Critical National Need Idea Title: ***Chemical Imaging for Better Healthcare.***

Infrasign LLC (www.infrasign.com)

3685 Whitsell Avenue
Palo Alto, CA 94306, USA

Phone: (310) 760-6196

Contact Person:

Dr. Anadi Mukherjee Ph.D.

E-mail address: anadi@infrasign.com

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This white paper describes a new chemical imaging technology and its applications for our nation's healthcare industry. In today's fast moving world, pharmaceutical products are manufactured and transported across borders in vast quantities. The health and prosperity of United States depend on high quality drug manufacturing in and 100% quality check of all imported drugs. The recollection of the Heparin episode in 2008 (http://archives.chicagotribune.com/2008/mar/06/business/chi-thu_tainted-heparin-baxter-bmar06) suggests the dangers of counterfeit medical products. Neglect of safety amounts to a National Security threat and the failure to protect the citizens and corporations of the United States. Neglect of efficiency leads to unnecessary waste of billions of dollars, depletes the resources and pollutes our planet. While we do have Government Agencies, protocols, processes and practices in place there is a constant need of new technologies that will meet or exceed the high standards set by the Agencies such as FDA.

Improving our nation's healthcare through a new technology that offers higher quality assurance in drug manufacturing and high quality testing of imported drugs that exist today is an area we identify as a ***national critical need***. The aim of this white paper is to address our nation's ***societal challenge*** for Quality Assurance/Quality Control) QA/QC in drug manufacturing and ensuring no counterfeit drugs penetrate our borders. Quoting directly from the Whitehouse website (http://www.whitehouse.gov/issues/homeland_security/), one of the ways to combat biological threats is described as "By building on America's unparalleled talent and through international partnerships, we can create new drugs, vaccines, and diagnostic tests, and manufacture them more quickly and efficiently". The ***transformational results*** of this white paper will enable disruptive changes to current practiced methods and strategies while radically improving our understanding of methods, systems and technologies. An additional benefit of this white paper is to promote and accelerate innovation in the United States and open new markets for high power quantum cascade lasers and maintain world leadership in this cutting edge technology.

A. Maps to Administration Guidance

Recently we see a great upsurge of activity in US Government Agencies, pharmaceutical companies and academia regarding high quality and lean drug manufacturing since the kickoff of US Food and Drug Administration's (FDA) twenty-first century Process Analytical Technology (PAT)[1,2,3,4] initiative. In the national and international scene we observe that the existing technologies address the issues laid down in PAT guidelines only partially. It takes between 10 to 15 years and costs nearly 1 billion dollars in research and testing to bring a new medicine to patients[5]. New technology that can be PAT complaint would ensure far higher quality healthcare for our nation as well as save ~ $32 billion per year to the pharmaceutical industry. Also counterfeit drugs entering our borders are a national threat – a loop hole for terrorist adventure. Most of today's QA/QC in pharmaceutical manufacturing and testing for counterfeit drugs are generally accomplished using batch processing with laboratory testing conducted on collected samples to

evaluate quality[2]. Today's chemical imaging technologies that address these needs partially offer poor sensitivity and/or selectivity or scan times too long for practical use and are very limited in scope. If this area of national critical need is neglected and this societal challenge not addressed with a focused effort, the health and quality of life of the Nation will be compromised and may be in jeopardy. A new innovative chemical imaging technology homegrown in the United States with high-risk high-reward that addresses these two ***societal challenges*** with new capabilities and has the potential for ***transformational results*** is the subject of this white paper.

FDA's PAT FRAMEWORK:

"*The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design. Consequently, the tools and principles described in this guidance should be used for gaining process understanding and can also be used to meet the regulatory requirements for validating and controlling the manufacturing process"*[2].

A guiding force in the FDA's PAT movement was the Center for Drug Evaluation and Research (CDER)'s Office of Pharmaceutical Science (OPS) Deputy Director, Ajaz Hussain, who is the chair of the PAT steering committee. The development of FDA's PAT initiative has been clearly outlined in reference 3. In this reference, Dirk C. Hinz states *"..a Co-operative Research and Development Agreement was signed between the FDA and Pfizer in 2003 that will allow the two to collaborate on* ***chemical imaging studies****"*. This points out to the importance of this national critical need and the societal challenge identified in this white paper.

