# *Promoting the Uptake of Green and Sustainable Methodologies in Pharmaceutical Synthesis: CHEM21 Education and Training Initiatives*

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Abstract

An extensive suite of educational and training resources have been created by the CHEM21 project to promote the uptake and application of green and sustainable methodologies in the synthesis of pharmaceuticals. They include a bespoke online learning platform containing free, shareable and interactive material suitable for distance learning; easy to use tools and guides that can be readily embedded into everyday practice; and a new RSC text book available in both print and electronic format. These initiatives were specifically designed to result in the elaboration of an educational program to train both students and those currently working within the industry. The involvement of EFPIA partners in their development has ensured that the training materials and methods developed have practical applicability within the medicinal and process chemist community. The research originated by the CHEM21 project has also informed the development of the educational and training material and provided case studies to exemplify the benefits of adopting sustainable chemistry in medicinal and process chemistry.

Keywords: Pharmaceutical synthesis; Green Chemistry; Metrics; Education; Training; Online

## Introduction

CHEM21 (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries) is Europe’s largest public-private partnership dedicated to the development of manufacturing sustainable pharmaceuticals ([http://www.chem21.eu](http://www.chem21.eu/)). The overall aim of CHEM21 is to develop a broad based portfolio of sustainable technologies for green chemical intermediate manufacture aimed at the pharmaceutical industry by 1) identifying reactions and methodologies that address current bottlenecks in the sustainability of processes applied to synthesize APIs and 2) developing new reactions or methodologies with improved green metrics to demonstrate superiority to existing tools.

Funded by the Innovative Medicines Initiative (IMI)[[1]](#footnote-1), CHEM 21 brings together six pharmaceutical companies, 5 Small and Medium-sized Enterprises (SMEs) and research groups from 10 universities. (see Table 1) The partners span the breadth of Europe and bring a wealth of complementary skills and experience. The project has been realised through a synergistic relationship between the 5 core Work Packages (WPs) (see Figure 1).

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| **Universities, Research Organisations & Public bodies** | **SMEs** | **EFPIA (European Federation of Pharmaceutical Industries and Associations)** |
| University of Manchester, UK | Austrian Centre of Industrial Biotechnology (ACIB GmbH), Austria | GlaxoSmithKline Research and Development Ltd, UK |
| Leibniz Institute for Catalysis (LIKAT), Germany | CatScI Ltd, UK | Bayer Pharma AG, Germany |
| Stichting VU-VUMC, Netherlands | Charnwood Technical Consulting Ltd, UK | Janssen Pharmaceutica NV, Belgium |
| Technische Universität Graz, Austria | Evolva Biotech A/S, Denmark | Orion Corporation, Finland |
| Universität Graz, Austria | Reaxa Limited, UK | Pfizer Limited, UK |
| Universität Stuttgart (Institute for Technical Biochemistry), Germany |  | Sanofi Chimie, France |
| Universiteit Antwerpen, Belgium |  |  |
| University of Durham, UK |  |  |
| University of Leeds, UK |  |  |
| University of York, UK |  |  |

**Table 1: CHEM21 Partner Organisations**

**Fig. 1: Core CHEM21 Work Packages**

The CHEM21 project has a particularly strong emphasis on education and training, with an entire Work Package dedicated to this, led by the Green Chemistry Centre of Excellence (GCCE) at the University of York. This WP was specifically designed to result in the elaboration of an educational program to train graduate students and medicinal chemists from the pharmaceutical industry in sustainable chemistry, taking advantage of the input from the EFPIA partners’ experience and benefit from the outcomes of the CHEM21 consortium.

Since it began in 2012, the CHEM21 project has utilised new, more efficient catalyst classes in greening processes, generating novel molecules and producing alternative pathways/transformations with broad applications. Bio-derived platform molecules have been incorporated into drug synthesis, with such building blocks coming from existing pathways and modified microorganisms. Training materials have also been developed for implementation in driving education and long term innovation in the sector and beyond. This paper will focus on the education and training aspects of the CHEM21 project, and describe the genesis of a range of public-facing resources and activities that have been delivered throughout the past four years.

## Education and Training within CHEM21

The incorporation of sustainability principles into post-graduate and post-doctoral training is essential to ensure that green chemistry techniques and practices become second nature to the next generation of scientists involved in drug design and synthetic process identification. (Clark & Smith 2005; Clark and Summerton 2007).

