



Absorbable Polymers INTERNATIONAL

A Subsidiary of  Corporation
DURECT



Engineering The Future

The world's preferred supplier of biodegradable polymers, polymer-based technologies, and polymeric products for the drug delivery and medical device industries.



Greetings



When I founded Birmingham Polymers (BPI) in 1987 and later Absorbable Polymer Technologies (APT) in 1997, my single focus was to give each of my customers the right technology for the right application.

Now, nearly 20 years since BPI was founded, Durect has merged the resources of BPI with those of APT to form a fully integrated company, Absorbable Polymers International. But the focus has never changed. Our primary mission now is the same as always: to use our extensive experience, skill, knowledge, and intellectual property to give our customers exactly what they need.

From 20 grams custom-made for your proprietary application to hundreds of kilograms for commercial products (of which we supply several), we want API to be the company you trust, the company you turn to, and the company you want to do business with when you need biodegradable polymers and polymer-based technologies.

We hope you will give us this opportunity.

Sincerely,

James P. English

Chief Operating Officer

Absorbable Polymers International

The Established Leader

To pioneer advances in medicine requires much more than just a good idea. It requires courage, determination, and most of all, leadership. Because to see your idea become a reality, you must lead the way. You must have the confidence to help others see the value in your product and the knowledge and experience to make your product work for your customers every time and in every instance.

That's exactly what we do at Absorbable Polymers International. And here's how:

API has more experience than anyone else in the industry. Our scientists are recognized leaders in the biodegradable polymer industry.

We have the technical expertise and cGMP manufacturing capabilities to meet all your biodegradable polymer requirements. We provide far more than just polymers: you can count on us for analytical services, drug delivery and medical device research and development, and much more.



We understand the challenges you face. We understand that you have exacting specifications and tight deadlines. We know that sometimes you need advice and recommendations to make sure you get the right product. And we know how to help you face these challenges and achieve your goals.

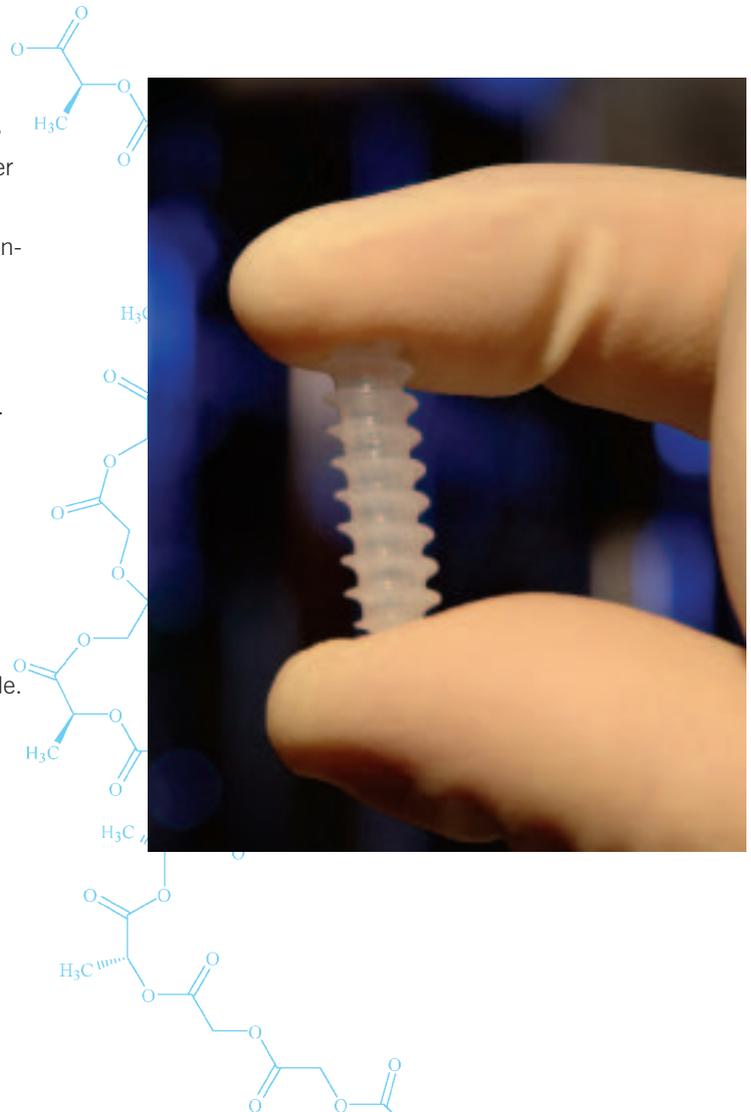
Absorbable Polymers International has the experience, knowledge, skill, and ability to create and deliver innovative, on-time solutions for you. Every time.

