



Experts in small molecule API  
development & manufacturing

# Capabilities and Expertise Brochure

# Who is Onyx Scientific?

**Located in the UK, we are a small molecule CDMO with chemistry at the heart of our services, specialising in:**

- Process R&D
- Solid state chemistry
- Non-GMP and GMP API manufacturing

## Your molecule, our people - it's good chemistry

Onyx has carved a niche and reputation in the delivery of integrated CMC including chemistry services, process R&D, solid state chemistry, analytical method development and validation, and small molecule API manufacturing. We deliver creative solutions to achieve important milestones for our customers. Our team of highly skilled scientists take a responsive and flexible approach in collaborating with customers to ensure the most effective chemical synthesis of their API.

## A unique integrated approach to CMC

We combine proven expertise in chemistry, solid state, analytical, scale up, and GMP manufacture to provide an integrated CMC service which ensures our customers achieve a high quality API to take to the clinic and to market. This has made us the preferred small molecule CDMO partner to a cross section of academic, biotech and pharmaceutical clients across the world.

## Our flexible CMC services include:

- Process research and development
  - Chemical development
  - Analytical development
  - Solid state development
- Non-GMP manufacture
- GMP API manufacturing (Phase I to III)
  - Analytical validation
  - Stability testing
- Commercial API manufacturing
  - QBD/DoE
  - Process validation

## Integrated solid state:

We use solid state chemistry to mitigate risk throughout the development process by gaining an in-depth understanding of the physicochemical properties of your API.

We take an adaptive and collaborative approach to development, flexing with your needs and working closely with you to help you meet your crucial milestones.

Our solid state services include:

- Salt screening and co-crystal screening
- Polymorph screening and amorphous screening
- Pre-formulation studies
- Crystallisation screening
- Chiral resolution screening
- Crystallography
- Milling

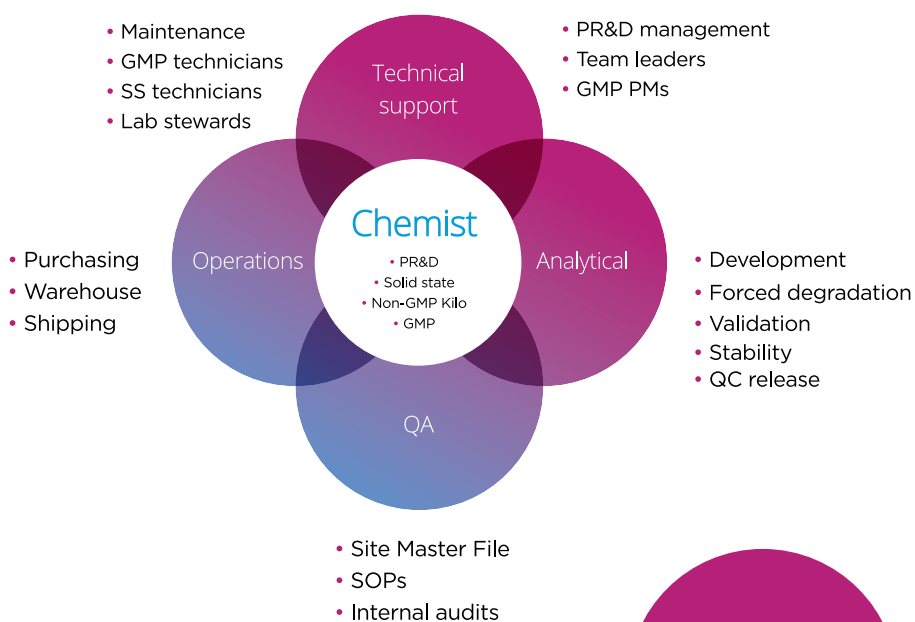
## We'll treat your small molecule API as though it is our own

Through identifying issues and taking a consultative approach, we'll develop efficient processes to increase productivity and create value. Our GMP chemistry-led approach means that our customers can trust us to take care of their project. From start to finish, we'll be there to guide your drug substance through its journey.

# Our ways of working

## Driven by science

Our project teams are all led by experienced scientists, with seamless integration with experts in their fields in chemistry, analytical, solid state, operations and quality departments. This allows our scientists to utilise their skills to the maximum and execute projects without the distraction of essential supporting activities, and results in increased productivity throughout all our projects.



