Plastic Electronic Technologies for Biosensors: Workshop Report

Workshop Report

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Final

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Workshop Background

Printed biosensors for the point of care (POC) market are a future and key development opportunity for a large supply chain of organisations in the UK. The global In-vitro-diagnostics (IVD) market is currently worth $50Bn per year and the printed biosensor market for glucose monitoring is currently worth $6.4bn (IdTechEx). In general, using POC devices and systems offers lower cost routes towards continuous monitoring of patients and reduces dependency on primary health systems. The challenge therefore is to get them developed, certified and adopted by national healthcare providers which have slightly different care and cost models. In the UK, the POC market use equates to typically around £13 per capita which is currently around 50% lower that Western Europe's use per capita (£26) which points to issues with adoption however other countries markets are accessible in Europe. The technical development of biosensors is driven by the ability to be able to make many millions and potentially billions (in the case of blood glucose) of packaged devices that are cost effective to both the private and public health provider and consumer. The UK has a large NHS system which is capable of adopting these technologies and a good scientific and engineering community which has a good innovation capability.

Plastic electronic technologies can potentially offer manufacturing solutions for the production of biosensor devices. Large area Roll to Roll (R2R) printing, coating, deposition and encapsulation technologies used in the development of printed circuits could be applied. The technical challenge therefore is to be able to produce sensors using a variety of materials systems and techniques which integrate ultimately with roll to roll manufacturing techniques which drive down the unit costs. A commonly used technique for producing biosensor electrodes is screen printing but equally photolithographic and other traditional techniques can be explored.

It is under this context that the Knowledge Transfer Network collaborated with the HVM Catapult's National Printable Electronics Centre in Sedgefield to explore the commercial issues and technical factors for the successful up-scaling of research level sensor devices (TRL 1-3) to the next stage of development where clinical trials are then possible (TRL 6/7). Design for manufacture becomes an important element when translating research. The workshop was attended by 39 invitees with 21 from the SME base and 8 academics in the sector. The workshop was also supported by Innovate UK and Business Innovation and Skills department.

Key Conclusions

- There are several manufacturing techniques that plastic electronics uses which are very applicable towards low cost biosensor development
- The key technical challenges are developing, depositing and ensuring good reproducible quality of the biomarkers
- The adoption and certification of products is not easy and innovation timescales are long
- The UK has a good base of research and SMEs however the market is dominated by 4 non-UK companies
- Funding for biosensor development is good although late stage manufacturing and support for clinical trials are relatively rare in the UK

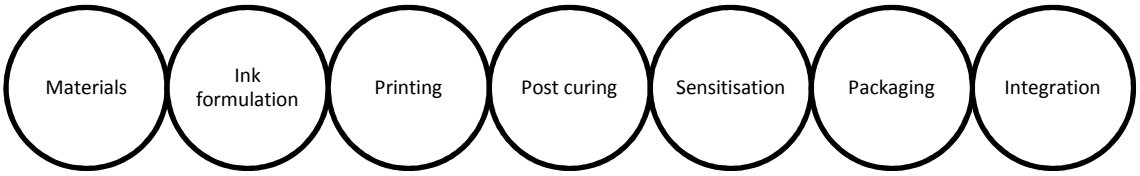
Workshop Methodology

The workshop invited a group of current sensor developers, plastic electronics manufacturers and academics. In the morning, presentations were given by manufacturers and academics and then in the afternoon the group discussed 9 questions designed to explore the key innovation issues that face UK innovators from academia and industry. The cohort was split into 6 groups which addressed 3 questions each such that each question was addressed by 2 groups. The groups were facilitated by members of the KTN (Martyn Cherrington and Matt Butchers), CPI (Tom Taylor, James Johnstone and Tom Harvey) and a consultant (Brian Birch). Each group was asked to consider their 3 questions and write the important messages onto a flip chart which was then reported back to the main group. The facilitators then wrote up their notes which were collated into this synthesis report.

Workshop Discussion Topics

Question 1: What printed electronic manufacturing technologies are amenable towards industrial scale-up of biosensors?

A typical development process for biosensors might need to consider some the following process steps.



Materials and ink formulations

Materials for biosensing encompass a large range of potential technologies. The active bio molecules can range from simple molecules through to antibodies, proteins and DNA. They all present challenges in synthesis, purification and storage. These materials may form the active constituents or the support materials which will hold the ink together or provide useful functionality. These might include supports (metal oxides or nanocarbons e.g graphenes, nanotubes), photoactive polymers (for UV curable inks) and rheological modifiers. Ink formulations need to be carefully matched to the printing and curing techniques to ensure that the correct functionality can be achieved in the finished device.

Additive manufacturing techniques

There are several technologies which are amenable to the industrial up-scaling of biosensors. They can be divided into two generic types, digital and analogue. They can be also separated by the form

in which the end sensor is manufactured, either in batch (sheet) or by roll. Many of the manufacturing techniques for biosensors have a basis in the traditional printing industries and also the thin film coatings industries however many alternative techniques can be applied to the process once the cost points have been identified. These techniques can be modified or used in combinations to provide a wide variety of structures and devices either in a sheet or continuous form. The table below shows a range of manufacturing techniques which can be used.

