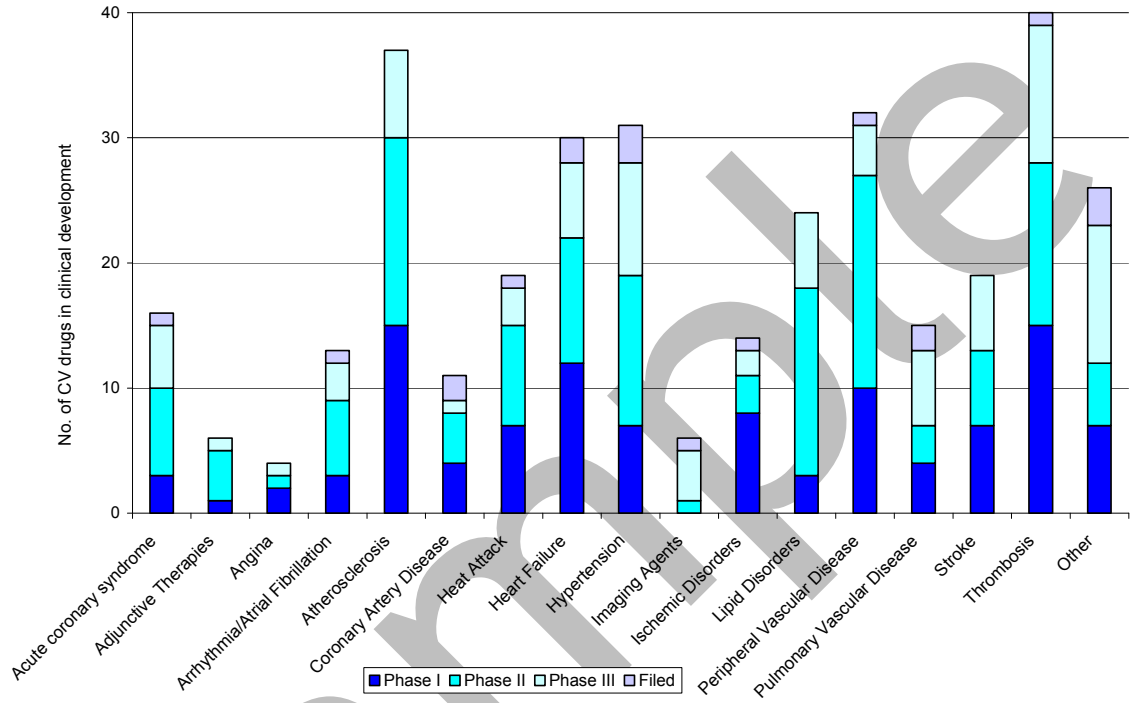
1.3.1 Cardiovascular pipeline products

According to PhRMA over 340 products were in clinical development for the treatment of CV conditions during 2006 with the greatest research focus on thrombosis, atherosclerosis and peripheral vascular disease (see Figure 1.7). Whilst this is only a snapshot of what is occurring in CV research it highlights areas of the most intense research activity and potential opportunities for drug delivery companies to address drug delivery issues specific to targeting different regions of the vascular system – myocardial, peripheral and coronary.

Figure 1.8: Cardiovascular medicines in development 2006



Source: PhRMA, 2006

3 Key drug delivery companies and academic researchers in cardiovascular research

Despite significant advances in the development and delivery of CV agents and devices there still remains a high unmet clinical need within niche conditions and patient subsets. For example, acute heart failure may result in permanent damage to a patient's heart affecting CV efficiency where administering CV agents may become critical and where novel cell and gene-based therapies may be administered via minimally invasive catheterization or injection. Alternatively, diabetic patients may require multi drug treatments where chronological delivery of multi-agents could improve patient compliance and disease control.

The table below summarizes some of the key players, their technologies, devices and products that are approved or in clinical development (Table 3.1).

