for telling genuine medicines from fakes without having to remove the medicines from their packaging utilizing a technology known as “Quadrupole Resonance” (QR).

The project objectives have been framed around the anticipated operating procedure for the prototype QR-based medicines authentication device:

Operating Procedure for the CONPHIRMER Medicines Authentication device

1. Genuine medicine classified by a QR "fingerprint" of QR characteristics specific to that medicine
2. Purported identity of packaged medicine to be investigated is read into device (barcode/name on label)
3. Package scanned: QR response of packaged medicine under investigation is recorded
4. The QR response is compared with fingerprint held in device database
5. Yes/No: do the contents match the label?

Each element of this procedure has a work package built around it within which there are additional key scientific and technical objectives:

Key scientific and technical objectives of the CONPHIRMER project
1. To establish a database of drug QR fingerprints for use on the CONPHIRMER Medicines Authentication device
2. To determine those key characteristics of the QR signals of the targeted medicines that give the best discrimination between active pharmaceutical ingredients (APIs) in different solid formulations; and then to develop pulse sequences to target those key discriminators.
3. To design and implement data-processing algorithms for detecting and discriminating true QR signals from noise, interference, and various forms of spurious signals; and to provide information on line width and line shape to discriminate between genuine and counterfeit medicines.
4. To build up the proof of concept demonstration and thereafter develop a prototype CONPHIRMER medicines authentication device suitable to be used for performance trials in the field.
5. To demonstrate the completed CONPHIRMER device in a real environment, first to participants and then to the European Commission and other parties outside the consortium.

The main objectives for the first period were to start-up and push forward all key scientific and technical objectives in line with the project plan with a view to be able to complete the design of the prototype device by just after the end of the period. In order to achieve these aims, key questions had to be asked and answered within this first period:

- What medicines being transported across EU borders were at risk of counterfeiting, what were the characteristics of the QR responses of the active pharmaceutical ingredients (API) of these medicines, and how did these characteristics vary with temperature across the range of temperatures encountered at EU borders?
- What aspects of the QR response could be used to discriminate the API being targeted from other APIs to ensure correction authentication, and how should the QR signals be captured to ensure that these discriminating characteristics could be measured?
- Could signal processing tools be developed to measure the discriminating characteristics of the QR response and provide reliable authentication?
- Given the configuration of packaging of medicines arriving at EU borders could a prototype portable device be designed to ensure that the QR response from the medicines being targeted could be captured in a minimally invasive manner?

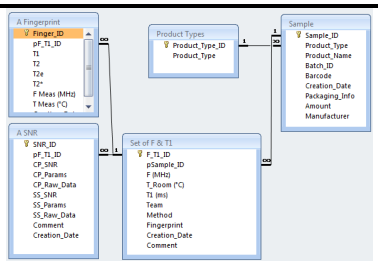
Milestones for the period were designed to allow the project Scientific Steering Committee (SSC) to assess progress towards answering all these questions within the period, and ensure that, by period end, the design for the prototype device was nearing completion.

Key objectives in the second period were milestones on the road to completing the device:

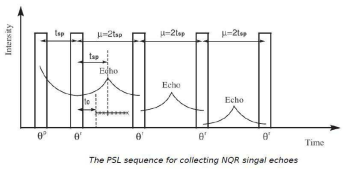
- Growing the QR fingerprint database to a degree sufficient to ensure that the device could be used with multiple brands and configurations of multiple medicines (milestone MS2)
- Device power configuration decided (milestones MS3 & MS4)
- RF pulse sequences for authentication written (milesone MS6)
- Prototype Assembly (milestones MS8 & MS9)
- Venues for the laboratory and field trials selected (milestone MS10)

The main function of the Scientific Steering Committee (SSC) in this period was to ensure that milestone were met, and, in the event of a milestone being missed, that this did not have a negative impact on other goals.