Patented Technology

Recently, API received US patent #6,532,667, a novel process for making biodegradable polymeric implants. This enabling technology has numerous process advantages over conventional injection moulding including:

1. Biodegradable polymer implant devices can be inexpensively manufactured.
2. Higher molecular weight and higher-strength implant devices can be prepared using the new process than can be prepared with conventional molding processes.
3. High molecular weight parts can be made with a greater degree of detail than can be with conventional molding processes.
4. The crystallinity and mechanical properties of the final device are more easily controlled.
5. Homopolymer, random copolymer, block copolymer, and segmented block copolymer implants can be made.
6. Crosslinked implant formulations are possible.
7. Fiber- and particle-reinforced implants are possible.
8. Implant devices incorporating controlled release of drugs are possible.

* This technology is available for licensing.



Let's Get Specific

Current Applications.

The most active area of research using biodegradable polymers is in controlled delivery of pharmaceuticals. In the last decade, this research has led to the commercial development of numerous drug delivery systems in Europe, Japan, and the United States. The two most common commercial delivery systems using biodegradable polymers are microspheres (Lupron Depot®) and implants (Zoladex®). The implants can be rods, films, or other shapes depending upon the specific needs. Recently, gel-based systems using biodegradable polymers have been introduced, further expanding delivery system options.

These delivery systems are also being considered for the treatment of cancer, viral and bacterial infections, birth control, chemical dependency, AIDS, and chronic pain.



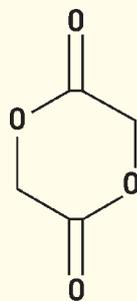
Polymer Details

At Absorbable Polymers International, we specialize in the preparation of biodegradable polymers from glycolide, lactide, and ϵ -caprolactone monomers for use in medical applications. These three cyclic monomers can be assembled into a wide variety of polymers and copolymers. Polymer properties can be tailored from soft elastomeric materials to rigid engineering plastics.

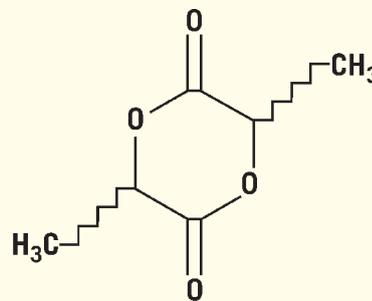
In addition to mechanical properties, other polymer properties — including degradation rate, hydrophilicity, and solubility — can be customized for individual applications.

Researchers continue to develop new and varied classes of biodegradable

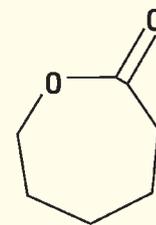
polymers such as polyanhydrides, polyorthoesters, polyphosphazenes, polyphosphoesters, and other materials. However, products prepared from glycolide, lactide, and ϵ -caprolactone remain the materials of choice for use in humans.



Glycolide



Lactide



ϵ -caprolactone

Medical Devices

Biodegradable polymers of lactide, glycolide, and ϵ -caprolactone are currently being used to produce a variety of commercial medical devices. These include:

- Biodegradable sutures — product names include Dexon[®], Maxon[®], Polysorb[®], and Biosyn[™], among others
- Interference screws — including Bioscrew[®], Sysorb[®], Endofix[®] and more
- Pins and rods — product names include Biofix[®], and Resor-Pin[®]
- Other products — Bio-Anchor[®] (Suture Anchor), Drilac[®] (Dental), LactoSorb[®] (plate, mesh, screws), and more.

In addition to biocompatibility and non-toxicity, other properties that make these polymers uniquely suited for medical devices include thermoplasticity, strength, controlled crystallinity, degradation, and hydrophilicity. Because of these same properties, these polymers are also being considered for bone plates and other orthopedic applications, ear vent tubes, nerve growth tubes, stent coatings, and wound dressings.



The Near Future

Many new controlled drug delivery products are expected to emerge in the near future, as a result of the extensive research and development efforts currently underway. Because polymers and copolymers of glycolide, lactide, and ϵ -caprolactone have a proven record of success, it is expected that they will be the dominant excipients used in most formulations.



