Syngene

Putting Science to Work

Small Molecule Development & Manufacturing

30 years of Putting Science to Work

A Global CRO/CDMO

- Integrated Drug Discovery, Development and Manufacturing service provider
- Small Molecules and Biologics, ADCs, Oligonucleotides
- Listed on Indian Stock Exchanges (NSE and BSE)

Scientific Ecosystem

- 2.2 Mn sq. ft. world-class R&D and Manufacturing infrastructure
- Sites in Bangalore, Mangalore, and Hyderabad
- 6000+ qualified scientists including 550 PhDs
- Highly effective supply chain practices

IP Position

- IP assigned to clients
- Strong track record of Data Integrity and Security
- Over 400 patent assignments by clients recognizing Syngene

Marquee Clients

- 420+ active clients last FY
- Partnering with large / mid-size / emerging BioPharma (EBP) and other industries
- Clients concentrated in US, Europe & Japan
- Track record of working with diverse industry sectors

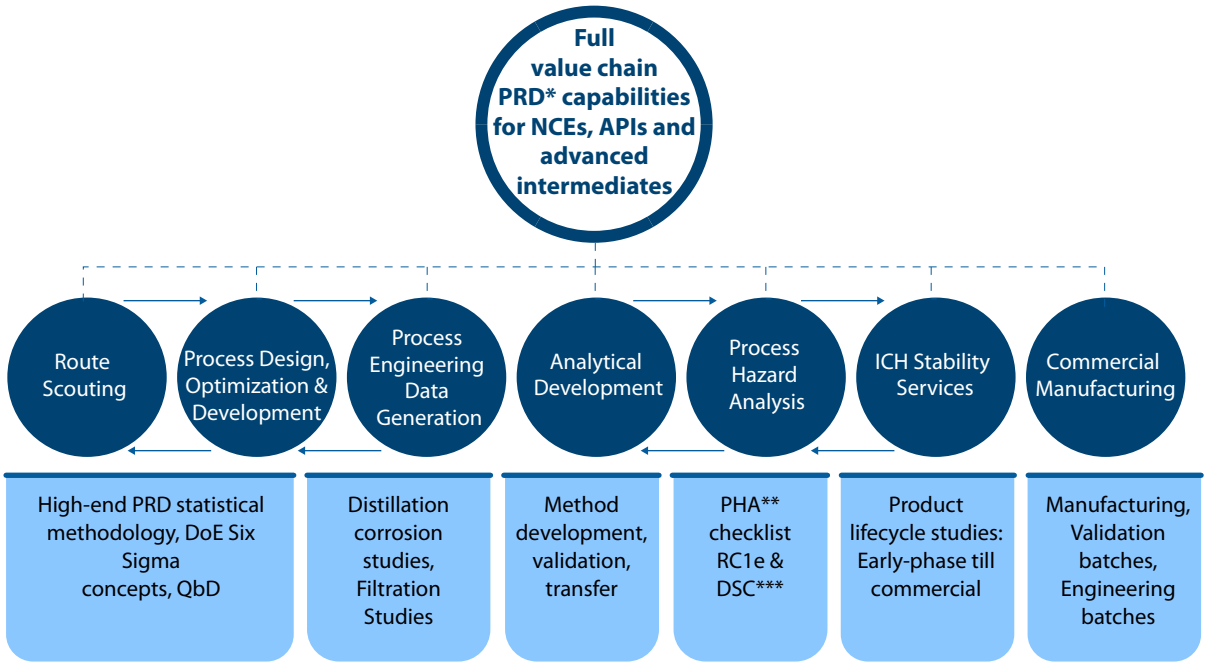
Quality Focus

- Quality driven organization
- Excellent track record of compliance with global regulators
- US FDA, EMA, ANVISA and PMDA approved, GLP Certified, Ministry of Health of Russian Federation, AAALAC & CAP accredited/certified facilities
- 15+ regulatory and 160+ client audits in the last 3 years

Track Record

- Collaborations and partnerships to deliver numerous clinical candidates
- Delivery history for integrated CMC programs towards FIH and beyond