Main S&T results/foregrounds

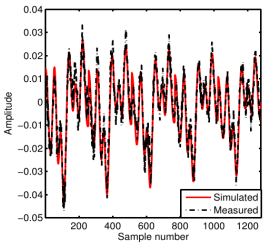


QR Drug Fingerprint Database building

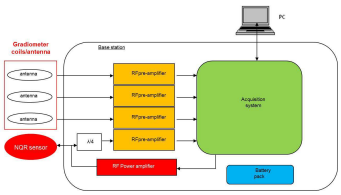


The PSL sequence for collecting NQR singal echoes

QR Discriminators and Detection Methodology



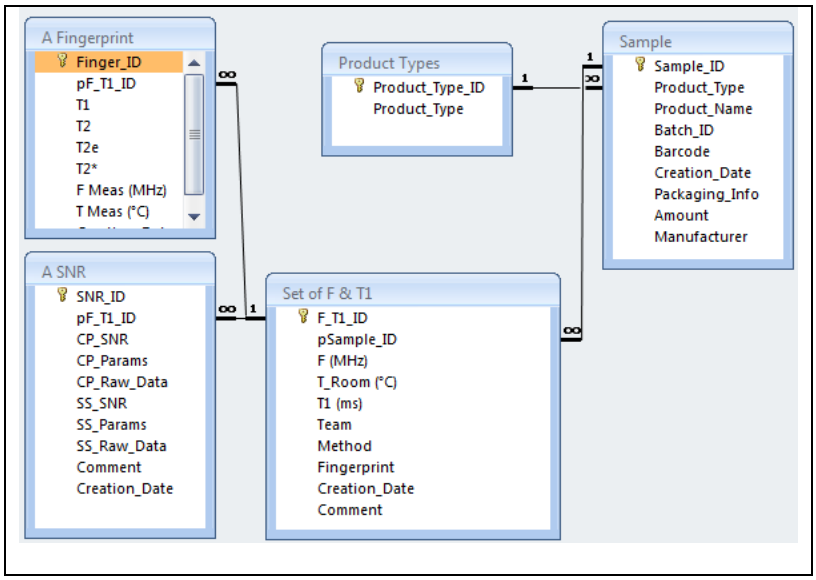
Signal Processing

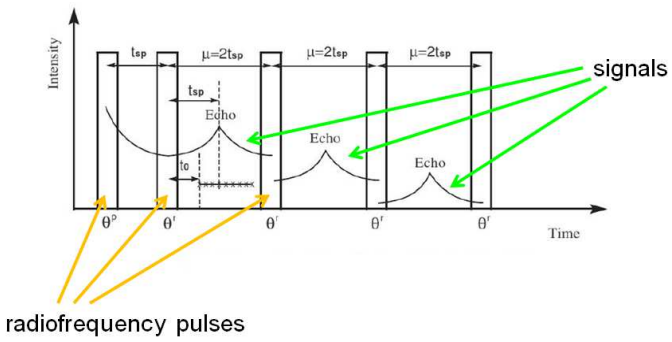


Prototype Medicines Authentication Device Build

WP2 Drug Fingerprint Database: A three-step protocol for building the Quadrupole Resonance (QR) fingerprint of the medicines of interest has been drawn up. Based on a survey of medicines seized at Polish borders, the project Scientific Steering Committee (SSC) drew up a list of medicines to be added to the database, with priority given to much-counterfeited medicines such as sildenafil and orlistat; Paracetamol was chosen as the test compound to be used in all aspects of QR development due to its low cost, ubiquity across the EU and availability in different formulations and configurations of packaging. Methods of bringing about possible reductions of RF excitation power in QR experiments, which could lead to reduction of QR instrument complexity, size, weight and external power requirements, were also explored.

The database was then extended. This involved adding the range of brands and package configurations for the target medicines for which fingerprints were generated. Possible packaging configurations included loose blister packs (blister packs with one metal and one plastic side, or with two plastic sides), blister packs in boxes and loose pills in bottles. Blister packs could contain pills or capsules (filled with loose powder). Single brands could be encountered in different packaging configurations; for example, for the analgesic acetaminophen brand "Tylenol", it was necessary to construct fingerprints for both loose pills in bottles (sourced from US-based sellers) and pills in all-plastic blister packs (sourced from the Indian subcontinent). Similarly, separate fingerprints were required for, for example, Tylenol bottles containing 325 pills and Tylenol bottles containing 500 pills. It was decided to add the diabetic treatment metformin [hydrochloride] to the range of different drugs to be explored in the trials. Fingerprints were generated for different configurations of metformin encountered (sourced from the Indian sub-continent).





WP3 Discriminators and Detection Methodology: The intensity of a captured Quadrupole Resonance (QR) response is directly-relatable to the amount of material present, making the technique both qualitative and quantitative. The challenge in using QR to authenticate a medicine is in positively identifying a QR response as having come from the active pharmaceutical ingredient (API) of the targeted medicine. Comparative studies of several medicines were carried out to identify those characteristics of the QR response (frequency & time-specific behaviour) that allow one API to be told from another. QR device uses pulse techniques, in which one or more RF pulses are used to excite the sample, with the emission signals from the sample being acquired in the quiescent period following the pulses. When two or more pulses are used signals known as echoes can be observed in the quiescent period between pulses. For the purposes of discriminating between QR responses from the API of interest, and all other QR responses at or near this frequency, multiple-pulse pulse sequences have been designed that allow the time-specific behaviour of the response to be monitored as well as the frequency of the QR response and its intensity. A laboratory-based proof of concept exercise assessing the separate elements of a complete QR-based medicines authentication system was successfully carried out.