Our Expertise

At Absorbable Polymers International, we can synthesize and manufacture polymers to meet your specific needs. We know that choosing a polymer for your particular application depends upon a number of requirements — including mechanical properties, degradation rate, and processing. There might be a standard polymer that meets your exact specifications, and we can help you select that polymer. However if additional product optimization is required, we

provide experimental input and custom synthesis. For example, increased polymer solubility aids in the preparation of many microsphere products. To meet our customers' needs in this area, we have used our synthetic expertise to increase polymer solubility of 50/50 poly (DL-lactide-co-glycolide). We have also used end group chemistry, such as free carboxylic acids and PEG to effect degradation and tailor release kinetics.

Synthesis

All polymer production is in accordance with applicable current Good Manufacturing Practices (cGMP) of the FDA. Polymers are produced in class 100,000 clean rooms with controlled temperature and humidity in our modern, well-equipped production and laboratory facilities in Pelham, Alabama, USA. Large-scale processes are computer controlled to maintain consistent processing parameters and to automatically log all data for quality assurance record retention. Both Drug and Device Master Files are maintained with the FDA.

Our commitment to quality includes a thorough analysis of each lot of polymer. Polymer lots are tested before shipment, and each lot is supplied with a Certificate of Analysis (COA). Our basic analyses include identification by FTIR or ¹H-NMR, inherent viscosity (IV), monomer ratio by ¹H-NMR (copolymers only), residual Sn⁺² (from catalyst), bioburden (total aerobes, anerobes and spores), and pyrogens (LAL). Other analyses can be provided if desired, including other metals and molecular weight by GPC.

Product Number	Chemical Name	Common Name	Inherent Viscosity
50DG020	50/50 Poly (DL-lactide-co-glycolide)	50/50 DLPLG	0.15 - 0.25
50DG040	50/50 Poly (DL-lactide-co-glycolide)	50/50 DLPLG	0.26 - 0.54
50DG065	50/50 Poly (DL-lactide-co-glycolide)	50/50 DLPLG	0.55 - 0.75
50DG085	50/50 Poly (DL-lactide-co-glycolide)	50/50 DLPLG	0.76 - 0.94
50DG105	50/50 Poly (DL-lactide-co-glycolide)	50/50 DLPLG	0.95 - 1.20
65DG065	65/35 Poly (DL-lactide-co-glycolide)	65/35 DLPLG	0.55 - 0.75
75DG065	75/25 Poly (DL-lactide-co-glycolide)	75/25 DLPLG	0.55 - 0.75
85DG065	85/15 Poly (DL-lactide-co-glycolide)	85/15 DLPLG	0.55 - 0.75
100D020A	Poly (DL-lactide-COOH)	DLPLA-COOH	0.15 - 0.25
100D040A	Poly (DL-lactide-COOH)	DLPLA-COOH	0.26 - 0.54
50DG020A	50/50 Poly (DL-lactide-co-glycolide)-COOH	50/50 DLPLG-COOH	0.15 - 0.25
50DG065A	50/50 Poly (DL-lactide-co-glycolide)-COOH	50/50 DLPLG-COOH	0.55 - 0.75
100D040*	Poly (DL-lactide)	DLPLA	0.26 - 0.54
100D065	Poly (DL-lactide)	DLPLA	0.55 - 0.75
100L0105	Poly (L-lactide)	LPLA	0.90 - 1.20
100G160	Poly (glycolide)	PGA	1.40 - 1.80
100C115	Poly (ε-caprolactone)	PCL	1.00 - 1.30
25DC080	25/75 Poly (DL-lactide-co-ε-caprolactone)	25/75 DLPLCL	0.70 - 0.90
75DC080	75/25 Poly (DL-lactide-co-ε-caprolactone)	75/25 DLPLCL	0.70 - 0.90