Good chemistry is at the core of everything we do.

## Our approach to CMC services

We understand that there is no one-size-fits-all approach. At the beginning of a relationship we take time to understand what is important to you and your project so that we can offer tailored programmes that outline multiple approaches while balancing risk and reward. Our aim is to deliver a pragmatic, transparent, controlled and suitably risked programme for each individual project.

## Our chemistry-led approach targets:

Milestone progression - improving productivity and speed to hit targets.

- Risk mitigation - decreasing risk of error and project deviation.
- Value - creating efficient processes.
- Future-proofing - protecting against downstream development and production issues, safeguarding the timeline.

# Process Research and Development

**We deliver process research and development services (PR&D) for your small molecule API to meet specific requirements.** Our chemists develop your small molecule API to the highest standards, ensuring progress through the development process is as swift as possible. We aim to provide a safe and scalable route whilst generating reproducible quality material.

## Chemistry is at the core of everything we do

At Onyx, we deliver phase-appropriate studies tailored to a project's needs, with our early-phase work incorporating the production of process outlines, stress testing, impurity tracking (including PMI control) and specification setting. This creates a sound basis for later phase development where we look at more detailed specifications and impurity synthesis that will ultimately lead to process validation.

We offer our customers defined work programs with a fixed budget and timeline along with milestone targets and costed assumptions that allow for transparency in scale-up estimations. The development is supported by expert analytical development and process chemistry for complete understanding of your compound and GMP manufacture in our custom-built laboratories.



## Development Laboratory Capabilities

Our team of highly skilled chemists take a responsive and flexible approach in collaborating with customers to ensure development of the most effective chemical synthesis of the target API. Depending on the phase of development, this will include the following capabilities:

- Multi route scouting
- Complex synthesis and route design
- Route efficiency evaluation
  - Development/scale up of selected route
  - Optimisation of conditions through variation of process changes: stoichiometry, temperature, reagents etc
  - Work-up improvements including avoiding chromatography
- Solubility investigations
- Crystallisation/slurry development
- Heavy metal scavenging
- Cryogenic techniques down to -70oC
- Pyrophoric handling
- Fate and purge investigation of impurities/solvents
- PMI identification
- Stressing and hold point assessment
- Design of Experiments (DoE) investigations
- Failure Mode and Effects Analysis (FMEA) investigations



## Equipment

A range of development equipment is available ensuring progress through the development process, including scale up assessment and the production of a process typical batch is as swift as possible.

- Reaction carousels for fast parallel screening
- MYA parallel platform
- Range of Huber controlled jacketed vessels from 250mL up to 10L
- Range of heating/mixing options - hot plates, overheads, mantles
- Controlled dosing (syringe pumps, peristaltic pumps, HPLC pumps)
- Scavenger, catch & release columns
- Pressure vessels – from 300mL (with insert for parallel screening) up to 20L
- Chromatography
- Microwave reactor
- Flow equipment
- Distillation – range of columns, packing and heads
- Wiped Film Evaporator
- Milling
- 2 x 400MHz NMR
- Range of HPLCs in development labs

## Development Output

As part of Onyx's development campaigns, we offer an array of deliverables as appropriate for the phase of development:

- Process descriptions
- Weekly development reports
- Final development report
- Process typical development batch with detailed Certificate of Analysis
- Specification setting – RSM, IPC, INT and API as per ICH guidance
- Data interpretation: NMR, HPLC-MS, GC
- PMI control strategies
- Cleaning methods between stages and API
- Impurity identification and purge information per stage
- DoE analysis and interpretation using MODDE Pro – including Normal Operating Range (NOR) and Proven Acceptable Range (PAR) values
- Critical process parameter assessment
- Failure Mode and Effects Analysis (FMEA)
- Structure elucidation using NMR – 1H, 13C, HSQC, HMBC
- CMC writing and support

# Expert Integrated Solid Form Development services

**We specialise in offering an integrated solid form, preformulation, crystallisation and chemical development service that facilitates manufacture of candidate APIs for clinical phases through to commercial supply.**

Our dedicated teams provide full-service, independent, outsourced projects to complement or support your in-house campaigns in addition to our integrated full service approach. With a wealth of early phase development experience and success, we focus on rapid process development with a view to future GMP campaigns.