Central to the vision of the CHEM21 project is to influence the both existing and next generation medicinal and process chemists by exemplifying cutting edge low environmental impact chemistry. To realise this CHEM21 partners have come together to combine research, educational and practical expertise to develop a suite of resources to promote the uptake and application of green and sustainable methodologies. The involvement of EFPIA partners in this process was critical to ensure that the training materials and methods developed have practical applicability within the medicinal and process chemist community. The research originated by the CHEM21 project has also informed the development of the educational and training material and provided case studies to exemplify the benefits of adopting sustainable chemistry in medicinal and process chemistry.

Before creating education and training material for a wider audience, an important aspect of education and training within CHEM21 was that of the internal consortium partners, with partners coming from a wide range of scientific backgrounds (chemistry, biochemistry and synthetic biology) with varied existing knowledge and appreciation of green and sustainable methodologies. The GCCE played a key role in interconnecting all work packages and embedding green chemistry principles throughout, both through training and the development of new tools and guides. One of the key tasks for members of the Education and Training WP was to devise a way to evaluate and verify the green credentials of the research carried out by the project, and create a level playing field to compare chemo-and bio-approaches. This was achieved via the creation of a unified sustainability metrics toolkit. By having sustainability metrics embedded within all WPs the project has been able to monitor, measure and evaluate methodologies and ensure that they are genuinely greener than the state of the art and that any changes do not have significant detrimental effects elsewhere.

Figure 2 summarises the activities of the education and training work package. The following sections will describe these activities in more detail.

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**Fig. 2: Summary of CHEM21 Education and Training work package activities**

## 2. Background to the development of the CHEM21 Education and Training Package

A framework for the CHEM21 education and training package was developed over a number of stages. Firstly a survey of the opinions of CHEM21 members, external stakeholders and external experts was carried out, followed by a literature survey of currently available material. The results of the surveys were used as the basis for discussions at a face to face Education and Training workshop held in York in July 2013 where in depth discussions resulted in the production of a draft work plan, with CHEM21 members and external experts invited to become ‘Champions’ for the various identified topics.

### 2.1 Gap identification and analysis of existing education material

The first step in realising a CHEM21 education and training package was to scope what relevant material was already available. Consortium members identified and reviewed existing training material both within the consortium and externally. This was achieved by:

* Surveying EFPIA members, external experts invited to attend CHEM21 workshops and environmental regulators to obtain their views and discover what in-house material could potentially be shared with the consortium.
* Examining lectures, workshops, online training courses, books laboratory based training and other material in the public domain and evaluating their applicability in terms of both content and format.
* Approaching academics with recognised and complementary expertise in the field of green and sustainable education to gauge their interest in engaging with the CHEM21 project.

This information was subsequently used to identify gaps and future work necessary to develop tailored education and training material to promote the uptake of green and sustainable methodologies amongst medicinal and process chemists and the European academic community.

The perceived gaps in education and training in green and sustainable chemistry included a wide range of topics, although they all broadly aligned into the following categories:

* Foundation: training on basic green chemistry that is designed to give a good grounding in key concepts and bring users up to the same level.
* Topics of specific interest to the pharmaceutical industry, such as biocatalysis and process design.
* Effective tools and guides: in particular guides on solvent and reagent selection and tools for LCA. Such tools allow chemists to make choices based on best available practice, a key principle of the CHEM21 project. One of the issues for the project to address here was that although tools already existed, they were not unified and hence it was unclear which to use, as different tools would result in different outcomes and assessments.

One of the major issues identified with existing materials was that they were not easily accessible. This was due to them being hard to find; not at the right level (i.e. too basic or too detailed); not industry specific; or not in a user-friendly format. Therefore one of the major challenges to be addressed via the creation of the CHEM21 education and training resources was to bring information together in a suitable, accessible and easy to use format in order to avoid the aforementioned pitfalls.

### 2.2 Education and Training Workshop

To map out the content of the education and training package, identify target audiences and decide upon preferred delivery methods and formats, the GCCE as WP leaders organised a face-to-face meeting on education and training. This workshop was attended by representatives from the pharmaceutical industry and academia from within the CHEM21 consortium, as well as a number of identified ‘external experts’ who had complementary expertise in the areas of both research and graduate level green chemistry education. This was critical to ensure a balanced viewpoint was obtained and that the outputs were not skewed to favour either to the needs of industry or academia.