Chemical Properties of Selected Polymers

Polymer Type	Inherent Viscosity (DL/G)	Melting Point (°C)	Glass Transition Temperature (°C)	Solubility At 5% W/W	Approximate Resorption Time (Months)
50/50 DL-PLG	0.55 - 0.75	Amorphous	45 - 50	1,2,3,4,5,6	1 - 2
65/35 DL-PLG	0.55 - 0.75	Amorphous	45 - 50	1,2,3,4,5,6	3 - 4
75/25 DL-PLG	0.55 - 0.75	Amorphous	50 - 55	1,2,3,4,5,6	4 - 5
85/15 DL-PLG	0.55 - 0.75	Amorphous	50 - 55	1,2,3,4,5,6	5 - 6
DL-PLA	0.55 - 0.75	Amorphous	50 - 60	1,2,3,4,5,6	12 - 16
L-PLA	0.90 - 1.2	173-178	60 - 65	1,4,5	>24
PGA	1.4 - 1.8	225-230	35 - 40	5	6 - 12
PCL	1.1 - 1.3	58-63	-65 - -60	1,4,5,6	>24

* Solvents (partial listing only):

1 = dichloromethane

2 = tetrahydrofuran

3 = ethyl acetate

4 = chloroform

5 = hexafluoroisopropanol

6 = acetone

Physical Properties of Selected Polymers

Polymer Type	Specific Gravity (G/ML)	Tensile Strength (PSI)	Elongation (%)	Modulus (PSI)
50/50 DL-PLG	1.34	6000 - 8000	3 - 10	2 - 4x10 ⁵
65/35 DL-PLG	1.30	6000 - 8000	3 - 10	2 - 4x10 ⁵
75/25 DL-PLG	1.30	6000 - 8000	3 - 10	2 - 4x10 ⁵
85/15 DL-PLG	1.27	6000 - 8000	3 - 10	2 - 4x10 ⁵
DL-PLA	1.25	4000 - 6000	3 - 10	2 - 4x10 ⁵
L-PLA	1.24	8000 - 12000	5 - 10	4 - 6x10 ⁵
PGA	1.53	10000+	15 - 20	1x10 ⁶ +
PCL	1.11	3000 - 5000	300 - 500	3 - 5x10 ⁴

DL-PLG = poly(DL-lactide-co-glycolide)

DL-PLA = poly(DL-lactide)

L-PLA = poly(L-lactide)

PGA = poly(glycolide)

PCL = poly(ϵ -caprolactone)

Custom Synthesis

A large percentage of our work at Absorbable Polymers International is devoted to the development of polymers with customized characteristics. For example, we have worked closely with clients to:

- Increase polymer solubility
- Tightly control polymer molecular weight
- Vary monomers and molecular ratios to give desired drug release profiles
- Tailor polymers with hydroxy, ester, carboxylic acid, or polyethylene glycol (PEG) end groups to influence hydrophilicity, degradation, and drug release rates

Subtle changes in molecular architecture can have a profound effect on degradation rate and drug release rates. For example, altering the polymer end groups can affect water

uptake and degradation rate. Typical examples are shown in the table below.

Not only are we dedicated to creating the ideal polymer for each of our clients' specific applications, we're also committed to working closely with our clients throughout the FDA approval process. Our custom synthesis capabilities help anticipate validation questions for new production processes. For example, we can supply three identically made lots for process validation, or we can target molecular weights ten percent above or below your mean to set raw material specifications. The knowledgeable professionals at Absorbable Polymers International can also help you pinpoint the exact characteristics you need for your application through experimental input and custom synthesis.

Initiator — Polymer End Group Effects

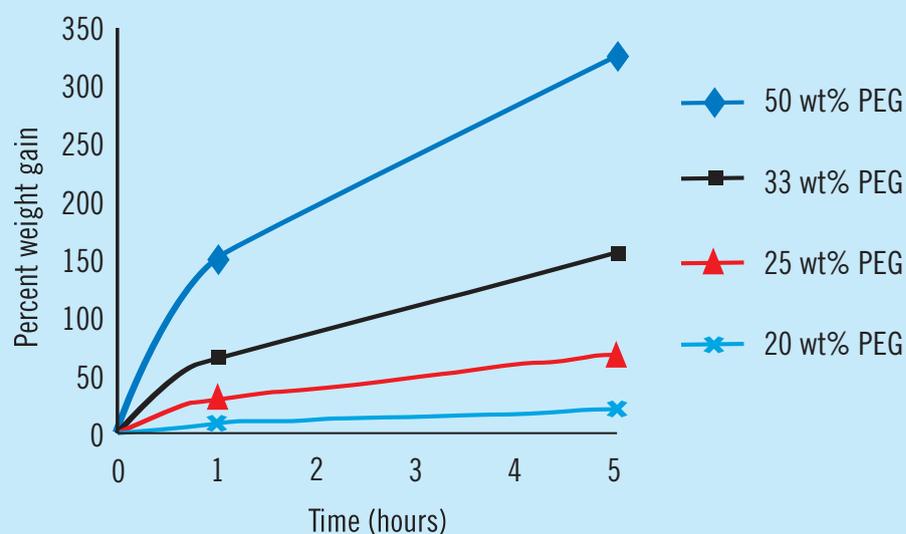
Initiator	End Group	Effects
Monofunctional alcohol	Ester and Hydroxyl	Slightly hydrophilic
Water or α -hydroxyl acid	Carboxylic acid and Hydroxyl	More hydrophilic; increased water uptake and degradation rate
Polyethylene glycol (PEG)	PEG and Hydroxyl	Most hydrophilic