Chemical Development



Highlights

- 125+ fume hoods in multiple suites
- Automated lab-scale jacketed reactors (-70- to 180 °C)
- Flow Chemistry
- Dedicated process engineering and safety lab
- HPAPI development from lab to manufacturing scale
- Therapeutic and diagnostic oligonucleotides – lab to manufacturing scale
- Performance and Speciality Materials – synthetic organic chemistry, polymer chemistry and scale-up activities
- Integrated analytical services – analytical method development, validation, transfer and reference standard qualification
- Regulatory Support

* Process research and development | ** Process hazard analysis | *** Differential scanning calorimetry

Process Engineering and Scale-Up

Capabilities

- Design of experiments (DoE)
- Quality by design (QbD)
- Reaction Kinetics studies
- Process modeling and simulation
- Reaction Optimization studies
- Unit operation and processes
    - Filtration, distillation, extraction, drying, corrosion studies etc
- Process Crystallization studies
- Advanced process analytical technologies (PAT) for process understanding (FBRM, PVM, React-IR etc)
- Flow chemistry development
- Mass and energy balances
- Technology absorption and transfer

Process Safety Management

Capabilities

- Process Safety studies (DSC, RC1e, ARC, vent Sizing etc)
- Powder Safety studies (Fall Hammer test, MIE, MIT, Ignition test, MEC, LOC etc)
- Process Safety Information
- Process Risk Assessment (What-if, HAZOP, PHIRA, FMEA, Qualitative and Quantitative Risk Assessment etc)
- Pre-startup Safety reviews
- Asset Integrity and Reliability studies

Oligonucleotides services

Salient Features

Process Development

- Natural & Modified | siRNA | ASOs | Anti-microRNA | Aptamer | CpG
- Conjugated oligos | Molecular beacons | Fluorescent oligos | Probes & Primers
- Backbone modifications | Base modifications | Sugar modifications
- Synthesizer & Scale: ÄKTA oligopilot 100 | 250 µmol - 6 mmol (100 mg - 5 g / batch (non-GMP))

Analytical Support

- Comprehensive Analytical support | Method Development & Validation
- Combination of orthogonal techniques
- Impurity Analysis | Identification | Sequencing | Characterization
- Release specifications: General | Compendial | Oligo-specific methods
- Forced degradation | Informal stability | ICH stability

Manufacturing

- cGMP facility of 1500 sq. ft. | Fully qualified equipment and area
- Controlled environment to limit endotoxin and bio-burden
- Located in a GMP certified/ USFDA inspected facility
- Synthesizer & Scale: ÄKTA oligopilot 400 | 4 mmol - 45 mmol (5 g - 135 g / batch (GMP/non-GMP))
- Support for regulatory filing | CMC documentation suitable for Phase 1/2 IND

Formulation

- Drug Substance characterization and method development
- Formulation development and optimization
- Analytical methods development and pre-validation for the Drug Product
- Supportive stability study
- Component compatibility study and miscellaneous studies

High Potent APIs

Capabilities

- Integrated solutions from Discovery, Process R&D, optimization, scale-up and clinical supplies to commercial
- OEL determination toxicity studies
- cGMP manufacturing
- Facilities designed to handle cytotoxic, cytostatic, and high potent compounds with OEL values in the range of >100 µg/m^3 to 0.01 µg/m^3
- Isolators for full spectrum of unit operations from sampling, dispensing and weighing, reactor charging, filtration, drying, milling & sieving to packing
- Broad range of reactors (stainless steel, glass lined, hastelloy)
- Dedicated facility for Prep-HPLC and lyophilization of HPAPI molecules
- Development and manufacturing of ADCs, including linker development, optimization, and characterization

Highlights

- Highly experienced process chemists, analytical chemists, process engineers, manufacturing and quality control team
- cGMP facility for lab-scale to commercial-scale manufacturing including registration and validation batches for regulated market
- Integrated with a separate cGMP facility to manufacture non potent compounds.
- Provision to add reactor and matching downstream equipment to enhance capacity/capability
- PAI inspection for the API registration and validation batches

Performance and Specialty Materials

Capabilities

- Synthesis and purification of monomers/polymers
- Functionalization chemistry
- Material characterization
- Process Development & Process Engineering
- GMP and non-GMP manufacturing capabilities