"The main goal of PAT has often been summarized as simply being to "achieve greater process understanding" and thereby mitigate risks to product quality"[4]. FDA's PAT document[2] adds *"..(PAT) is intended to support innovation and efficiency in pharmaceutical development, manufacturing and quality assurance."*[2,4]. This guidance[2] continues with *"..(efficient pharmaceutical manufacturing) is a critical part of an effective U.S. health care system. The health of our citizens depend on the availability of safe, effective and affordable medicines"* [2,4].

FDA's Pat guideline[2] adds:

"Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to evaluate quality. This conventional approach has been successful in providing quality pharmaceuticals to the public. However, today significant

opportunities exist for improving pharmaceutical development, manufacturing, and quality assurance through innovation in product and process development, process analysis, and process control.

Unfortunately, the pharmaceutical industry generally has been hesitant to introduce innovative systems into the manufacturing sector for a number of reasons. One reason often cited is regulatory uncertainty, which may result from the perception that our existing regulatory system is rigid and unfavorable to the introduction of innovative systems. For example, many manufacturing procedures are treated as being frozen and many process changes are managed through regulatory submissions. In addition, other scientific and technical issues have been raised as possible reasons for this hesitancy. Nonetheless, industry's hesitancy to broadly embrace innovation in pharmaceutical manufacturing is undesirable from a public health perspective. Efficient pharmaceutical manufacturing is a critical part of an effective U.S. health care system. The health of our citizens (and animals in their care) depends on the availability of safe, effective, and affordable medicines.

Pharmaceuticals continue to have an increasingly prominent role in health care. Therefore pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, along with the best principles of quality management to respond to the challenges of new discoveries (e.g., novel drugs and nanotechnology) and ways of doing business (e.g., individualized therapy, genetically tailored treatment)."

On the implementation of PAT Dirk C. Hinz writes[3].

"The PAT concept of process understanding and control has long been implemented in the semiconductor, petrochemical, automotive, and food and beverage industries. Investments have always been made in these branches of industry to improve quality and reduce cost. Drug companies often put resources into developing the next new product that may offer the chance of being sold without competition."[3]

"According to the Wall Street Journal[6]*, however, laboratories are currently producing fewer new drugs, which mean that the payoff from investing in drug discovery is diminishing. At the same time, sales forces have hit the saturation point and savings from improving manufacturing processes make more sense as a way to boost profits. As a result, attention is now being focused on investment in more efficient manufacturing through the use of PAT."*[3]

Besides the need for a new chemical imaging technology that will satisfy PAT's guideline for pharmaceutical manufacturing we also identify high quality screening of imported drugs for counterfeits. Here too we see that only batch testing is done for quality assurance of the imported drugs. Our Nation faces great risk to public health and well being under improper screening of imported drugs as we have

seen in the Heparin episode. This poses a potential loop hole for terrorist attacks by the way of inadvertently importing counterfeit drugs. An innovative solution to this problem such as a new chemical imaging technology that will screen 100 % of imported drugs reliably is a national critical need.

What existing efforts are addressing these problems?

Mass spectrometry (MS) and liquid chromatography (LC) are 50 year old techniques that tests minute samples, involve quarantining batches, are destructive by nature, slow and are not chemical imaging platforms that will allow noncontact screening from raw materials to finished pills. Present chemical imaging technologies that are being used to address the PAT guidelines are Raman Spectroscopy and Near IR (NIR) reflectance techniques. While Raman relying on nonlinear optical effect is very sensitive to intensity variations of the laser beam (entire sample has to be on the same plane) and very slow and impractical for "quality-by-design" approach of PAT, NIR is based on diffuse reflectance of IR beams and suffers from low sensitivity and selectivity. A new high throughput Chemical Imaging Technology is needed that offers high sensitivity and selectivity non-contact mapping (Spectral Hypercube) of molecular species such as active pharmaceutical ingredients (API) and excipients. This high-risk high-reward new chemical imaging technology will make QA/QC of pharmaceutical products complaint to FDA's PAT guidelines and take the present technology to the next level of accuracy and reliability. The characteristic features of Raman, NIR, LC & MC are compared with that of the New Chemical Imaging Technology in the table below.