Proven Expertise

Birmingham Polymers and Absorbable Polymer Technologies have independently commercialized numerous polymers in FDA approved medical devices or pharmaceutical products. Also, each company, at the time of their merger, had dozens of different projects with clients in various stages of clinical and pre-clinical development. In addition, Absorbable Polymers International (API) has patents relating to the use of biodegradable polymers for improved processes in drug delivery and the manufacture of biodegradable medical devices.

PEG-DLPLG Hydrogels

Water uptake by PEG Hydrogels



- Rate of water absorption controlled by ratio of PEG to DLPG
- Polymers continue to absorb water
- Ultimate water weight gain also controlled by ratio of PEG to DLPLG

Packaging, Storage & Handling

Special packaging is required to protect biodegradable polymers from degradation by moisture. At Absorbable Polymers International, we package our polymer lots in polyethylene bags under high-purity dry nitrogen. These polyethylene bags are heat sealed and packaged in outer heat-sealed, foil-lined pouches. A pouch of desiccant is placed between the inner and outer bag. All packaging is performed in a clean room. Special packaging, such as multiple containers or alternative sizes, can be arranged to assist your production or R&D needs.



Biodegradation

The principal mode of degradation for glycolide, lactide, and ϵ -caprolactone polymers and copolymers is hydrolysis. Degradation proceeds first by diffusion of water into the material (initially into the more amorphous zones) followed by random hydrolysis; fragmentation of the material; and finally, a more extensive hydrolysis accompanied by phagocytosis, diffusion, and metabolism. The hydrolysis is affected by the size and hydrophilicity of the particular polymer implant, the crystallinity of the polymer, and the pH and temperature of the environment.

In general, the degradation time will be shorter for lower molecular weight polymers, more hydrophilic polymers, more amorphous polymers, and copolymers higher in glycolide. Therefore, at identical conditions, low molecular weight

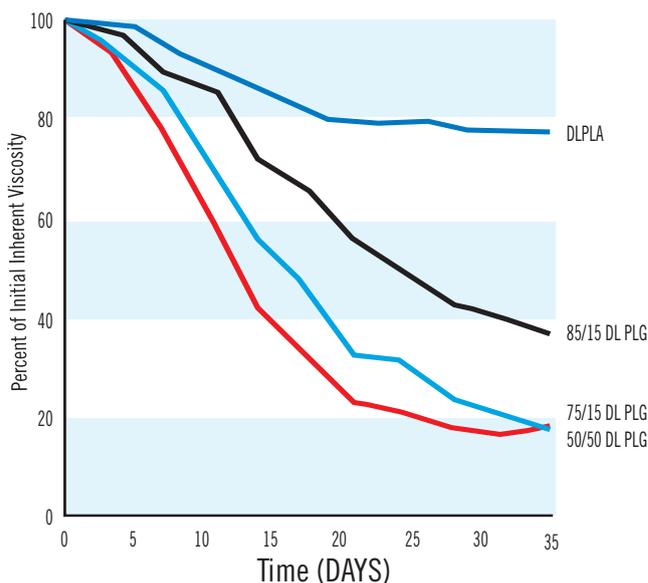
copolymers of DL-lactide and glycolide, such as 50/50 DL-PLG, will degrade fairly rapidly, whereas high molecular weight homopolymers, L-PLA, and PCL will degrade much more slowly.

Once hydrolyzed, the products of hydrolysis are either metabolized or excreted. The lactic acid generated by the hydrolytic degradation of PLA becomes incorporated into the tricarboxylic acid cycle and is excreted as carbon dioxide and water. PGA is also broken down by random hydrolysis accompanied by non-specific enzymatic hydrolysis to glycolic acid, which is either excreted or enzymatically converted to other metabolized species.