## 3. Education and Training Work plan

The outcomes of the face-to-face meeting and the recommendations from the scoping study were then combined and distilled to establish a preliminary work plan for the delivery of a CHEM21 education and training package (see Figure 3 for an outline of the content in terms of key topics and sub-topics contained therein). This was a time-consuming process as a very broad range of topics were suggested with a considerable amount of interconnectivity and overlap, which required a substantial amount of discussion to rationalise and prioritise the core areas to be addressed by the CHEM21 project. This was done in close consultation with CHEM21 academic and EFPIA members that are part of the Education and Training work package team, young researchers working on the CHEM21 project (see Section 4) and external experts that were engaged to complement the expertise existing within the CHEM21 consortium and ensure the longevity of the work package outputs. The GCCE also led on an affinitisation exercise to determine the connectivity between topics in the work plan and allow related topics to be mapped. This provided intuitive links for future users of the education and training package for additional areas of interest.

The work plan provided detail on the audience, topic and specific content to be incorporated in the education and training package and it was decided to match specific content with nominated champions who have a particular interest/expertise in that area. Through the identification of these so-called champions we were able to overcome the barrier of engaging with partners to participate in the process and identify clear roles and responsibilities. The role of a champion was to provide expert advice and guidance on the specific content of the modules; contribute material to the project; develop new material and recommend both good sources of information and other people who could potentially contribute.

**Fig. 3: Summary of the Preliminary Education and Training Workplan**

### 3.1 Target Audience for the Education & Training Package

It was decided that to reach as wide an audience as possible priority should be given to making the material developed open access. It was agreed that undergraduates need to be ‘drip-fed’ information throughout their time at university. ‘Training the trainers’ was also emphasised as essential to bring about a step-change in the way material is taught at universities. For the pharmaceutical industry, it was agreed that training material would be relevant for existing staff, both for new starters and as Continuing Professional Development (CPD) for experienced chemists. The material could be directed at what they don’t do as ‘part of their day job’ to broaden understanding and raise awareness.

The following priority audiences were agreed upon at the Education and Training workshop in July 2013, which were grouped into three different levels:

* Foundation level (undergraduates & other stakeholders including regulators, policy makers, medical practitioners, lay people);
* Graduates (Masters, PhDs);
* People working within Pharmaceutical Industry (medicinal chemists; process chemists; wider groups impacted e.g. procurement).

Further discussion at the CHEM21 Annual General Meeting in Helsinki later that year led these levels to be rationalised to form two levels:

* **‘Foundation level’**, which would cover introductory level material pitched at undergraduate level and;
* **‘In depth topics’**,which would be pitched at graduate level for both graduate students and pharmaceutical industry staff.

Thus learners would be able to pick and choose what material they require using the introductory level material to bring them up to speed and the in depth material to study a particular topic or issue in more detail.

### 3.2 Format and Mechanism of Delivery of the Education & Training Package

The proposed format of materials and mechanism of delivery of the education and training package are summarised in Tables 2 and 3. It was envisaged that materials would be produced and presented in a variety formats and mechanisms depending on the topic and target audience. Furthermore the consortium planned to develop a cohesive training package which included a variety of methods to suit individual needs.

|  |  |  |
| --- | --- | --- |
| **Format(s)** |  | **Mechanisms of delivery/dissemination** |
| * F2F lectures and workshops
* Videos
* e-book
* Recorded lectures
* Interactive Q&A
* Podcasts
* Laboratory practicals/workshops
* Tools/Guides
* Tutorials/Problem solving exercises
* Reading materials
 |  | * On-line platform – free access, flexible and adaptable to allow freedom of choice
* ‘Bite size ‘ modules
* CHEM21 website
* YouTube
* Summer school (combined practical & taught material)
* Embed in existing graduate courses
* On-site training to industry partners
* Publication in journals e.g. in J. Chem. Ed
* Face-to-face short courses
* As part of new employee induction training
* CPD - design learning course to meet own needs ‘pick and choose’
* Centre for Doctoral Training (CDT)
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**Tables 2 and 3: Suggested Formats (left) and Mechanisms of Delivery (right) for the proposed CHEM21 Education and Training Package.**

### 3.3 Decision on the Overall Vision for the Education and Training package

Following a considerable amount of investigation and consultation, the CHEM21 consortium decided to create an integrated web-based Education and Training eLearning platform in order to realise its objective of providing training for the next generation of chemistry, biotechnology and process development engineers and scientists, as well as current practitioners in academia and industry. This would be supported by the creation of new user-friendly tools and guides that could be readily integrated into everyday practice.