Monomers	Polymers	Materials
Acrylates; Schiff bases; Ionic liquids; Radical compounds; Macrocycles; Heterocycles, End functionalization of polymers; Light and air sensitive compounds	Supramolecular Polymer; Conducting Polymers; Polymer Self Assembly; Self-healing Polymers; Hydrogels; Silicones; Random/Block/star/comb copolymers	Inorganic Materials; Additives; Catalysts; Biomaterials; Nanomaterials-Nanofibers, CarbonNanoTube (CNT)

Highlights

- Excellent track record of continuous supply of polymers & specialty materials (250-500 kg/batch), Nano materials (1-2 kg) and additives (10-100 kg scale)
- cGMP compliant facilities inspected by USFDA and audited by global customers and quality persons from Europe
- Innovation in specialty materials and polymers – lab-scale to commercial

Syngene offers Formulation Development services to help clients determine optimal dosage levels for therapeutic formulations across oral solid, liquid, and injectable forms. Our integrated services extend to new chemical entities (NCE), late-phase product development, and over-the-counter products with a focus on quality, speed, and cost-efficiency.

Our Formulation Development capabilities

- Formulation Development – oral solids, liquids, semisolids (OEL up to 1 µg/m^3), injectables (OEL up to 0.1 µg/m^3)
- Conventional and complex injectable product development (nanosuspensions, nanoemulsions, polymeric nanoparticles, and liposomes) – small molecules, large molecules (proteins, peptides, oligonucleotides), and biologics (mAb, ADC, m-RNA vaccines)
- Pre-formulation profiling, including salt and polymorph screening
- Preclinical formulation development
- Development of palatable dosage forms for companion animals (hard chews and soft chews), spot-on formulations
- Formulation development of oral solids (modified-release, controlled-release, timed-release, delayed-release)
- Novel drug delivery systems (liposomes, nanoemulsions, biodegradable polymers-based microspheres, nanoparticles, and in situ depots)
- Enabling formulation approaches – spray-dried dispersion (SDD), hot melt extrusion (HME), lipid-based, complexation-based, self-micro emulsifying drug delivery system (SMEDDS), and nanosuspensions
- Analytical method development and validation

Our Drug Product Manufacturing capabilities

Oral solids

- cGMP manufacturing and clinical supplies for solid orals (OEL up to 1 µg/m^3)
- Unit operations such as dry and wet granulation, wurster coating, blending, spray drying, tablet compression, tablet coating, encapsulation, extrusion, and spheronization
- Automatic capsule filling machine for pellets, powders, and mini tablets
- Blister packing machine; ALU- ALU, PVC-ALU, PVC/PVDC-ALU, and automatic bottle packing machine for tablets and capsules
- Phase 1/Phase 2, and Phase 3 clinical supplies/registration batches/process validation batches
- Small-scale drug product commercial supply for niche and orphan drug products (current batch size of up to 120 kg scaling up to 400kg by 2024)

Syngene Injectable Fill-Finish facility

- Capability to manufacture ready-to-use solutions, enabled formulations (liposome, LNP, micelles, drug-polymer conjugates, PLGA microparticles, and nano pharmaceuticals) and lyophilized products (pre-sterilized vials and prefilled syringes) OEL: ≥ 1 µg /m3 – ready-to-use format for vials (2R to 30R) & PFS (1cc – 10cc)
- Aseptic filtration and filling and terminal sterilization
- Batch size of 500 to 25,000 vials, volume: 5L- 100L
- Lyophilization capability for vials (3500 vials of 10R size)
- Capability to handle clinical batch manufacturing and small volume commercial of small molecules and biologic products

Our Animal Healthcare Manufacturing facility

- Dedicated GMP facility for animal health products (up to OEL 1µg/m^3). Batch size of up to 60kg
- Manufacturing and packing of conventional and bolus tablets
- Capability to manufacture hard chews and soft chews tablets
- Blister packaging capability for small and bolus tablets; PVC-ALU, PVC-PVDC/ALU, Alu-Alu, and Aclar, and bottle packaging

Highlights

- Quick-to-clinic approaches for Phase-1 Clinical studies (first-in-human)
- Expertise in animal healthcare formulation development (complex palatable formulation development and long-acting injectable formulations)
- Skilled in developing and manufacturing niche technologies like polymeric biodegradable nanoparticles for sustained release, depot formulations, chronotherapeutic drug delivery systems, and sustained/modified/delayed release formulations
- Delivered numerous Phase 1/I2/3 clinical supplies for customers across the globe.
- Delivered successfully 505(b)(2)/Hybrid application programs as early as the ideation process, repurposing of molecules and identifying the unmet medical need
- Clean regulatory track record with different regulatory bodies across the globe (USFDA and Russian Regulatory Agency-approved, oral solid manufacturing facility)
- Drug product supplier for commercial products in the US