Having established the key discriminators in the QR response to be used for the fingerprints in the first period, and having carried out a proof of concept exercise also, WP3 was brought to a conclusion early in the second period with the decision to focus on the high-power so-called "pulsed spin-locking [PSL]" pulse sequence as the main sequence to be loaded into the device. At the same time, low-power pulse sequence of the "stochastic" or "noise" spectroscopy form was held in reserve as

risk mitigation. With these considerations set, the final design of the device was set as part of the Product Design Review (PDR).

The NQR fingerprint would consist of some or all of the following measureable, quantifiable characteristics of the NQR response:

measureable, quantifiable characteristics of the NQR response			
Intrinsic to the material	**A convolution of an intrinsic characteristic of the material and sample processing (e.g. pressure applied in creating pill)**	**A convolution of intrinsic characteristics of the material and pulse sequence parameters**	**A convolution of an intrinsic characteristic of the material, of the amount of material present and pulse sequence parameters**
Line frequency Temperature coefficient (Hz/K) Spin-lattice relaxation time: T_1 Spin-Spin relaxation time: T_2	T_2*/linewidth lineshape	T_{2e}	signal intensity

Note: an nqr spectrum generally consists of a number of lines, so there is a selection choice in which line or lines(and therefore frequency or frequencies) to target for the fingerprint; T1 and T2 each require a series of experiments to measure and thus are unlikely to be a direct part of the fingerprint (present indirectly in T2e and T2*); knowledge of temperature is required for use of frequency information allied to the temperature coefficient

The fingerprint could be in the form on an image of the NQR response (e.g the spectrum) for direct comparison with that acquired during the authentication event, but would more likely be a string of acceptable values for some or all of the characteristics above that could be compared [automatically] against values extracted from the authentication event following signal processing.

WP4 Signal Processing: Key progress has been made in the evaluation of first generation detection and classification algorithms, and in the development of improved second generation methods. In addition, improvements have been introduced, both, in the computational aspects, and the interference cancellation capabilities, of the current algorithms. A Cramer-Rao lower bound has been proposed for the estimation of the signal parameters. Further work is being carried out to study and handle non-stationary interference signals, and to test the algorithms on more experimental data. The LUND team will also continue the further development of the Matlab code repository to reflect current and future developments.

$$y(t) = \sum_{k=1}^{d} \alpha_k e^{-\beta_k |t - t_{sp}| + i\omega_k(T)t} + w(t)$$

example of one of the signal processing algorithms

Third, and final, generation detection, authentication and classification algorithms were composed and integrated with the prototype. Following feedback from the laboratory trials, modifications were made prior to the field trials.

WP5 Prototype Build: the prototype CONPHIRMER medicines authentication device was constructed. A 1st-generation device was tested in the laboratory trials. Feedback from the trials led to a slightly-modified 2nd-generation device being taken to the field trials location. A second 2nd-generation device were fabricated, but not assembled into a device, being used, rather as essential spares to be taken to the field trials location.

WP6 Dissemination: the CONPHIRMER website is up and running (www.conphirmer.eu) and project beneficiaries have engaged in dissemination activities at a variety of conferences, meetings and workshops to audiences consisting of members of the scientific community, industry representatives and also representatives of regulatory authorities within Europe.

Figure Project website front page

The first workshop took place at Institut Saint Louis in February 2013, presenting the project to interested parties and outlining early results.

A second, and final, workshop was held at King's College London following the successful conclusion of the trials, and the main outputs from the project were presented there to a small, but varied audience including members of the external scientific advisory board (SAB).

WP7 Trials: laboratory trials were held at the headquarters of project beneficiary STELAR near Milan, Italy, in September 2014. Following preliminary trials in July 2014, the final field trials took place across the week of 24 – 28 November 2014 at a postal sorting facility near Warsaw Chopin Airport, Warsaw Poland. The field trials were organised by beneficiaries BAG[tronics] and PCS [Polish Customs Service] and hosted by PCS. A sorting facility was chosen as the trials venue following advice that most counterfeit articles entering the EU enter via the postal system (e.g. according to an EU press release 19/04/13 in 2011 63% of fake articles seized came in through this route [the same press release revealed that 20% of all articles seized are fake medicines]).