Manufacturing Techniques	Batch or Sheet	Roll 2 Roll
Digital Techniques (includes directed patterning techniques which require specific placement)	Ink-jet, bio spotting, syringe deposition, photolithography, laser ablation & cutting, aerosol jet, , glue dispensing, laser sintering, chemical plating, DLP and FDM printing, pick and place (for SMD electronics).	Industrial Ink-jet, atomic layer deposition, digital lithography (experimental)
Analogue Techniques	Screen print, embossing, electroforming, lamination, etching, vapour deposition (CVD, PVD), atomic layer deposition (ALD)slot-die coating	Rotary screen, Flexography, Gravure, Off-set lithography, slot-die coating.

Screen printing was felt to be the most applicable common manufacturing technology currently, due to its relative accessibility. It has the advantages that it is cheap, scalable and is a mature technology. R2R (rotary) screen printing can also be used when large volumes are required or when the biosensor material needs to be provided on a roll or a tape for ease of lamination into other layers of a test strip product. One potential problem identified with screen printing is how to protect already printed layers from damage during printing of additional layers on top, particularly if the already printed layers contain bio-materials. Since the biomaterial will almost always contact an aqueous analyte when in use, one approach here is to print a layer of water permeable material over the biolayer. This is then followed by the other print steps patterned so as to expose a measurement window. Clearly the (single use) sensor must acquire data before sample ingress reaches the non bio regions.

There are common raw materials requirements between the two modes of digital and conventional printing. For example the materials of the flexible substrate are common (PET, glass, PC, polyimide). Also both modes may require coatings, such as moisture barrier coatings or bio-compatible coatings which are manufactured in the same way (e.g. using ALD). Typically, transparent conductive substrate materials may also be required by both, therefore methods for manufacturing such materials using for example ITO or Silver nanowires may be important.

Developers may need to be able to solder or make other conductive joins onto the substrate film, after making the biosensor, in order to add other electronic components. This is also a requirement in printed electronics manufacturing so mounting technologies such as pick and place are likely to become important.

Digital photolithography was highlighted. It can be used for high resolution patterning of electrode arrays or for high resolution patterning of biomaterials into arrays of small sensor pixels. Digital

methods have the relative advantages of low ongoing tooling costs (once the asset has been installed) and fast turnaround times (as used in the silicon microfabrication arena). Because the pattern is generated digitally, the sensor can be personalised very easily. If digital photolith could be combined with R2R production at high line speeds then it could be applied to industrial scale manufacture of biosensors in high volume applications.

Inkjet printing was mentioned as another printing method which could be used in the scale up of biosensor manufacturing. It can be used for the printing of the transducer element. It is not the ideal method for printing of the bio-receptor because of the high chance of damaging the bio-receptor during printing as high shear forces bear on liquids as they are forced through small apertures.

Flexographic printing was mentioned as a suitable technique but it is only really applicable to very large volume biosensor applications which at this time, means blood glucose sensors. There is a need for new inks for flexographic printing, especially carbon based inks to drive down production costs.

Micro-pipetting is a method commonly used for depositing the bio-component. This method is less commonly used in printed electronic components but it is commonly used for printing adhesives. It has the advantage that it does not apply large forces to the solution being printed, nor does it heat it up or force it through a screen, unlike other printing methods such as inkjet or screen printing.

Ink formulation is needed in both digital and analogue printing technologies. In the biosensors case, it is possible to formulate an ink which contains both the conductor (e.g. carbon) which forms part of the transducer and also the bio-material which does the sensing. Recent thinking is not to incorporate biomaterial or expensive graphene. Rather to form an active layer on the surface of the ink.

Encapsulation and over-protection methods are needed for both biosensors and printed electronics. In the case of printed electronics, the active organic materials susceptible to moisture damage and so need to be fully encapsulated to ensure that they have a lifetime of >50,0000 hrs (in the case of a display for example). This means that manufacturing methods for applying thin film coatings, lamination, edge seal and metal printing are required. In the case of biosensors, the sensor needs to be able to withstand long term storage and temperature cycling over a wide temperature range (e.g. many freeze-thaw cycles) prior to use, without this affecting the result of the test. The bio-receptor material is normally the most sensitive part and it needs to be protected. This can be done by drying it, preventing it from coming into contact with air or moisture, by incorporating it into a more stable matrix of some type or by over-coating it in some way.

In printed electronics the final product may have to be thermoformed or made into a label or converted in some way to integrate with the finished product. In biosensors, the sensor film might have to be made into the form of a lateral flow test strip or a bag or some other suitable form, perhaps using microfluidic technology. The same manufacturing technologies such as lamination, sealing, slitting, thermoforming may therefore be used.

Integration - Smart systems integration was highlighted. This tends to be commonly overlooked but is the last piece in the puzzle. Taking finished biosensor components and making tapes and converting them to smart patches or laminating technologies is crucial in making a viable product.