Feature	Raman Spectroscopy	NIR Spectroscopy	LC & MS	New Chemical Imaging
High background	**Yes**	**Yes**	**Yes**	**No**
Sensitivity	**Medium**	**Medium**	**High**	**High**
Specificity	**Medium**	**Low**	**High**	**High**
Source	**Point**	**Point**	**Sample**	**Full spatial pattern**
Spatial Information (high speed)	**No**	**No**	**No**	**Yes**
Sensitivity to minor components	**No**	**No**	**Yes**	**Yes**
Tolerance to sample geometry	**No**	**Yes**	**No**	**Yes**
Quantitative information without having to run separate calibration runs	**Yes**	**No**	**No**	**Yes**
Acquisition Time	**Long**	**Long**	**Long**	**Fast**
Fluorescence Problem	**Yes**	**No**	**No**	**No**

Being a general spectroscopic tool, this new Chemical Imaging Technology as described here will benefit easy inspection and detection of unsafe and illegal transportation of Explosives, Chemical Warfare Agents, counterfeit drugs, narcotic drugs, counterfeit flavor and fragrances and contaminated food (such as melamine). This technology will improve the efficiency of manufacturing goods such as medicines, electronics, semiconductors, Green Technologies including Solar Cells. This technology will also help accelerate innovation and accelerate the discovery of new drugs, help break the 22nm node barrier in semiconductors and help in numerous other fields by giving users more knowledge and control of their process in real time.

As mentioned above, this high-risk high-reward new chemical imaging technology has a broader agenda for a national participation. We intend to organize a consortium involving companies, academic institutions and government agencies at a national programmatic level. We recognize the importance of partnership between institutions and organizations of United States in developing a key technology from start to an established level. As an example we focus on the emerging technology of quantum cascade lasers. Although millions of research dollars have gone into US Government sponsored R&D project for the development of highly efficient and high power quantum cascade lasers (QCL) (e.g. EMIL program of DARPA) the market of this industry has been predominantly US military (Infrared Counter Measures, IRCM). We realize the strong potential of these high power QCLs in commercial sectors that urgently requires a brand new Chemical Imaging Technology with far reaching market and economic consequences.

B. Justification for Government Attention

- Magnitude and nature of the problem.

    A. The societal challenge mentioned above costs billions of dollars[4] per year to the pharmaceutical industry together with low quality and high risk healthcare of the citizens of United States.

    B. As shown in the table above, the existing chemical imaging technologies perform poorly and do not comply with FDA's PAT initiative and impractical to use for screening counterfeit medical products. A new chemical imaging technology is essential to address the societal challenge outlined in this white paper.

    C. This new technology is a material composition analysis technology only made possible by a new laser called a Quantum Cascade Laser (QCL) and a recent new spectroscopy and imaging technology invented by our team members. Recently our team has proven and demonstrated this new chemical imaging technology in remote sensing for defense applications using tunable CO_2 lasers. We have demonstrated standoff detection of explosives and gases with very high sensitivities and selectivities at distances previously unreachable (200m)[7]. There is currently a large interest in the defense arena for this

technology. We have also developed efficient and most powerful single mode tunable QCLs, applied them to build multigas sensors[8] and own the Intellectual Property for this technology. This effort focuses on combining the two capabilities together to build the much needed new chemical imaging technology for improving the healthcare of United States. Our team has the scientific know how, engineering know how, management know how and the track record of delivering products on time and on budget. We have experts in Lasers Physics, Material Science, Engineering, Mathematics, Information Technology, Management and Business Development.