Figure Field trials venue, Polish Postal Service Sorting Facility, near Warsaw Chopin Airport, November 2014

Field Trials

1	**M2**
2	M3
3	M3
4	O2
5	O1
6	O1
7	O2
8	M1
9	M2
10	M1

Trials took place across the week of 24 – 28 November 2014. The plan, worked out during and after the laboratory trials, and subsequently approved by the SSC. A record of the trials, including deviations from the original plan necessitated by events, is given on the next page. As the trials team could not rely on suitable packages coming through the sorting office on the days the trails team would be there, a set of test samples consisting of actual medicines purchased over the internet, kept inside their original postal packaging was assembled in advance. A randomized sample running order was constructed to remove system biases. An example of part of one run in given left. "M1" "O1" etc. refer to specific samples (M – metakelfin O – omeprazole). Photos of some of the samples are shown on the second page following.

It was discovered on unpacking that the system had been damaged in transit, specifically one of the two signal amplifiers on the receiver side of the system had ceased to function. This resulted in a drop in signal gain (intensity) that rendered the pre-set signal processing useless. A work-around based on a partial implementation of the algorithm employing signal-side only, neglecting the noise cancellation was improvised on site. This allowed the trials to proceed but made it impossible to have real-time authentication outside of the shielded box provided for the first level measurements. In the event this did not greatly hamper the trials as it proved that customs officers were happy – and indeed in some respects preferred – to work with the static system.

CONPHIRMER Field Trials Record, Postal Sorting Facility near Warsaw Chopin Airport			
Day	**09.00 – 13.00**	**14.00 – 17.00**	**Notes**
24/11	Unpacking and system set-up	System repairs following discovery of break during shipping; followed by measurements to discover best system configuration	*Damage to system made it impossible to used pre-calibrated noise cancellation algorithms making working within the shield only way to proceed for red light/green light authentication during trials*
25/11	Tests inside shield, 50 measurements, randomized order, five samples 3 x paracetamol, 2 x omeprazole (as a red light)	Tests inside shield, 50 measurements, randomized order, five samples 3 x metformin, 2 x omeprazole (as a red light)	*Red light green light authentication, 98% authentication 100% detection*
26/11	Tests without shield, 50 measurements, randomized order, five samples 3 x paracetamol, 2 x omeprazole (as a red light)	Performance review; meeting to discuss if any way to short-cut process of calibrating noise cancellation even with damaged system	*Decision taken to proceed with allowing customs officer to use system with samples placed inside shield*
27/11	Short series of test runs to check still achieving good authentication red light green light with samples inside shield Followed by allowing customs officer to try system for himself	Results work-up; consultation with project partners on work for final day	*Decision made to complete unshielded measurements for processing after trials*
28/11	Tests without shield, 50 measurements, randomized order, five samples 3 x metformin, 2 x omeprazole (as a red light)	System repacking and clean-up	

Working within the shield, with the new sample gain factors, and the test samples the trials team had brought with them (3 x paracetamol, 3 x metformin and 2 x omeprazole – the latter used as blanks [i.e. samples that, although medicines, should generate red lights as not paracetamol or metformin]), the trials team were able to achieve *98% authentication* (is the sample what it is supposed to be, and present in the correct amount, yes or no?) & *100% detection* (is the sample what it is supposed to be, yes or no?), for both paracetamol and metformin. That was across 133 measurements in total. Total measurement time from sample in to red light/green light: 120 – 150 seconds (depending on time it takes to tune). The samples were run using a randomised sample order. The running order for both the metformin and paracetamol runs are presented as an appendix.

The procedure followed was: place sample on top of the coil inside shield – close lid – press "tune" on handle; system tuned using handle with tuning feedback provided by lights and number on a digital display on the handle – press "scan" on handle; system starts acquisition, data capture, signal processing and decision making – system outputs green light/red light on laptop screen & "00" (red) or "01" (green) on handle digital read-out. The important thing to note is that, once the name of the medicine to be searched for is entered on the laptop screen, everything else happens on the handle.

With this level of performance the trials team felt confident enough to allow an officer of the Polish Customs service to have a go. He picked up the operating procedure in a matter of a few minutes. He then ran through seven samples searching for paracetamol, six picked at random from our sample set (including blanks), & one he just picked up from the packages being processed elsewhere in the sorting hall. All returned the correct lights (the package the officer picked up was food supplements – so red light for paracetamol).