Where required, scale-up through Phase II towards commercial manufacture is retained either at Onyx or within the Group through transfer to our sister sites and colleagues in the USA and India.

## Our Approach

We use solid state chemistry to mitigate risk throughout the development process by gaining an in-depth understanding of the physicochemical properties of your active pharmaceutical ingredient (API).

We take an adaptive and collaborative approach to development, flexing with your needs and working closely with you to help you meet your crucial milestones.

The combined expertise of our leadership group and our dedication to our partnership ensure that the right decisions are made to progress your product from development through to commercialization.

## Our Capabilities

### Early phase lead profiling screens

It is not unusual late in the Discovery Phase to be presented with more than one suitable candidate molecule. Alongside in vitro potency and ADMET predictions, solid form material characterisation and preformulation performance testing can help to differentiate which to select.

We offer a lead differentiation screen using 250-500 mg of material that can help to select the optimum structure to take forward.

### Salt and Co-crystal Screening

In the early stages of your product's lifecycle, we recommend a thorough performance evaluation of your API to determine whether a salt or co-crystal version is required and developable.

As part of our preformulation activities, we perform in-depth salt screening and a risk/benefit assessment of appropriate versions. This includes identifying biorelevant dissolution and solubility characteristics to help inform your future development strategies.

### Polymorphic Screening

Early in the development lifecycle, we can define the ideal polymorphic variant of your API using a robust yet pragmatic screening approach and articulating in detail its available solid state landscape.

Polymorphic screening allows us to map out the characteristics of your molecule, identify potential development challenges and therefore de-risk the transition from discovery into clinical manufacture and beyond.

### Preformulation

In the preformulation stage of your drug development journey, we analyse the characteristics and behaviours of your API to determine its optimal solid state.

We examine the chemical stability, solid state stability, shelf-life and solution behaviour of your chosen version, both in the presence and absence of excipients, enabling us to identify and troubleshoot any solubility-related issues early in the development phase.

### Crystallization Development

A critical stage in your drug's development journey is the study of crystallization and the identification of a purifying recrystallization, or salt forming crystallization.

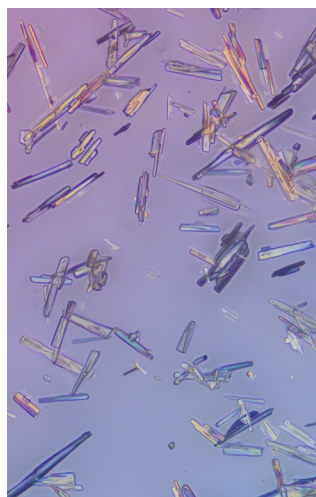
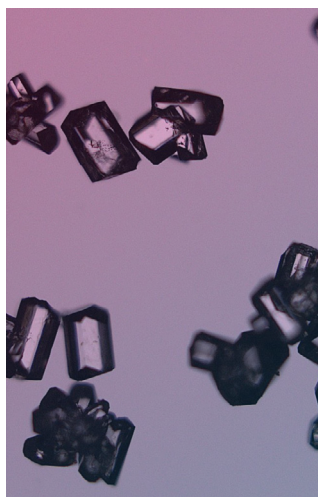
Our solid state chemistry teams work together to ensure that process-typical material is well defined and its behaviour can be contrasted with that of the pure phase.

We'll successfully navigate complex solid state challenges with state of the art equipment and gain a robust understanding of the unique attributes of your molecule, allowing us to ensure that your chosen solid form can be reproduced at scale.

### Chiral Resolution Screening

An extension of our solid state chemistry services, our chiral resolution screening enables us to crystallize and isolate your enantiopure API.

Conducted in parallel to screening phases, our well-established approach selects the most efficient processes to enable the straightforward isolation of your bulk enantiopure product.



### Crystallography

Across all our screening activities, we endeavour to isolate candidates fit for single crystal structure determination. We also offer a bespoke crystallography service to grow single crystals of your molecule and provide a fully detailed report.

### Milling for Oral Solid Dosage (OSD)

Our milling services help prepare your molecule for a range of formulation approaches, allowing you to deliver a product with an improved surface area to a defined particle size.