Converting technologies include, splitting, moulding, encapsulation, folding and packing. The sensor elements and transducer elements often need to be linked to the outside world in some manner. Often they are just inserted into a reader which makes an electrical connection to the transducer or provides an optical readout. However if there is a need, or advantage in the sensor being interrogated wirelessly then an antenna and an RFID or similar chip is required. For an active sensor tag a battery is also needed. It is possible to provide power in favourable cases e.g. urine sample by using the liquid as electrolyte with on board battery elements The technology for integrating these additional components with the biosensor needs to be scalable to large volumes and they need to be low cost, especially for certain one-time use biosensor applications.

Question 2: What are the main commercial issues that need to be considered?

Equipment and skills

Capital cost of investing in large manufacturing equipment versus the numbers of devices required to address market need. Careful consideration and matching of the manufacturing techniques and their associated cost models to the volumes of sensors required is needed so that businesses are not burdened with expensive capital equipment that may be either overloaded or underutilised.

Access to printing equipment and/or manufacturing facilities. For innovative SMEs, it may pay dividends to outsource manufacturing to other organisations to reduce economic burdens. Access to printing equipment can be achieved via contract manufacture either within the UK or overseas. Some large scale manufacturing equipment may have constraints of minimum run volumes as they may also be used for other manufacturing requirements. Alternatively if volumes are smaller then there are facilities around Europe such as the Catapult centres which offer open access facilities to develop manufacturing processes before engagement with full scale production. There are several Catapult centres that can help development. The High Value Manufacturing Catapult can alleviate some of these issues. Medical AMRC in Sheffield[5] is focussing on the design and manufacturing of medical projects. The CPI Printable Electronics facility in Sedgefield[6] offers printing, photolithographic and advanced thin film coating capabilities whilst the National Biological Centre in Darlington is being built to look at biomolecule manufacture. There are also plans for a personalised medicine Catapult in the pipeline.

Dedicated equipment considerations for biological production (GMP). Making biosensors is not suited to the contract manufacturing business model because, generally speaking, no two bio-receptor materials will behave in exactly the same way during manufacture. This means that companies making biosensors have to be vertically integrated (i.e. they have to manufacture the biosensor in-house). Producing biological sensors will involve the use of biological materials and there may be requirements for strict control of equipment under GMP. This will have significant a

[5] http://www.amrc.co.uk/research/medical/
[6] http://www.uk-cpi.com/printable-electronics/

cost implication as production may have to be dedicated and there is a cot burden associated with the systems and processes involved in GMP operations.

Multi-disciplinary nature of the work. This means that the development team needs a wide range of people with different technical backgrounds including; product designers, software engineers, electrical engineers, biologists, physicists, chemists, regulatory affairs, market researchers and IPR specialists. This is not an easy mix of people to find and to get to work together so building the right team is crucial.

Economics

Cost comparisons in production, normally expressed in costs per test or other metrics. On the supply side, when developing a process, a careful analysis of the costs per device is needed so that margins are maximised against reimbursement models. It is no good including such an expensive antibody in the sensor that it will never be cheap enough for example. A good example of this is in the provision of monitoring for the process industry. Typically this application area is only interested in continuous monitoring – not suited to expensive antibody use, as the selling price of the resulting chemical may not be sufficient to support the cost of the testing. On the demand side, customers often ask for a cost per test or per patient to suit their own budget scenarios so the two models need to correlate to understand the potential profitability of the product and or service. Business models can vary, however a popular one is the printer/cartridge example where the sensor (which is the disposable element) needs to be connected to a reader. Knowing the pricing elasticity is important again to drive profitability. Different manufacturing techniques will also lead to different cost models.

Are plastic electronic approaches really cheaper? Again careful understanding of costs is important. Very small features on sensors may increase performance, however they may also dictate the use of very specialised and expensive manufacturing techniques such as photolithography with the subsequent adverse impact on the unit cost. Gwent group presented their work on screen printed biosensors in which they are able to print many thousands of sensors on sheets of substrates.

Reimbursement models need to be understood to model cash flows effectively. Again different healthcare systems in different countries operate slightly different fiscal models so careful understanding of the procurement/payment cycles is important. Understanding who is paying the bills is critical, is it the general practise, hospital, healthcare authority or even the patient themselves? Supply contracts are often time related which could be for several years which could obstruct disruptive technologies.

M&A models for SMEs developing new technologies. “Have to be bought out” – in healthcare applications in particular, there are so many barriers to market entry that this statement is true if a biosensor development is to get to market. The costs and timescales for development (10-15 years) are at odds with typical angel/VC investors exit strategies (5 years or less). This means that multiple rounds of investments for companies are often the only practical way to fund commercial development. This has a large bearing on the business plans of many spin-out and start-ups.

High cost and length of clinical validation of biomarkers and biosensor systems. There is a long time to market for clinical applications because of all the approvals and testing that is required. Therefore investors need to wait a long time to get their money back and the risk of failure is high. Cash flow issues can be a problem. Typically biosensors will need to be validated in clinical environments. This can be is an onerous, time consuming and expensive process so careful financial planning is required at this stage. There are several models which can alleviate this cost:

- SMEs may partner with a large company who are interested in the final results and product.
- Seek to raise money from external investors who see value in the product being further de-risked and hence more attractive for an end sale.
- Apply to the public funding agencies who recognise the issues involved and contribute via grants to off-set costs. This can be accessed via Innovate UK, or the European Commission.

