A DNP polarizer designed for clinical use

A. M. Leach[1], J. Urbahn[1], D. Anderson[1], N. Clarke[2], T. Skloss[3], and J. Ardenkjaer-Larsen[2]

[1]GE Global Research, Niskayuna, NY, United States, [2]GE Healthcare, Amersham, United Kingdom, [3]GE Healthcare, Waukesha, WI, United States

Introduction: Dynamic Nuclear Polarization (DNP) in the solid state and dissolution has demonstrated the ability to increase the polarization for aqueous contrast agents by factors exceeding 100,000 fold (>25% polarization over 3 T for ^{13}C).[1] Such increases enable the real-time imaging of cellular metabolism, the early detection and staging of disease,[2] and the determination of treatment efficacy.[3] To enable this method in the clinic a number of new technologies have to be invented and developed. Primary concerns are patient and operator safety, performance of the method, as well as operator convenience. A polarizer of novel design has been successfully built and tested (Figure 1). The polarizer differs from those previously used in that it is designed with capabilities required for future clinical use. These features include:

1) multiple clinical doses for high throughput operation;

2) no consumption of liquid helium or nitrogen;

3) a disposable fluid path maintaining a sterile product;

4) an integrated, non-contact quality control system for measuring agent safety and efficacy.

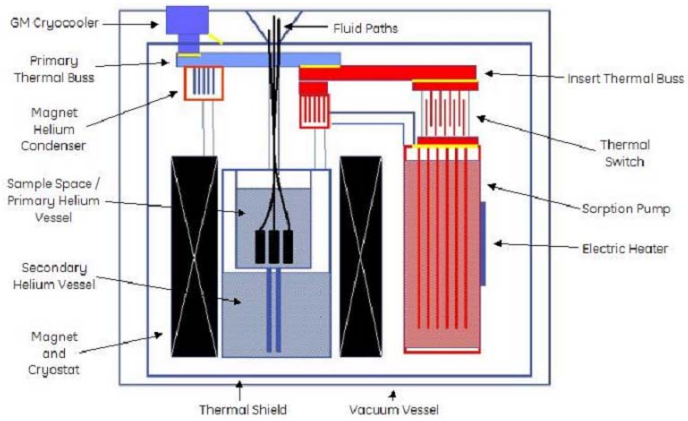

Figure 1. Diagram of the multi-sample, closed-cycle hyperpolarized components.

Methods: The system uses a sorption pump in conjunction with a conventional GM cryocooler to create temperatures below 1 K. Cryogenic regeneration and polarization compose equal portions of a 24-hr operation cycle. Up to four doses of >1g of [1-^{13}C]pyruvic acid to generate injectable doses at 250 mM pyruvate at volume of >45 mL has been demonstrated. Polarized [1-^{13}C]pyruvic acid is dissolved with superheated water, the paramagnetic agent is removed with an inline filter and the acid is neutralized in a receiving vessel prior to quality control measurements and release. This entire dissolution process is contained within a sealed plastic fluid path. The quality control system measures six product characteristics within 10 s. Typical product characteristics include a pH of 7.5±0.3 pH, pyruvate concentration of 256±6 mM and a liquid-state polarization of 18±2%.

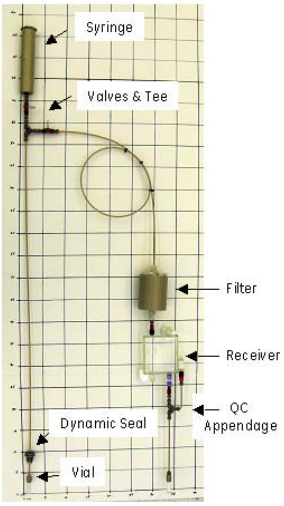

Figure 2. Sealed fluid path prototype. Grids are 5 x 5 cm.

Discussion: Extensive studies have been performed to detail the relationships between manufacturing and process related input parameters and the generation of a safe and efficacious contrast agent. A matrix analysis has been used to document these interactions. Based on these relationships, a description of key design and process control factors for the generation of robust dissolutions will be provided to demonstrate that the DNP polarizer is expected to meet regulatory and clinical requirements.

References: (1) Ardenkjaer-Larsen, J. H. et al. Proc. Natl. Acad. Sci. USA 2003, 100, 10158-10163; (2) Albers, M. J. et al. Cancer Res. 2008, 68, 8607; (3) Day, S. E. et al. Nat. Med. 2007, 13, 1382-1387.