Table 3.1: Leading drug delivery technology companies in the cardiovascular arena

Company	Technology Platform	Route of administration
Abbott Vascular	Drug-eluting stents, catheters, guidewires	Xience V everolimus-eluting coronary stent system Gen X-ACT stainless steel coronary stent system
Advanced Cell Technology	ACTCellerate platform	hESC derived cell lines for myocardial regeneration
Alltracel Technologies	Altracell Bioactives	The first of the current series of pre-clinical trials examining dosage, timing/phasing, and also combination effects with specific sterols and omega-3 fatty acids
ALZA	Oral, transdermal	ALZA delivery technology is used in a variety of CV marketed products including: Aplress™ LP, Cardura® XL, Covera-HS®, DynaCirc CR®, Procardia XL ®, Catapress-TTS®, Transderm-Nitro®
AnGes MG	Viral and non-viral vector systems	HVJ-liposome viral vector technology and HVJ-E non-viral vector technology for the delivery of gene-therapies
Angioblast Systems, Inc	Allogenic cell generation platform	Mesenchymal stem cells for myocardial regeneration
Ark Therapeutics	Adenoviral vector gene therapy device	Trinam® [VEGF-D gene / AV Ad 5) bio-degradable local drug delivery device made from collagen
AVI BioPharma Inc	Proprietary microparticle delivery system for intravenous (IV), subcutaneous, intracoronary (IC) catheter, oral delivery	AVI's Neugene Antisense technology (for downregulating c-myc gene expression in the field of cardiovascular disease)
Bioavail Pharmaceuticals	Oral controlled-release technologies using - encapsulated in microspheres using Biovail's CEFORM™ technology and Biovail's Shearform™ technology for orally disintegrating tablet (ODT)	Bioavails drug delivery technology has been applied to a number of marketed CV products including Cardizem LA, Isordil®, Lescol® XL, Moncor®, Vasotec® and Vasretic®. It is currently evaluating a new formulation of the antihypertensive, Carveilol
Bioheart	Autologous cell generation platform and catheterization delivery	Myocath disposable endoventricular catheter, TGI100/TGI1200 system for acute, autologous cell therapy treatment BioPace™ for non-acute treatment of abnormal heart rhythm
Biophan Technologies	MRI medical devices	Biophan's technologies enable medical systems such as pacemakers, interventional surgical devices such as catheters and guidewires, and implants such as stents to be safely and/or

Similarly lipid-encapsulated microbubbles have been shown to adhere to sites of arterial endothelial damage and improve transgene expression in skeletal muscle cells even in the absence of ultrasound (Tsutsui et al, 2004). For example, PESDA microbubbles and ultrasound have been applied in the delivery of proteins such as vascular endothelial growth factor (VEGF) in mice and canine models of chronic myocardial ischemia. Intravenous infusion of VEGF combined with ultrasound and an albumin-based contrast agent significantly reduced the infarct area/risk area ratio, and increased myocardial blood flow.

These preclinical studies demonstrate the depth and breadth that ultrasound microbubbles may have in the future delivery of drugs, genes and proteins in a range of CV conditions. However, it is clear that the type of microbubble generated and ultrasound parameter adopted can have a significant effect on the delivery of bioactive substances (Tsutsui et al, 2004). Researchers have taken this a step further by adding targeting ligands to the surface of the microbubbles to form "targeted-microbubbles", these are currently being explored in CV diagnostic and therapeutics (Liu et al, 2006).

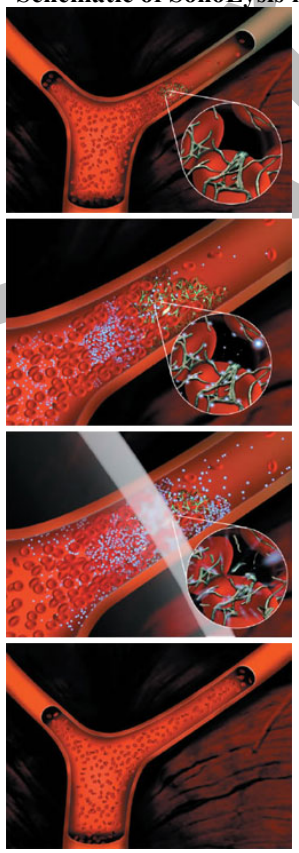
5.2.1 Case Study: MRX-801 microbubbles (ImaRx Therapeutics)

ImaRX is currently evaluating the SonoLysis program which focuses on two product candidates that involve the administration of its proprietary MRX-801 microbubbles and ultrasound with or without a thrombolytic drug, alteplase (tPA) to disperse blood clots and restore blood flow.