Access to finance and cash-flow issues. Generally the issues faced by UK SMEs accessing funding are similar to those in many other areas of commerce. Access to finance via angel and VC investors is still alive in the UK and there has been a history of raising finance in this area. There are many groups and networks which deal with private financing of companies at, or up to various stages of development before exit strategies are executed. Unfortunately, in the UK the investors tend to be risk capital averse and work to rather short timescales, which makes funding for biosensor development hard to obtain.

Integrating sensors to readers and health services (value chain considerations). The general business proposition needs to carefully consider the value chain and how far a company will build on primary sensor innovation. For point of care diagnostics, inevitably there will be a reader platform which will also need to be developed as part of the business solution. On this basis it is important that **all** of the areas of product development and design are carefully considered. There are however interesting developments in the mobile and tele-health arena which could provide better inter-operability across multiple POC tests. This also opens up the opportunity to form partnerships with organisations that provide services in this arena.

Liability – if the biosensor goes wrong because of a fault in its manufacture, this can result in litigation and the manufacturer could be held liable. Therefore, liability insurance is needed which can be very expensive or impossible to obtain, especially in these medical applications.

Markets

The target market needs to be identified and understood as early as possible. This includes understanding how the supply chain for this market works, the competitors and barriers to market entry for example. Conor O'Brien's presentation, highlighting Porter's competitive analysis as a tool for examining these factors, exemplified this issue.

Social business models – it may be that developing a biosensor for a certain application means that there will be an additional cost burden in the initial stages of adoption. However, as a result of the use of that sensor, the costs to the health care service as a whole will be less due to lower instances of chronic incidents which involve high costs services. It might be difficult to

persuade that customer to adopt the product based on this argument. Alternatively, the biosensor might be a diagnostic test for a chronic medical condition which is common in poor countries but not in developed ones. In this case, one needs to look towards charitable organisations and foundations (such as the Gates Foundation) for funds to support the sensor development. Another example is where the sensor targets a medical condition which is rare but nevertheless affects a significant number of individuals worldwide. In this case, funding for the sensor development needs to come from national healthcare systems or charities. In general the "Free Market" might not always develop the needed diagnostic tests.

Different countries have different health care systems and hence different cost and adoption models. The presentation given by Conor O'Brien, illustrated that most countries in Europe have different delivery models which have advantages and disadvantages in their adoption and acceptance rates. A varying mix of private and public services mean that procurement and regulating authorities often differ in scope and jurisdiction so careful analysis is required to work out who the procurement body really is.

Breaking into lucrative foreign market is especially hard due to passive discrimination. Anecdotal experience has found that individual countries are quite protective of their own industries such that breaking into overseas markets can be difficult. One strategy that was described was to establish a direct company in the area of interest. This can work effectively for countries like the USA where the market is very large.

"We don't want to know". In some cases the biosensor might provide information which is detrimental to another company in the supply chain. For example, a water company might not want the consumer to be aware of exactly what is in the water supply, so long as it complies with legislation.

Regulation

Conformance to European IVD regulation. Any medical Point of Care device is regulated within the European Economic Area and the IVD regulation governs this area. This is comprehensively outlined in 4 sub classes of device regulation. CE marking is the key commercial goal to place a POC device on the market and the regulation outlines the conditions and requirements for obtaining this and conforming on an ongoing basis.

Guidance for this by the MHRA can be found at (http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007521.pdf)

Licences may be required for manufacturing of bio materials for POC. There are several organisations in the UK which are the 'competent authorities' which include the MHRA (Medicines and Healthcare Products Regulatory Agency - http://www.mhra.gov.uk/index)

Need to connect with the NHS when developing a biosensor for healthcare. Finding the right person or group to speak to is not always easy and it is good practise to engage early in development to avoid issues when a full device has been developed. Having clinicians on board is a crucial preparation for clinical trials and they often give valuable feedback on needs and adoption issues.

Intellectual property

Large players move in quickly to the market if a valuable application is identified. The only way of avoiding this problem is to take the best possible intellectual property protection (IP). However this is expensive and can take a long time to be granted, plus a small company is unlikely to have the resources needed to defend its IP against a much larger company.

Ethical issues – would you want to be able to carry out a test in your own home which was able to diagnose you with cancer or with Alzheimer's disease for example? Not all biosensors are suitable for point of care use as the implication of a positive test could be devastating for the individual without a health care professional or counselling being present.

Ownership of the bio-part of the biosensor – this needs to be in-house and therefore it is expensive.

Freedom to operate considerations - multifaceted IP tends to be the case in this space as there are many technologies that need to be brought together to make a system. It was felt that careful analysis is needs so that a viable commercial route can be identified.

Risk of competitors threatening action – There could be scenarios whereby large companies may feel threatened by a smaller company's disruptive innovations. I this case there is the risk that larger incumbents threaten litigation which could deliberately slowdown full deployment of biosensor systems.

Question 3: What are the key technical obstacles that need addressing?

The factor which we highlighted as our top concern could be summarised by the phrase "the Bio in biosensor".