We can offer:

- Analytical-scale ball milling to aid your pre-formulation assessments
- Ytron-Quadro Fitz and Comil milling capabilities to reduce the size of your solid form particulates and improve blending
- MC DecJet 30 - scalable jet milling to micronise your molecule, enabling a range of formulation approaches

All milling activities are supported by amorphous content determination and our in-house particle size distribution (PSD) method evaluation to take your molecule from early phase batch profiling to formal method development and validation.

### Our Equipment

- Dedicated business unit and laboratories
- Panalytical XPert Pro XRPD
- Multiple Waters TA Discovery series thermal stations
- Malvern 3000 with Hydro MV
- Olympus microscopy bench
- MT82 HS-microscopy
- 2 X Hiden DVS
- PE Raman station
- MYA crystallisation parallel platform
- Blaze Micro probe
- Crystal 16 station
- Multiple Diehm reaction vessels
- Ytron-Quadro Comil/Fitz mill
- Retsch PM100 ball mill
- MC DecJet 30 - scalable jet milling
- Copley Tap/bulk density

# Analytical Services

**Our analytical services department supports all our development and manufacturing processes, including impurity identification and validation, from phase I through to Commercial API manufacture.**

## Our Capabilities

Our analytical labs are equipped with the following instrumentation, all of which are maintained and qualified to the appropriate standards:

- HPLC-UV
- LCMS
- HRGC
- Headspace GC
- IC
- vKF, cKF & KF Oven
- Residue on Ignition
- NMR
- Prep-HPLC
- Autotitrator
- FTIR
- UV Spectroscopy
- Melting Point
- Dissolution Apparatus
- Disintegration Apparatus
- Friabilator
- Tablet Tester
- Moisture Balance
- Water Activity Meter



## Analytical Method Development

Analytical method development ensures that the methods used to measure purity and potency of small molecule APIs are of high quality and suitable for a cGMP synthesis. By partnering with Onyx, our customers access a highly experienced team of analytical specialists providing expert advice to ensure all the analytical needs of their projects are met. This includes methods to support raw material release, in process/intermediate testing and final product analysis. Bespoke, highly sensitive methods are also often required for PMI analysis and these are developed and proven during this phase. All of Onyx's methods are developed with cGMP quality in mind and will be suitable for validation at the appropriate phase.



## API Stability

An understanding of API stability will be obtained during the development phase of a project, with this informing the ICH stability study. Onyx recommends a formal ICH study is carried out as soon as material is available from the developed synthesis.

Our recently upgraded stability suite has capacity to house a large number of ICH compliant stability studies under the following range of conditions:

- -20 °C
- 2-8 °C
- 25 °C/60 % RH
- 30 °C/65 % RH
- 40 °C/75 % RH

We have a flexible science driven approach regarding what tests form part of stability studies and vast experience running the studies. Results are reported and documented in a timely fashion.

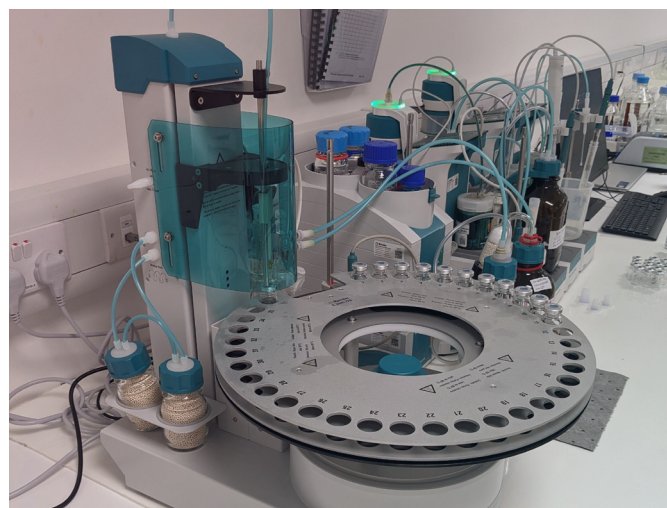
## Analytical Method Validation

Our Phase I-III small molecule API analytical support includes reference standard characterisation, forced degradation and method validation.

During early phase, the main API purity methods are validated as standard. This typically includes the HPLC achiral and chiral (if appropriate) methods and GC headspace for solvents. As part of the validation activity and to understand the stability of the API, a forced degradation study is carried out which provides evidence that the method is stability indicating.