Absorbable Polymers International can tailor polymers to meet specific degradation requirements.

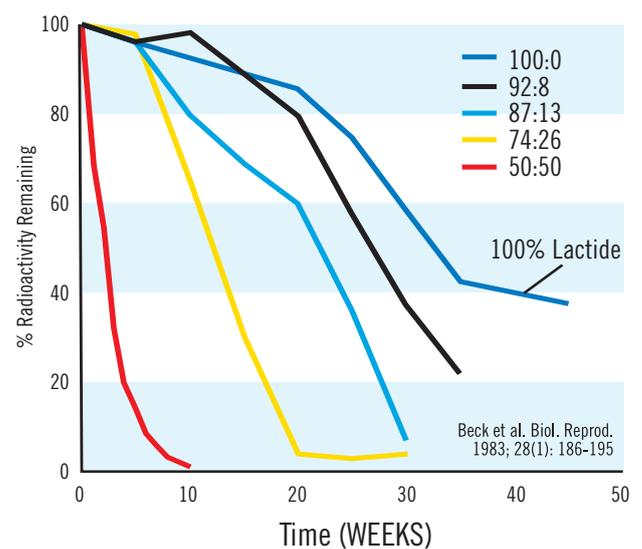
In Vitro Degradation of Selected Polymers

Molecular Weight Loss



In Vivo Biodegradation of ¹⁴C-Labeled DL-PLGs

Mass Loss



A Leader In Service, Too

It takes more than just producing polymers to meet our customers' needs. We must also provide the best service in the industry. And we believe that's exactly what we do today. For example:

Fast shipping. Most orders for standard products are shipped within 48 hours.

Custom Synthesis. We custom synthesize polymers for orders as small as 20 grams. From the smallest order to the largest, we deliver the same responsive customer service with each one.

Easy Ordering. We want to make your job easier, so we give you several easy ways to get more information or to place an order. You can visit our web site, email us, call us, or fax your order. Regardless of which method you choose, you'll get great customer service and your order delivered fast.

Biodegradable Polymers — Past, Present, and Future

In the first half of the 20th century, research into polymers synthesized from alpha-hydroxy acids was abandoned because the resulting polymers were too hydrolytically unstable for long-term use. However, over the past four decades, it has been found that this very instability has made these polymers ideal for numerous important medical uses, including pharmaceutical drug delivery and biodegradable medical devices such as sutures, staples, fixation rods, and more.

Today, a new, exciting area of application for biodegradable polymers is in tissue engineering. Several universities and companies are investigating these materials as matrices for growing living cells. The polymer matrix may represent the device itself, or it may be a scaffold for in vitro cell growth that is degraded by growing cells prior to implantation. The matrix can also be formulated to contain active agents, such as growth factors, for more rapid tissue growth.

In the future who knows? But we at API look forward to your partner of choice as your pioneering ideas move forward.

Engineering The Future

As research continues and new applications are devised, the field of biodegradable polymers is changing daily. The future of this industry — which we have been involved with since its infancy — is very promising.

As the industry grows and changes, you can continue to count on Absorbable Polymers International to provide an unsurpassed level of experience and expertise, to deliver outstanding service, and to find the solutions you are looking for.

For example, we recently made it possible for our customers to place orders on our web site using our online catalog and hassle-free shopping path. This means that ordering and receiving the products you need is now faster and easier than you ever imagined possible.

www.absorbables.com

email: info@absorbables.com

phone: 205.620.0025

fax: 205.620.9888

“Medical Device Technologies brought Absorbable Polymers a complex, fast track project with some significant technical issues to be solved. The team at Absorbable Polymers responded to the challenge and helped us meet our very aggressive product launch requirements. I really appreciate a vendor such as API with the combination of superior technical expertise and ‘can do’ attitude.”

Chris Blake

Engineering Manager

Medical Device Technologies

Division of InterV

Gainesville, Florida

A Subsidiary of  Corporation
DURECT



Absorbable Polymers
INTERNATIONAL

2683 Pelham Parkway
Pelham, AL 35124
USA

phone: 205.620.0025
fax: 205.620.9888

www.absorbables.com
info@absorbables.com

A Subsidiary of  Corporation
DURECT