- Cost of the bio-materials can be too expensive (£1000's per mg in some instances)
- Stability of the bio-materials is not good enough – do you need cold storage of devices?
- Each different bio-material behaves differently.
- 70% of antibodies are not fit for purpose. Are you sure that the antibody you just bought from supplier A is what they say it is and that if you order more of it the new batch will be exactly the same? Traceability and quality assurance are crucial.
- New bio-markers are needed, so you know what to target. These must be validated.

Need for a ubiquitous reader platform which can be used with many different types of biosensor (could this be a mobile phone for example but if so then which one?). This is important to avoid the scenario where a GP who might end up with a cupboard full of POC diagnostic readers which are dedicated to individual tests.

The FDA rules on error margin are getting tighter. This means that the performance of the biosensors needs to improve in order for them to approved. Empirically, glucose sensors are 20% repeatable which is 'accurate enough'. A push for 5 – 10% would require much tighter control of manufacturing processes.

How to get your sample to the biosensor in the right form – when analysing blood or food what pre-treatment protocol is required and how are you going to provide it with your sensor? Sample pre-treatment technologies such as filtration, concentration and presentation are key.

Biosensors are generally for one-time use – could they be made for continuous monitoring? This enables further cost reductions. Bio-fouling is a significant technical issue which affects device performance. For example current versions of implanted blood glucose sensors need to be changed after a few days.

Different technologies are needed for the manufacture of the bio-receptor and the transducer electrodes. One involves subtle molecular synthesis whilst the other maybe involve semi-conductor and solid state physics. Effective Integration of technologies is crucial.

The development of conductor materials which have low resistance and are also bio-compatible (not Cu or Ag for example). Gold has been used for several years as its biological inertness is considered preferable. New plasmonic materials (nano carbons and 2D materials) are also interesting classes of materials which have been used to enhance sensor performance.

Lack of performance – often the sensor might work well in laboratory conditions but in the real world, when measuring small concentrations of analyte in the presence of a large number of interferences or in non-ideal sample matrices, it does not work so well or does not work at all. Also it may be the case that the bio-recognition part of the sensor has been damaged prior to use by the fact that it has been stored for a long time or freeze-dried many times prior to use.

Raw materials – there is a lack of bio-materials and the means to produce them in large enough quantities with the required purity and consistency for some sensors to reach the market.

Repeatability – need to understand how variations in the performance of the sensor will affect the intended outcome in the end application.

Yield – if the yield of manufacture is tool low then it will not be possible to make the biosensor at a cost which enables them to enter certain markets and complete with other technologies. This is especially true when making arrays of biosensors, If one sensor in the array is faulty then the whole array may not work.

Specificity and/or selectivity of sensor – Biological systems are complex mixtures of molecules which can be very similar in nature. Sensing for a particular protein or virus within these complex matrices often requires separation technologies. The challenge is also to tackle non-specific binding events which will lead to a reduction in sensor performance.

Packaging and Integration with conventional electronics – Printed and or flexible bio sensors often need to be integrated with conventional electronics and there can be requirements for integrating

liquid and sample handling (microfluidics) within the cartridge and reader systems. These require additional costs and time in perfecting optimal designs.

Balancing physical feature size and printing speed – often the speed of printing can be limited by the feature size and printing below 20 microns is a challenge. Some biosensor electrodes require very small elements to help improve signal performance and sensitivity (fouling of these small elements must be considered). However traditional (screen, gravure) and even modern (ink-jet) printing techniques have limitations on ultimate feature size. Typically, to go beyond this limit then photolithographic methods are required which are more expensive and can slow down production.

Ink formulations – Again one of the key challenges is to formulate inks which work well with the choice of printing methodologies. Some require solid carrier materials (pigments, silicas, carbons etc.), UV curable polymers (meth/acrylates) so understanding the interaction with those materials is critical.

Printing sensitive molecules on to structures without damaging them – Sensitive biomolecules such as proteins and DNA may denature on temperature fluctuations and high printing shear rates (e.g. ink-jet) so care and post characterisation of materials on surfaces is needed to confirm minimal damage has occurred and functionality retained

Characterising molecular orientations for maximal signal response – Often sensor responses are governed by delicate steric interactions and binding events between molecules. The metrology challenge is the characterisation of molecular orientation at surfaces.

Defect analysis and monitoring of roll formed products – When volume manufacture of sensors is underway the defect monitoring of sensors is needed. On-line machine vision techniques need to be applied to production to ensure high yields and real time feedback for process control

Question 4: What are the missing links in the UK supply chain to enable exploitation of research?

Group A

The perception of this predominantly academic, group was that the key missing links in the UK supply chain are:

- Realising the concepts coming from the academic community to full commercialisation.
- Finding industry partners based in the UK to collaborate with due to the size of the UK manufacturing sector with a limited microelectronics base
- Focused UK funding options with most funding sources coming from the EU.
- A lack of support through clinical trials and regulatory guidance.

Group B

There was general agreement that the UK supply chain suffers from a lack of direction to target applications. Specific points were:

Healthcare

Health economics. - The NHS has a lack of understanding of the cost benefits regarding e.g. health centre diagnosis and treatment vs hospitals

Defining the clinical case. - Do simple sensor systems deliver real clinical benefit? It is not often clear that there is sufficient evidence to show that this is the case for several research based devices although the glucose monitoring is the stand out example of where it has worked.