A fully characterised reference standard of the API is also produced to support HPLC assay analysis.

During late phase development, further validation is carried out on the final API methods including all specified impurities, PMIs and all methods used in the GMP stages of the synthesis.



## Analytical Support

The developed and validated methods are used to support all the manufacturing which takes place at Onyx. This analysis is performed in both GMP and non-GMP environments. Our team will produce and adhere to monographs and work with our quality management system, producing non-conformance, out of specification and change controls where necessary. This documentation is key to the quality of the material we produce.

A Certificate of Analysis (CoA) always accompanies any final product which is produced at Onyx.

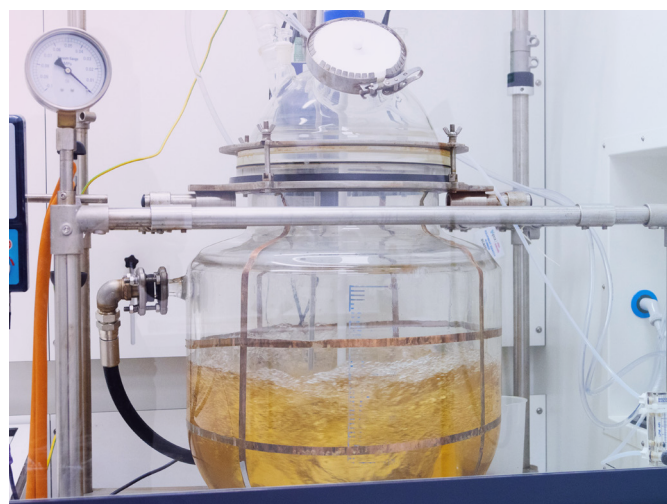
# Non-GMP Large Scale Production

**At Onyx, we perform non-GMP scale up campaigns for your small molecule API.** Our expertise in process development and efficient production protocols ensure the balance between fit for purpose and robustness is perfectly balanced.

Our specialist production chemists scale up processes to deliver kilo quantities of materials to the highest standards, maximising efficiency and working in tandem with the development and solid state teams as part of our integrated services.

## Experts in small molecule development and manufacturing

We aim to deliver reproducible quality material to the desired specifications utilising our 50L vessels and associated large scale equipment. The large-scale team is also supported by expert analytical and development staff ensuring processes run smoothly and as expected.



## Kilo Lab Capabilities

Our custom-built kilo manufacturing laboratories feature 50L reaction vessels and 100 L work-up vessels. Following process development or familiarisation, each stage of chemistry is translated to a PRS, with rigorous safety and manufacturing controls put in place. Onyx typically manufactures 3-5 kg of material per campaign, with suitability for GLP tox studies. Certificates of Analysis and TSE statements are provided for each batch of API generated.

The synthesis of key intermediates for GMP production campaigns is also carried out in this facility, ensuring the supply of GMP starting materials is efficiently completed and is in safe hands.

## Integrated approach for maximizing efficiency and value

Throughout each campaign, the production chemists are supported by our development and analytical services. This ensures success for your compound and campaign, by putting the chemist at the centre of everything we do.

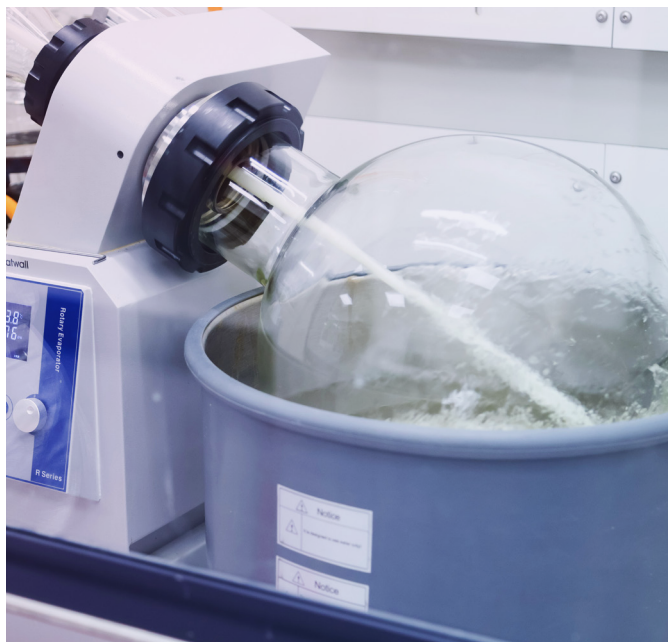
Our facilities include 4 separate laboratories, each with up to 4 x 50L vessels and a 20L rotary evaporator per laboratory. Our flexibility also allows for each suite to be modified, meaning that bench-scale chemistry or even 12kg column chromatography can be performed with ease. The facility also houses a segregated drying room for vacuum ovens and additional rotary evaporators, maximising process efficiency.