To know more about our Formulation Development services, **contact our experts**

Analytical Development

- Method development
- Method verification/validation
- Structural characterization and elucidation
- Reference and working standards qualification
- Identification and characterization of impurities
- Prep HPLC/chiral purification
- Residual Solvent Analysis
- Elemental impurities analysis
- Impurity analysis
- Method transfer
- Stability studies
- Phys-Chem studies/5-batch analysis

Analytical capabilities for Drug Products

Tablets capsules:
Assay & content uniformity, related substances, water content, drug excipient compatibility studies, filter compatibility, solubility, degradation studies, antioxidant and preservatives, DT, dissolutions (release media, multimedia & bio-relevant media), PSD, pXRD and residual solvents.

Powder for Injection (lyophilized / dry powder, microspheres, liposomes):
Assay, related substances, residual solvents, reconstitution stability study, diluent/component stability compatibility, assay of encapsulated/free drug, polymer characterization, lipid characterization, assay of antioxidant/preservatives, dissolution, particle size distribution.

Suspensions, Solutions:
pH, viscosity, light transmission matter/color, Density (Wt/mL), solubility, AET, assay & CU, degradation studies, drug excipient compatibility studies, related substances, antioxidant and preservatives, dissolutions and PSD.

Suspensions (ophthalmic suspensions, vial suspension for injection):
Assay, related substances, residual solvents, component stability compatibility, assay antioxidant and preservatives, dissolution, particle size distribution, *Invitro* comparative nasogastric feeding tube studies for vial suspension.

Liquid Injections (ampoules, prefilled syringes, vials):
Assay, related substances, residual solvents, diluent and component stability compatibility, particulate matter.

Semisolid dosage forms:
pH, viscosity, physical appearance, density (Wt/mL), AET, assay & CU, degradation studies, drug excipient compatibility studies, related substances antioxidant & preservatives, IVRT, texture analysis.

Analytical capabilities for complex injectables

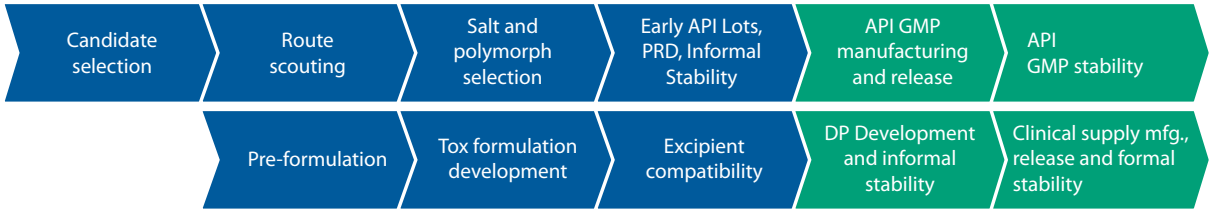
Pre-formulation studies	Liposomal injection	Injectable nanosuspension	Extended release injectable microspheres
• API characterization • API solubility • Excipient's evaluation • pH solubility and impact on stability • Impact of various parameters on API stability • Aggregate evaluation	• Assay; free/entrapped drug; other critical excipient • Related substances Phospholipid content (lyso forms) • Size and zeta potential • Internal environment (volume, pH, and ionic concentration): • State of encapsulated drug • *In vitro* drug release dissolution method using USP Type IV • Lipid degradation	• Dissolution method • Development – USP yype IV Assay • Related substances • Free fatty acid content • Phospholipid content • Drug partitioning • Globule size and zeta potential • Redispersibility	• Dissolution method development using Incubator orbital shaker or bottle rotating • Assay of free drug and encapsulated drug • Particle morphology size, shape • Molecular weight determi nation by GPC for polymer • Related substances • Polymer degradation

Analytical capabilities for Drug Substances

One-stop solution for all Analytical needs: Small molecules, oligonucleotides & performance and specialty materials (PSM)