Development costs vs potential income. Following initial research there are significant costs (market research, tooling up, clinical trials, advertising etc.) in bringing an invention to market. It is not clear whether developers have a realistic awareness of these costs

Other

Proper selection of application and market value. This area is key to the success of any proposed sensor system. The only two commercial biosensors (pregnancy and blood glucose; neglecting iStat which has restricted application) arose due to strong, identifiable market needs and realistic (if underestimated) value of that mass market

Defining the cost/value analysis. Clearly related to the last. It is essential to pick a commercial winner, not just to showcase your innovation

Lack of competitive analysis (comparing newer/older technologies). Generally, older technologies are laboratory based using well developed analytical science. In comparison, biosensors may be regarded as "quick and dirty". Perhaps they are!

Lacking proper competitive audits. Largely covered by the last comment.

Needs to be resource to guide market research. As mentioned earlier, good detailed market research is key to delivering realistic biosensor systems. It is often under resourced and comes too late in the project to be of value.. For biosensor research to be meaningful in the real world there must be an established road map leading from "blue sky" work to proven technology, with clear gates at intervals. Possible support to this challenge maybe found in with Innovate UK's SMART awards (Proof of Market) and the EC SME Instrument (Phase 1).

Question 5: What are the main barriers to the clinical adoption and acceptance of printed biosensor systems?

Lack of cost benefit information - As with Question 4, there was thought to be little quantitative and accurate information available on the costs of implementing clinical biosensors

Inertia arising from previous bad experiences - The area has suffered in the past from over-optimistic promises, leading to consumer disappointment when the over-hyped biosensor product did not deliver.

Costs in implementation - The true costs associated with the use of biosensors in a clinical environment tend to be glossed over. E.g. validation protocols usually have to be established and monitored.

Other specific points were:

Operational reliability - An issue of importance. Clearly clinical biosensor systems must perform reliably, preferably with a clear indication when possible malfunctions arise. Single use devices are particularly suspect as there is no opportunity for pre use calibration. Pregnancy tests arrange for a line of HcG to be plotted on the event window during manufacture; This appears as an extra line in the window during test, showing that the device has worked. Some blood glucose sensors use a "cal code" – a batch factor determined at source. This is inputted to the measurement device before use of that batch of sensors

Market positioning - A decision must be made early in the development of the product as to whether it should aim for the mass market (cheap) or the more expensive, bespoke area. This will determine costs of e.g. instrument quality, packaging, advertisement placing. Clearly, printed biosensor systems are targeted preferably at mass market applications

Personal preference by decision makers/ Support (or lack) by opinion leader - These points are very similar. Human decision making is not based solely upon facts and other evidence but also on a complex mix of experience, prejudice, self-interest and "gut feeling". Recognising and dealing with this is important for success.

Translation of that support into implementation - Having got that support, how is it best continued? Some early successes are valuable, especially in an area that shows economic advantages. Be scrupulously fair and honest in dealing with the inevitable hurdles. Give full credit to the team (and the decision maker) as the implementation process continues.

Workflow disruption during implementation - A test of management skills to maintain support

Tradition - "We've always done it like this". Accept that it happens and work around it. Breaking the mould and displacing incumbents should not be underestimated.

Question 6: What are the UK's key strengths and weaknesses and what capacities is there to exploit technologies?

Key strengths:

Clinical excellence - The UK is world renowned for the quality of its clinical practises. Ironically, this degree of rigour could mitigate against the adoption of novel, more economic approaches.

Strong science and innovation base - Again, the UK is in the forefront of world class science and innovation. This strong academic base attracts much overseas funding for biosensor research.

University research is channelled towards spin out companies - I am not sure that this is always the case. Certainly, many academics are active in forming small companies based on their research but it seems that their business plans are often not well thought through. For instance, there is a common view in academia that patenting a piece of IP has the goal of preventing any third party use and ensuring exclusivity. That might be so for the rich Oxbridge institutions that are able to police and service their patents over many years. For others however, the route to income generation should probably lie in licencing to third parties.

Key Weaknesses:

A perceived lack of knowledge transfer between the capabilities of the printed electronics community and the biosensor community – The academics (from a biosensors perspective) felt that there is an opportunity to connect the wider printed electronics and biosensors communities at a series of events to explore the capabilities of what is technically achievable for manufacturing biosensor devices.

A lack of interdisciplinary collaboration within the leading universities to develop ideas – Intra-departmental collaborations between university colleges/departments, for example engineering and biology, could be improved to increase early stage innovation.

Complex NHS procurement process – There is a lack of understanding, amongst UK companies and universities, of the NHS procurement process and who, within the NHS, should be approached to 'pitch' innovative technologies.

The visibility of UK funding options to academic institutions – It was the opinion of the group that whilst the industry funding competitions from Innovate UK were well advertised, academically focused funding from research councils in the UK was less visible

Failure to build sustainable companies - The world does not owe small companies a living. If there are no clear goals, a weak business plan and an ill-defined credible market then company failure is almost inevitable.

Main adopters of our technology are outside UK - This is unfortunately the case. There is an argument for being successful here by exporting our strengths in world class research and innovation for financial gain. Therefore effective management of IP is critical in this instance.