We also offer compound support services covering impurities, metabolites, and generating stable labelled compounds.

## Purification

Every effort is made during development to avoid purification via column chromatography and purification via slurry or recrystallisation is normally achieved.

However, retaining column chromatography in a process is occasionally deemed pragmatic for API production for early phase. Onyx has the capability to run chromatography, utilising 12kg columns where required.



## Equipment

- 50L borosilicate glass reaction vessels, each capable of maintaining an inert N<sub>2</sub> atmosphere for reactions and holding a vacuum of up to 0.095 MPa.
- Huber control units per vessel, allowing for precise temperature control using in-built oil jackets. This allows for TR / TJ tracking and for effective temperature ranges from -20 to 180°C
- Pressure vessels – up to 20L
- Large scale column chromatography – up to 12kg
- 20L rotary evaporators
- Dedicated lab space for small scale troubleshooting
- Dedicated oven room
- Distillation – range of columns, packing and heads
- Wiped Film Evaporator
- Milling
- HPLC for reaction monitoring
- 400MHz NMR

# Compound Support Services

We deliver custom syntheses in support of your small molecule API to meet specific requirements from milligram to kilogram scale. Route design, impurity and structural identification are at the heart of our compound support services alongside bespoke syntheses of challenging or routine molecules. Our chemists manufacture your target molecule to the highest standards against a set specification.

We offer our customers compound support for the following:

- Metabolites
- Stable labelled compounds
- Building blocks
- Impurities
- Reference compounds
- Compound libraries

## Synthetic Chemistry Services

Our team of highly skilled chemists take a responsive and flexible approach in collaborating with customers to ensure the most effective chemical synthesis of each target compound is achieved. Our compound support capabilities include, but are not limited to:

- Multistep organic synthesis
- Complex / challenging chemistry
- Hydrogenation
- Toxic chemistry
- Asymmetric synthesis using chiral auxiliary, catalysis, and resolution techniques
- Metal-mediated reactions

## Output

- Weekly reports
- Final report
- Custom synthesized batch
- Detailed Certificate of Analysis
- TSE statement
- Data interpretation: NMR, HPLC-MS, GC
- Structure elucidation using NMR – 1H, 13C, HSQC, HMBC



## Equipment

A variety of equipment is available at Onyx to support your custom synthesis requirements, allowing for the synthesis of target compound quantities ranging from milligram to kilogram.

- Reaction carousels for fast parallel synthesis
- Range of Huber controlled jacketed vessels from 250mL up to 50L
- Range of heating/mixing options - hot plates, overheads, mantles
- Scavenger, catch & release columns
- Pressure vessels (300mL up to 20L)
- Chromatography – up to 12kg silica
- Flow equipment
- Distillation – range of columns, packing and heads
- Wiped film evaporator
- 2 x 400MHz NMR
- Range of HPLCs in development labs

# GMP Services

**Onyx Scientific offers phase appropriate small molecule GMP manufacture from our bespoke MHRA accredited production site in the UK. With a proven track record of delivering clinical material for over 20 years you can trust in our reputation to deliver.**

## Phase-appropriate API Manufacturing

Our phase I-III small molecule API manufacturing and development services mean we can support your molecule throughout its clinical journey. Our chemists adopt a phase-appropriate approach to ensure fit-for-purpose development at each stage.

### Chemistry front and centre. Phase-appropriate small molecule API manufacturing.

Our team of chemists are specialists in small-scale drug substance manufacturing and work hand-in-hand with you to establish the most strategic pathway for your project. We have a strong track record of catering to the unique requirements of clinical phase projects and offer a flexible approach that is suited to today's increasingly complex APIs.