Solid state characterization	Structural characterization	Method development/ validation	Extraction and purification
• Optical microscopy • XRPD • DSC/ TGA • DVS • Particle size analyzer	• NMR • LC/MS • LC/MS-MS • HRMS • GC/MS	• HPLC, GC, IC • Quantitative NMR • Wet chemistry • LC/MS, GC/MS • Genotoxic impurity methods • Forced degradation studies	• Semi prep HPLC • SFC • Column chromatography • Flash chromatography

Integrated Analytical support: Non-GMP and GMP activities



Non GMP Activities

- Phase-appropriate API, intermediate, DP analytical method development
- Support to chemists/process scientists / formulators for:
    - Route scouting, PRD activities
    - Tox/clinical formulation development
- Salt and polymorph screening
- Preformulation and excipient -- compatibility support
- Development stability of DS and DP (in use, accelerated, follow-up)
- Processing and packaging component compatibility

GMP Activities

- Phase-appropriate method qualification/ validation
- Release of RMs/ Intermediates/ DS/ excipients/ DPs
- DS and DP GMP stability
- Use time study for injectable DP

Non- GMP activities

GMP activities

Stability services: Salient features

Our Study expertise

- Complete Product lifecycle studies: Early phase till commercial
- Developmental stability
- Follow-up stability
- Forced degradation
- Freeze-Thaw stability
- In-Use stability
- Photo stability
- Registration stability
- RLD stability
- Commercial stability
- Transport assessment studies

Formulation types we deal in

Drug substances, drug intermediates including HPAPIs

- Tablets
- Capsules
- Soft gels
- Injectables
- Creams
- Ointments
- Eye drops
- Parentrals
- Lotions
- Emulsions
- Gels
- Suspensions
- Patches
- Liquid Spray
- Aerosols
- Powders

Our State-of-the-art facilities

- Biometric chamber access
- Multi-client ICH stability facility with long-term and intermediate testing conditions
- Uniquely coded and appropriately labelled samples
- Chromatography data systems
- 24*7 Online Temp/RH monitoring with backup facility
- Data managed electronically with systems 21CFR, Part 11 compliant

Commercial Manufacturing

Capabilities

Manufacturing of Regulatory starting materials, APIs, HPAPI, NCEs & novel advanced intermediates

Mfg. facility	nGMP	S1 Kilo Lab	Unit 2 Kilo Lab	HPAPI	S14	Mangalore
Range	160 L - 5000 L	10 L - 20 L	10 L - 50 L	60 L - 630 L	60 L - 8,000 L	2000 L - 12,500 L
Total Capacity	26,640 L	120 L	90 L	2010 L	63,600 L	69,600 L
Largest reactor	5,000 L	20 L	50 L	630 L	8,000 L	12,500 L
# Reactors	15	3	4	5	32	11
Total number of reactors and manufacturing volumes					**70 reactors & >161,000L**	

Salient Features

- 24/7 operations to ensure optimal utilization of resources
- Broad range of reactors (stainless steel, glass lined, hastelloy)
- Broad range of chemistries (Asymmetry catalysis, halogenation, etc.)
- High potency expertise (Cytotoxic, Cytostatic compounds up to 0.1 µg/m^3 - 8h OEL)
- High vacuum (< 10 Torr) & high temperature (140°C) distillations
- Hydrogenator for highly acidic/basic reactions with capacity up to 4 KL and 26 bar pressure rating
- 12 KL cryogenic reactor operating within a temperature range of -90°C to 140°C
- Particle size reduction to < 10 microns with nitrogen and air in class 100,000 area
- Batch sizes range between 100kg (Bangalore) to 40 MT per annum (Mangalore)
- PMDA (commercial) and USFDA (RSM) approved Bangalore S14 manufacturing facilities
- USFDA-approved Mangalore manufacturing facility

Syngene

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Clinical Development

Clinical Development

Capabilities

BA/BE Studies to Support Development of Generic Drugs

- Conducted over 600 BA/BE or PK/PD or Phase-1 trials [incl. FIH studies]
- Clinic with 190 ward care beds and 12 ICU beds
- Over 200+ validated methods available as per USFDA guidelines
- Total Mass Specs: 11 [API 4000s and API 6500s]
- State-of-the-art instrumentation [with qualification]
- Analysis of drug(S) and/or metabolite(s) in biological specimen [e.g. blood, plasma, serum, human aqueous humor etc.] to support TK< PK, early phase clinical development, BA/BE and TDM studies
- Team of 45 qualified and experienced researchers with experience in method development, validation and regulated Bioanalysis for a wide range of chemically diverse drug molecules