Difficult to attract funding - This is (understandably) of concern to academics. In the UK most research funding comes from Government, Industry & Charitable Trusts. It could be useful for some university departments to employ a research funding officer, tasked to investigate and inform staff of funding opportunities on an equitable basis. Payment by results would be an interesting option!

Reduced NHS research budget - Comments as above

Timid about exploitation / Risk aversion - These issues are likely to arise due to the UK culture. Changing this attitude will be difficult and can be addressed only by fundamental changes in society's attitudes and educational practices

"hard" and "soft" sciences are disconnected, leading to a lack of appreciation of engineering in the area. - Again, this seems to be a cultural phenomenon, driven by social snobbery. After the professions come mathematics, natural sciences followed by the engineer – a bloke in oily overalls, wielding a spanner. There can be a similar progression in science. A solid state physicist of my acquaintance was fond of saying –to audiences of immunologists "if a physicist performs a repeat experiment 5 times he will get 5 identical answers within closely defined error limits; if a biologist does 5 repeat experiments, he will get 6 different answers!"

No large end user UK commercial players - Regretfully this is true but it has to be managed through licencing to larger players if rapid adoption is to be undertaken. Therefore the UK has a low exploitation capacity.

Little realistic understanding of the clinical value of diagnostics - I didn't believe it 25 years ago and I don't believe it now. Every clinician that I know has an appreciation of what novel biosensors could do for him. His concern is that that he is not being offered any that work well enough

Question 7: What public funding and collaboration mechanisms are open for SMEs, academics, Large Co's and institutes?

UK Funding mechanisms

There are various funding mechanisms in the public sector which are known by the delegates. Myrddin Jones (Innovate UK) highlighted the various funding mechanisms and the discussion involved which was best suited for the development printed biosensor technologies:

- **SMART** – only SMEs (open scope)
- **SBRI** – Government contract, 100 % funded, themed call.
- **CR&D** – opportunities to get academics involved
- **_connect** – the Innovate UK platform which holds the KTN communities, could be used to highlight useful opportunities to the communities of interest
- **KTP** – expenses and the length not always appropriate for purpose; shorter ones are better.
- **KTNs**, collaborations – business to business meetings
- **Catalyst funds (Large continuous funds)**
    - Biomedical
    - Agri-tech

Other (non Innovate UK) routes to funding were less well known, and it was discussed that this might be a role for the KTN to make sure that funding opportunities are properly communicated to the community/

- **NIHR** – Invention for innovation

- **CDE** – Enduring Challenge: Centre for Defence Enterprise, always open for a set list of broad challenges the MoD need addressed.
- **EPSRC** – Eng.D, Case, DTC and others
- **AMSCI** – supply chain good if market pull and job creation

The delegates were asked what would be the ideal make up of a public sector support? The needs for public funding include grow on space which are facilities of technology which are not universities - incubators are full.

European funding

- **Eureka schemes - Eurostars** – noted that the paper trail is far
- **H2020 – opportunities in;**
    - **LEIT (NMBP, ICT etc.), Societal Challenge and excellent science pillars**
    - **SME Instrument (PHC 12)**
    - **Marie Skłodowska-Curie actions**
- **ERDF,** capital focussed and job creation, but region specific

A general comment from a delegate concerning European funding was not to underestimate the time involved in preparing the paperwork and conforming to audits.

Question 8: What are the best ways to privately fund up-scaling of devices and start-ups?

At the table were people who had successfully managed to gain private funding for their start-ups. Suggestions included:

- Health and social and green charity investment
- Crowd sourcing. It was noted that this may seem an unlikely source of funding but the opportunity to contribute with no return on equity is can be seen as an attractive option to some
- Finding alternative applications that lead to development of technology
- Funding from customers – this is linked in to the SBRI scheme above.
- High net worth individuals
- Wealthy, tax savvy overseas companies or sovereign wealth funds (China, Kuwait etc.)
- Syndication, join together several ideas to de-risk & share the spoils
- R&D Tax Credits

In trying to obtain money from VCs and private investors, it was noted that it was important for a business be able to demonstrate competence and market pull. Schemes where end customers are involved in the running of the project were seen to be attractive as this keeps the project aligned to their needs and provides an in-built exploitation route.

Question 9: What application areas are closest to market in the next 5 years?

Security

Screening applications YES / NO applications where quantitative data are not critical. Airports and port screening for Infectious diseases (e.g. TB, Ebola and flu viruses).

Health Monitoring

Non-regulated biosensor applications were seen as the most likely to be achieved in the next 5 years. Applications where false positives are bearable such as health monitoring are non-critical e.g. wearables for heath monitoring (an example Oral health monitoring for biometrics e.g. on toothbrush). Wearables are seen as a strong market for PE. Smart sports/training clothing with real time feedback.