One last thing to note about this part of the trial: the trials team discovered that the numbers on the digital readout on the handle that are used to give an indication of how well-tuned the system is give a good indication of whether or not the sample is orientated correctly with respect to the coil for good signal return i.e. whether the plane of the blister packs is parallel to the plane of the coil (bad) or edge on (good). If the display read “00” in tuning mode (i.e. tuning is out of range), you need to flip the sample on its side, and then you are in the right orientation. Of course, this was only necessary with samples containing blister packs.

The customs service officer also tried this for himself as part of his working with the device.

Getting the correct orientation is an important part of guaranteeing reliable authentication.

It was not possible to do full authentication with the system outside the shield because of the system damage but test datasets for unshielded for both paracetamol and metformin were acquired for processing later. In the event the project concluded before this could be completed. However, the results will be included in a subsequent academic paper detailing the trials and the outcomes.

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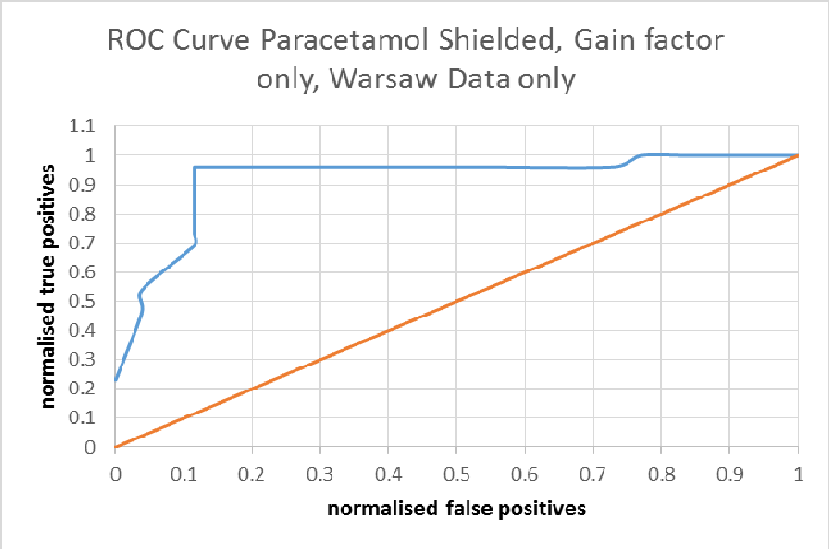
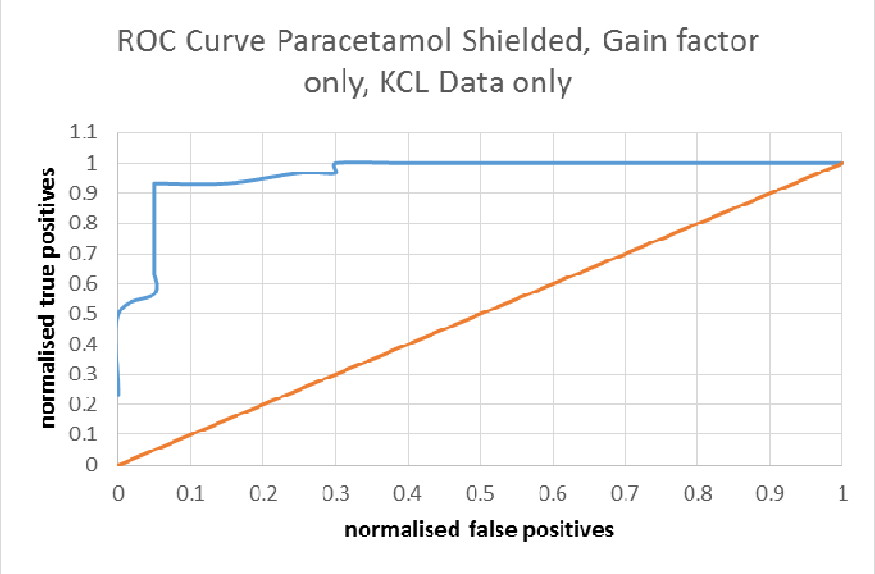
ROC curves were constructed based on the shielded measurements illustrating system performance based on the jury-rigged partial version of the signal processing algorithm. With the number of measurements curtailed by the initial teething problems and the need to pack and unpack the system after every session, the form of the ROC curves is not ideal, unduly-influenced as they are by occasional rogue results. Nevertheless, the curves make clear that performance with the shielded, static system, even with the partial version of the signal processing algorithm was excellent. This was further proven when the trials measurements were repeated at King's College London with comparable results. To illustrate this, the ROC curves for the paracetamol-frequency runs in Warsaw, KCL and combined are shown on the next page.

ROC Curve, Warsaw Data only



ROC Curve KCL Data only



ROC Curve Combined