Our laboratories support all phases of clinical trials. From quality assurance to GMP manufacture and analytical chemistry support to stability testing, we are here to optimise your drug substance supply with a focus on minimising risk and expediting timelines.

## GMP Contract Manufacturing

Our Wayfarer site in Sunderland, UK is home to the following:

- Six MHRA-accredited Class 100,000 API production suites for GMP manufacture of Phase I to III clinical trial materials
- Dedicated GMP warehouse
- Raw material sampling
- API dispensing unit
- Home Office schedule 1 licence

Each production suite is designed for flexibility of scale, enabling production of low gram to multi kilo quantities.

This flexibility also means other less standard activities can be carried out in the same area (e.g. solvent evaporation, chromatography, distillation etc).

To support GMP production, our Wayfarer site also houses our GMP analytical laboratory alongside our stability testing facilities all fully supported by Onyx's quality assurance (QA) team that maintains the highest level of quality standards.



*Flexible laboratory design, allowing for less standard activities to be carried out in the same area*

## Equipment

The following equipment are examples of what can be utilized in our GMP production suites:

- Range of Huber controlled jacketed vessels from 250mL up to 10L (for lower quantity requirements)
- Up to two Huber controlled 50L jacketed vessels
- Up to two 20L rotary evaporators
- 12kg chromatography capability
- Drying ovens
- Distillation equipment
- Wiped Film Evaporator
- Milling

## Regulatory Support

Onyx offers a full CMC technical writing service and application support for internal and external regulatory teams.

# Commercial API Manufacturing

**Onyx Scientific offers commercial API manufacturing services ranging from low kilo quantities.** We are ideally suited to meet the needs of a low volume drug substance (e.g. for orphan diseases), right up to the multi-tonne quantities required for high volume commercial supply.

## Flexible and responsive to each client's individual requirements

Onyx Scientific (Sunderland, UK) manufactures small molecule APIs in our six MHRA-accredited Class 100,000 laboratories, with a flexible approach that is suited to today's complex materials.

Our US sister company, Pisgah Laboratories (North Carolina), is an FDA-accredited pilot facility in the US. Pisgah provides GMP manufacturing services across three multi-purpose GMP manufacturing suites up to 2,000 gallons / 8,000 litres and is ready to manufacture the larger quantities needed for many projects.

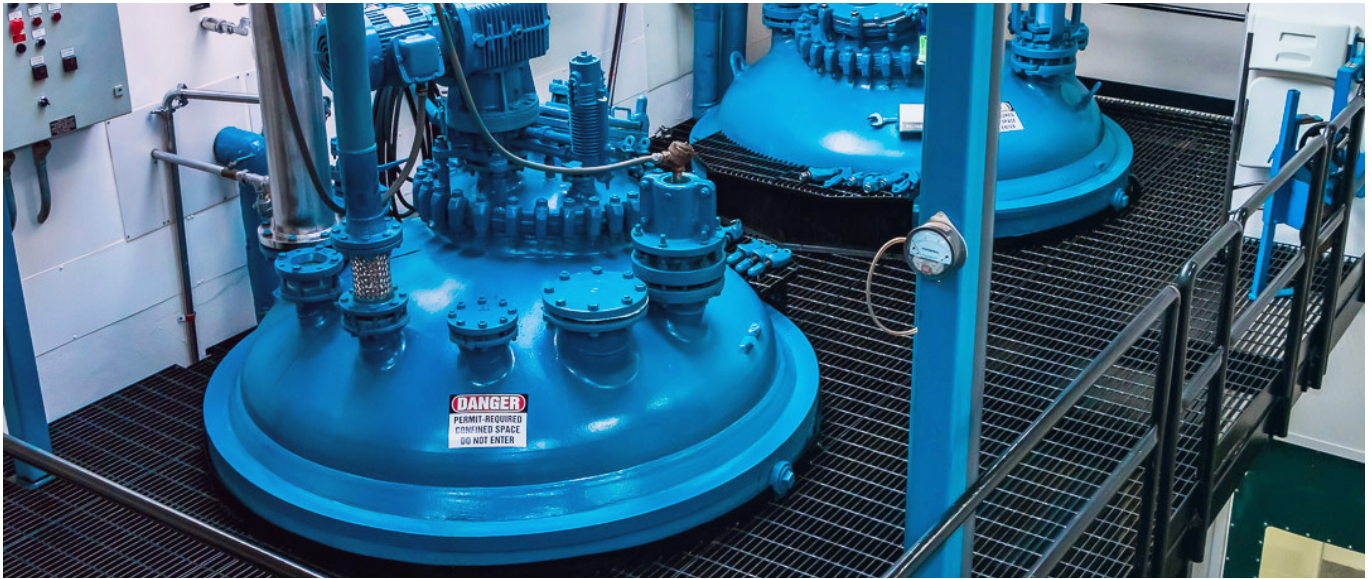
When scaling up a project, we offer dedicated scientists and rapid tech transfer between sites supporting our GMP manufacturing teams. Both sites have a proven track record of successfully validating processes at the required production scale and are fully supported by Onyx's quality assurance (QA) team that maintains the highest level of quality standards.