Smart Cities

Where large numbers of devices are needed, printed biosensors offer an attractive solution. This is also true for home environment sensors e.g. temperature, humidity and air quality, plus the following potential applications:

- Identification of areas requiring cleaning.
    - Identifying dust, dirt, stains
- Hygiene of kitchen work tops
- Assurance of in real time hygiene in toilets, baths, showers.
    - Particularly bacterial contamination
- Smells from toilets, sinks, drains.
    - Use of intelligent artificial nose
- Does bed linen need changing? Do clothes need dry cleaning?
    - Optical and “nose” sensors
- Intelligent burglar alarm (person sniffer)
    - Able to discriminate between house holders and intruders
- Intelligent washing machines
    - chemical/physical monitoring and real time dosing
- Food spoilage/ripeness in and out of refrigerator
    - Real time progress of bacterial growth
- Smart clothing
    - ready to wash
- Cleanliness of flooring/carpets
    - ready to clean

Annex 1: Workshop Attendees

Name	Company
Abdulaziz Ali	University of Teesside
Allen Reid	Nanogap
Alex Cole	Polyphotonix
Andrew Lee	Cambridge Display Technology
Brian Birch	Consultant
Conor O'Brien	O'Brien Marketing
Dale Athey	OJ-Bio Ltd
Deepan Shah	Orla Protein Technologies Ltd
George Dibb	National Physical Laboratory
Guido Drago	Gwent Group
Ian Williams	BIS
James Johnstone	CPI
Jeremy Lakey	Orla
Jon Helliwell	CPI
Juliana Haggerty	CPI (Biologics)
Lisa Hall	University of Cambridge
Marcus Swann	Swann Scientific Consulting Ltd.
Mark Buckingham	DZP Technologies Ltd
Mark Graham	Peratech Ltd
Mark Spratt	G24 Power
Martin Wickham	National Physical laboratory
Martyn Cherrington	The Knowledge Transfer Network
Matt Butchers	The Knowledge Transfer Network
Maxim Shkunov	Surrey University
Mike Simms	Peakdale Molecular Ltd
Myrddin Jones	Innovate UK
Neville Freeman	NanoFlex Ltd
Pankaj Vadgama	Queen Mary University of London
Ravinder Dahiya	University of Glasgow
Robin Page	OJ-Bio Ltd
Sam Whitehouse	QuantuMDx
Sharjil Siddique	Plastic Logic
Simon Scott	Teesside University
Stephen Cash	Sapient Sensors
Steve Thomas	CIT Technology
Timothy Robson	Newcastle University
Tom Harvey	CPI
Tom Taylor	CPI
Zulfiqur Ali	Teesside University

Annex 2: Meeting agenda

Workshop Agenda:

Time	Activity	Speaker/Facilitator	Room	Affiliation
09:30	Registration, refreshments		Entrance and Exhibition area	
10:00	Welcome, CPI introduction & to HVM Catapult facilities	Jon Helliwell (Printable Electronics) & Juliana Haggerty (Biologics)	Meeting rooms 4 & 5	CPI, Sedgefield
10:30	The Future of Biosensing Printing	Dr Guido Drago (Managing Director)	"	Gwent Group
10.45	Additive conductive circuit manufacture	Steve Thomas		Conductive Inkjet Technologies Ltd.
11:00	Coffee Break		Mezzanine Exhibition Area	
11:30	Supply chain, regulatory and commercial issues	Connor O'Brien	Meeting rooms 4 & 5	OBMC Ltd.
12:00	New research perspectives in biosensors	Prof. Lisa Hall	"	Cambridge University
12:30	Lunch break		Mezzanine Exhibition Area	
13:00	Clean room tour/Networking (please register)		Clean Rooms	
14:00	Breakout briefing	Dr James Johnstone	Meeting rooms 4 & 5	
14:10	Breakout discussions: Discussing topics of interest			
15:00	Report back & group discussion			
15:45	Event Finishes – Voting on preferred issues			
16:00	Optional window tour of clean room facilities			

Breakout session:

The breakout session was designed to explore the issues of translating basic research into pre-industrial production and beyond and some of the key issues that face innovators in the development of biosensors.

The workshop attendees were split into groups of 8 and each group had a facilitator, associated with a set of topics, who captured the thoughts and opinions of each group and the answers to the 3 allocated questions.

The session addressed 9 questions in total;

1. What printed electronic manufacturing technologies are amenable towards industrial scale-up of biosensors?
2. What are the main commercial issues that need to be considered?
3. What are the key technical obstacles that need addressing?
4. What are the missing links in the UK supply chain to enable exploitation of research?
5. What are the main barriers to the clinical adoption and acceptance of printed biosensor systems?
6. What are the UK's key strengths and weaknesses and what capacities is there to exploit technologies?
7. What public funding and collaboration mechanisms are open for SMEs, academics, Large Cos and institutes?
8. What are the best ways to privately fund up-scaling of devices and start-ups?
9. What application areas are closest to market in the next 5 years?

There were 6 marked tables set up and each table answered different questions.

Table	Questions
1	1, 2 & 3
2	4, 5 & 6
3	7, 8 & 9
4	1, 2, & 3
5	4, 5 & 6
6	7, 8 & 9

The opinion gathered from the breakout session was reported back by the facilitators to the whole group afterwards and a general discussion held.

Clean room tour

An internal clean room tour was conducted for about 8 people (2 groups) during the lunch time break. There was also an external "window tour" for those who were interested which was attended by 10 of the attendees

Presentations

Final versions of presentations are available on the KTN website (_connect).