Clinical Trial Management (Phase I-III Trials) of Novel Drugs and Biosimilars

- One of the most experienced Indian CROs in conducting patient-based trials
- Over 100 clinical trials conducted for registering products in US, Europe, India and ROW countries
- Deep experience in Oncology, Diabetes and Auto-immune disorders
- Conducted multiple COVID-19 related trials in India
- Full service solutions, incl. Clinical Supplies Management, Central Lab and CDM & Biometrics

Central Laboratory Services Encompassing Clinical/ Safety Lab and Bioanalytical Services for Small Molecules & Biologics

- CAP accredited Central lab offering clinical testing services exclusively for Phase 1-IV clinical trials and BA/BE studies
- GLP-certified, FDA-inspected bioanalytical lab offering PK, ADA and Nab assays
- 21CFR-11 compliant laboratory information management system with customizable project management and reporting capabilities
- Supported over 100 NDAs/BLAs submitted to US FDA, EMA and PMDA
- r HbA1c

Regulated Bioanalytical Lab for Large Molecules

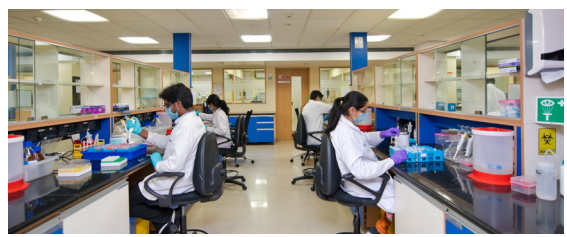
- 3 blockbuster MAbs approved by USFDA and EMA, based on the bioanalytical data submitted from this lab
- Experience with 7 Biosimilars, 22+ Monoclonal Antibodies and few vaccines
- 600,000+ samples imported (from various parts of the globe) and analysed till date, with a track record of Zero compromise on sample shipment
- Existing customers include 5 of the top 10 global Big Pharma/Biotech companies and 1 of the top Animal Health companies
- 15+ years of rich and diverse experience
- Adept at Method Transfer, Development and Validation based on FDA/EMA/WHO guidance
- Influenced favourable change in Indian Govt's policy on import of biological samples for testing – no wait period for license, ~4-6 days sample travel time from US/EU, no wait period for clearance from customs, expedited reporting can be handled, especially for Dose Escalation studies requiring 1 week TAT

Clinical Data Management and Biometrics

- Stand alone or integrated data management for Phase I-IV studies
- Statistics and SAS programming for Clinical and non-clinical development programs

Data Acquisition:

- Web based through in-house eCRF
- Paper CRF based data capture



Regulatory Track Record

- Audited by major life sciences Co's & Regulatory agencies from North America and Europe
- Certifications/ Accreditations: ISO 9001:2008, 14001, OHsAs 18001, AAALAC, GLP
- HPU & Bioanalytical labs are inspected by:
    - US-FDA – 9 audits
    - EMA – 3 audits
    - Thai FDA for GLP – 2 audits
    - ANVISA – Brazil – 3 audits
    - UK-MHRA – 1 audit
- Regulatory track record for Regulated Bioanalytical Lab for Large Molecules :
    - US-FDA – 1 audit
    - PMDA – 1 audit

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About Syngene

Syngene International Ltd. (BSE: 539268, NSE: SYNGENE, ISIN: INE398R01022) is an integrated research, development, and manufacturing services company serving the global pharmaceutical, biotechnology, nutrition, animal health, consumer goods, and specialty chemical sectors. Syngene's more than 6000 scientists offer both skills and the capacity to deliver great science, robust data security, and quality manufacturing, at speed, to improve time-to-market and lower the cost of innovation. With a combination of dedicated research facilities for Amgen, Baxter, and Bristol-Myers Squibb as well as 2.2 Mn sq. ft of specialist discovery, development and manufacturing facilities, Syngene works with biotech companies pursuing leading-edge science as well as multinationals, including GSK, Zoetis and Merck KGaA.

For more details, visit www.syngeneintl.com or write to us at bdc@syngeneintl.com

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