*Onyx scientific, UK: Ideal for low volume commercial drug substance supply*

## Commercial Manufacturing Services

- Process development (QbD / DoE)
- Failure Mode and Effects Analysis (FMEA) investigations
- Analytical development
- Analytical validation
- Process validation
- Reference standard manufacture (API, intermediates and impurities)
- Commercial API manufacture, including controlled substances
- Process verification



Pisgah Laboratories (North Carolina): For mid to high volume commercial drug substance supply.

## QbD / DoE

Quality by Design (QbD) brings a systematic approach to development. Statistical optimisation through Design of Experiments (DoE) is the main tool used to both optimise and understand the manufacturing process.

This data-driven method delivers better understanding of the manufacturing process, reducing the occurrence of batch failures, delivering proven and effective control, as well as bringing greater time and cost efficiencies.

By taking this approach we provide a robust process that will achieve a consistent and high level of quality suitable for process validation.

## Process Validation

Process validation is defined as the collection and evaluation of data, from the process design stage through commercial API manufacture, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process qualification through a validation campaign is the method by which a process is shown to be under control and capable of reproducible commercial manufacturing.

A validation master plan is written at the start of the validation project and defines the scope and goals of the overall validation project. A pre-approved validation protocol is written per stage which details the pre-requisites required ahead of validation batches (e.g. Equipment DQ, IQ, OQ, analytical method validations) and the criteria that must be met for successful validation campaign. The results of the development and DoE work allow critical process parameters and their normal operating ranges / proven acceptable ranges to be defined with confidence.

The analytical targets identified during the development, DoE work and purge studies are also included as these will be used demonstrate that a process is under control. At least three consecutive validation batches are nominated, although a five-batch campaign is recommended to allow for commissioning, especially if the material has not been synthesised at this scale previously. A validation campaign is then carried out and completed successfully if the nominated batches achieve the pre-defined criteria. The key to success at this point is to ensure a thorough understanding of the process has been achieved in the earlier work.

Once validation is complete continued process verification is performed with trend analysis used to identify problems early and ensure the process stays under control.

“NRG Therapeutics initially contracted work with Onyx for a 500g non GLP scale-up of our lead molecule. The high quality of the delivery, the rapid turn-around, the seamless communication, and the clarity of the weekly reports comforted us in our choice. We have since contracted more work with Onyx including additional scale-up, route optimisation, salt and polymorph screening. All have been conducted with the same high standard of quality showcasing their problem-solving skills and making Onyx one of NRG therapeutic’s trusted partners.”

**Gilles Ouvry, VP, NRG Therapeutics**

“Starting with a typical medicinal chemistry technical package, we have so far performed three API campaigns at Onyx including two GMP. I have been impressed by their ability to combine all the multi-disciplinary aspects of API small scale GMP production in a very pragmatic and efficient approach. What differentiates Onyx from other CDMOs on similar scale, is an impressive know-how in designing crystallisations, incorporating them in a very efficient process and delivering high purity batches.”

**Alain Priour, CMC Project Leader at Domain Therapeutics**

“I have worked with Onyx for over 14 years on projects spanning the pre-clinical phase through to process validation. They continue to deliver pragmatic, cost effective solutions for my clients when faced with the inevitable technical challenges that they will encounter on these projects. Highly recommended and a great CDMO to work with.”

**Ron Lawrence – Managing Partner Cerebro CMC**

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Your molecule, our people - it's good chemistry