SonoLysis+tPA therapy comprises the administration of MRX-801 microbubbles, ultrasound and the thrombolytic drug alteplase, or tPA. SonoLysis therapy comprises the administration of MRX-801 microbubbles and ultrasound without a thrombolytic drug. tPA is the only approved drug for the treatment of ischemic stroke and is restricted for use only to patients who are able to begin treatment within three hours of onset of symptoms of ischemic stroke – this accounts for around a fifth of ischemic stroke patients.

The MRX-801 sub-micron sized microbubbles are a proprietary formulation derived from a lipid shell encapsulating an inert biocompatible gas. This enables the microbubble to penetrate the blood clot and through cavitation (expansion and contraction) induced by ultrasound it can break down the blood clot (Figure 5.3).

Figure 5.12: Schematic of SonoLysis mode of action



Clot formed within arterial wall prevents the flow of blood.

MRX-801+tPA introduced systemically into the circulatory system, passes around the circulation and accumulates within clots

Ultrasounds are focused at the site of blood clot formation causing cavitation and the release of tPA which then breaks down the clot

Clot is broken down and the blood flows freely restoring O_2 flow to the tissues.

Source: ImaRx

7.5 Our opinion on gene-based delivery technologies

Where the technology is now, its evolution, achievements and pitfalls
Initially research in gene therapy relied on the transfer and delivery of genetic material by modified viruses which efficiently infected cells and released their "DNA payloads" into the host genome to program the production of desirable proteins. However, the tide has turned and researchers are increasingly using non-viral methods such as plasmid DNA (pDNA) - small rings of DNA produced in bacteria – and condensed DNA nanoparticles to delivery genes to the target cells.

However, whilst great progress has been made in non-viral vector delivery which allows organ specificity, the use of these delivery systems is often limited by low transfection rates and transient (temporary) gene expression. This is in contrast to viral-vector based transfer that is more efficient, but organ specificity may be reduced and immunogenic properties can limit their utility.

Increasingly companies are beginning to focus on alternative ways of switching genes on and off within host cells; there has been a trend away from antisense technologies and towards siRNA and miRNA technologies. However, delivery, delivery, delivery remains key and specialist companies are beginning to overcome the hurdles associated with the targeted delivery of these new gene-based therapeutics. Therefore, several issues remain to be overcome both in non-viral and vector delivery namely the selection and design of vectors for gene transfer and the identification of appropriate delivery systems, in order to make gene-based therapies a reliable and safe addition to the cardiologist's repertoire.

Competition
Whilst several companies continue to evaluate the potential of viral vectors as delivery vehicles for CV therapies, there has been a migration towards non-viral vectors which may be more cost-effective to produce and are less likely to be associated with immunotoxicity/safety issues. A variety of cell-based platforms and delivery systems are under evaluation which may offer stability and a selective method for gene delivery and which can provide an efficient method for genetic delivery to targeted host cells. Competition within this field is expected to increase as the first generation of gene-based CV therapies near clinical development and proof-of-concept data is obtained.

Potential future applications
As the underlying genetic mechanisms of CV disease continue to be explored new genes are identified that may offer new targets for CV disease. This together with advances in the design and systemic and localized delivery of viral and non-viral vectors will help to drive the development of regenerative therapies and make them become an important addition in the fight against CV disease in the 21st Century.

Activity in the market
During the last five years a number of gene-based companies have teamed up with delivery specialists and biotechnology companies to overcome the manufacture and delivery of gene-based therapies such as Cook Medical/AVI BioPharma, MaxCyte/Northern Therapeutics, Protiva Biotherapeutics/Alnylam Pharmaceuticals, Vical/AnGes and Vical/Centelion. We anticipate this trend will continue as more regenerative therapies enter the clinic.

Major players
The delivery of gene-based therapies is split into two camps, those focusing on non-viral delivery systems and those pursuing viral delivery platforms. The key players in physically derived non-viral delivery include: AnGes, Targeted Genetics and Vical and in chemically derived non-viral delivery systems include AVI BioPharma and Protiva Biotherapeutics. Key players in viral delivery include AnGes, Ark therapeutics and Cardium Therapeutics.

Winners
We believe that companies focusing on non-viral delivery systems are likely to be the near term winners as physicians will be less cautious of these delivery vehicles. Ultimately the viral delivery systems will break through as the long-term winners due to high efficiency of delivery and transfection but this will occur only once safety (immunogenicity and toxicity issues) have been surmounted, has become well-established and the publics and scientific communities' perception regarding safety has been reassured.