The uniqueness of this technology results from it's highly sensitive, selective and high speed non-contact mapping of chemical composition. It combines the good capabilities of all three existing techniques. Amongst its capabilities are the Compositional analysis of Solid and Liquid Chemicals and Biochemicals, 2D spatial compositional map and homogeneity information of different materials, Batch to Batch compositional variation feedback, impurity, contamination and foreign particle detection, Raw material inspection and detection of expired products used in process. Based on the description provided by the FDA guidance, the objectives of PAT systems are closely analogous with popular quality management systems, such as Six Sigma[9]. Current pharmaceutical manufacturers operate at Three Sigma region[4]. This new technology is expected to meet or exceed PAT guidelines and push quality of drug manufacturing from ***Three Sigma to Six Sigma***.

D. As pointed out in last section, this effort to be fully effective requires a national consortium of companies, research institutions, and universities with complimentary research and development capabilities. It is our intention to build up such a national consortium to address and solve several key science and technological issues to make this high-risk high-reward effort successful.

- Societal Challenge(s) unmet by others.
  A. If this new chemical imaging technology effort is not met or delayed, the health of our citizens and cost of the healthcare industry will be compromised. Lack of high quality drugs, lean manufacturing and influx of counterfeit medical products are too high a cost for United States.

- Evidence of commitment.
  A. Companies and Research Institutions working on Raman and NIR Spectroscopy as Chemical Imaging tools will be competitors for this effort. We will propose the new chemical imaging technology that we have already successfully demonstrated in-principle for standoff detection of solid explosives under a $1M grant from DARPA.

These experimental and theoretical results point at the enormous potential of this new chemical imaging technology.

B. Infrasign LLC (www.infrasign.com), a brand new spin-off company from Pranalytica Inc. (www.pranalytica.com) is looking for US Government support in developing this new technology. Pranalytica is the world's only supplier of high power (2W, cw) QCLs. The founders of Infrasign successfully led the DARPA project[7] which is the corner stone of this new effort.

C. Essentials for TIP funding

- Stimulates the Nation's scientific frontiers
  - A. This effort will stimulate Nation's capabilities in several ways. A highly sensitive and selective non contact chemical mapping technique with fast scan times is needed in all fields of material compositional analysis. A much needed new chemical imaging technology would stimulate new activity in the areas of materials analysis from drugs, chemicals, biochemicals, and biologics to semiconductors. Development of external cavity tunable quantum cascade lasers (ECQCL) is essential for this new chemical imaging technology. This effort will also stimulate the much needed development of thermally stable and mechanically robust ECQCLs. These products will stimulate new gas sensing products in return.
  - B. The technology leverage for success is high. The successful proof-of-principle demonstration in standoff detection of explosives point towards the success of this new chemical imaging technology.
- Meets a timely need not met by others.
  - A. Proof-of-principle demonstration of this new chemical imaging platform and prototyping requires capital expenditure towards high power QCLs, IR cameras, electronics, optical hardware and infrastructure not affordable by Infrasign. The founders of Infrasign are senior scientists, technologists and business managers with more than 20 years experience.
  - B. The current Venture Capital funding climate is very weak owing to the current market conditions. SBIR funds are too small to support such a capital intensive effort.
- Delivers the potential for impacts and transformations.
  - A. The currently available chemical imaging technologies, namely Raman and NIR are old and do not conform to FDAs PAT guidelines. Due to the lack of availability of a better chemical imaging technology, these two are the present *status quo* of research approaches and applications in non contact materials analysis. This new effort will offer transformational result and enable a disruptive change over and above the current methods and strategies.

B. We expect a great success in this new chemical imaging technology providing dramatic benefits to the Nation. Some of the dramatic benefits are:

- Extremely reliable and high quality drug manufacturing following FDA's PAT protocol.
- Very high quality healthcare products for the citizens of United States.
- Crackdown on counterfeit drugs.
- Billions of dollars per year savings to the Pharmaceutical industry.
- Open a large commercial market for QCLs.
- Stimulate R&D and manufacturing of ECQCLs like diode lasers today.
- Claim United States world leadership in a new chemical imaging technology with its myriad applications and staying ahead in the field of high power ECQCLs and material analysis.

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