Selecting to build a new online learning platform facilitated both the desire to make the education and training materials produced as accessible as possible by using a wide variety of formats and mechanisms, whilst maintaining cohesiveness and connecting elements together where there is natural overlap (as shown by the affinitisation exercise). Importantly, it was also built into the development of this educational and training package that the new material would be trialled in a selected number of universities and EFPIA companies and revised based upon the resulting evaluation.

## 4 Creation of the CHEM21 Young Researchers Network (YRN)

As stated earlier the CHEM21 consortium members came from diverse scientific backgrounds and had different existing levels of understanding of sustainability issues and green chemistry methods and technologies. To maximise the success of the project, not only did the consortium members need to work in a truly multidisciplinary manner, they also had to potentially adapt to a new way of thinking to incorporate green and sustainable practices and ensure that their work was verifiably greener than existing methodologies. In the early stages of the project the GCCE established a network of the ‘Young’ (early stage) Researchers within the consortium, which provided targeted training depending on individual needs and fostered collaboration between grass-roots researchers across the CHEM21 work packages,. The key driver for the formation of this network was to create a community with a strong green chemistry ethos, exchanging ideas across WPs and encouraging a change in mind-set, with green and sustainable principles embedded into everyday practice and holistic thinking becoming second nature.

As the training developed by the CHEM21 project was aimed primarily at those embarking on careers in medicinal and process chemistry, the YRN included both graduate students (MSc and PhD) and those in the early stages (i.e. first few years) of employment both in academia and industry (post-doctoral researchers and new starters).

By creating a cohesive cohort, this allowed the consortium to provide targeted training to the YRN and importantly to gain input from this community into the content and direction of the education and training activities. Through contact with the YRN both individually and as a group, the team working on education and training development received excellent suggestions on topics and issues that are important to the young researchers and gained valuable feedback, allowing further tailoring of the training material and continuous improvements to be made.

The inaugural meeting of the YRN was held in York in November 2013 and included research talks from academics, EFPIA members and a young researcher, training in the use of the metrics tool kit (see Section 5.1), networking activities and brainstorming on potential routes to essential medicines (as defined by the World Health Organisation (WHO) as medicines that satisfy the priority health care needs of the population (<http://www.who.int/topics/essential_medicines/en/>). Following the meeting, a dedicated section of the CHEM21 internal website was created with photographs and biographies of the YRN members to aid in making connections. Subsequently a periodic YRN Newsletter was also produced to allow more informal communication, aimed specifically at the YRN. Content of the newsletters included: breakthroughs/exciting results; conferences; publications; industry & academic partner profiles. A key advantage of the newsletter was that it ensured that information was passed down to the young researchers effectively, rather than concentrating on communication via the Principal Investigators (PIs), which is typical for large collaborative consortia.

Over the lifetime of the project, the young researchers benefitted from regular training delivered by industry and academics from within the consortium and externally, as well as opportunities to direct and tailor their own training based on their own interests and requirements.

## 5 External CHEM21 Education and Training Outputs

### 5.1. CHEM21 Metrics Toolkit

#### 5.1.1 Rationale behind the Development of a new CHEM21 Metrics Toolkit

As mentioned previously, one of the key education and training initiatives within CHEM21 was to embed green and sustainable thinking into everyday practice of consortium members through the creation of a unified sustainability metrics toolkit..

When developing the new metrics toolkit the partners had to address a number of challenges and ensure that the following aspects were considered and incorporated:

* The toolkit had to be able to assess both chemo- and bio-methods.
* The toolkit had to strike the right balance between being comprehensive enough to provide meaningful data but also straightforward enough to be used easily and allow it to be readily incorporated into everyday practice.
* The toolkit had to have sufficient transparency to easily identify positive and negative aspects of the research and allow meaningful comparison, rather than providing an overall ‘score’.
* The toolkit needed to incorporate upstream and downstream considerations to provide a holistic viewpoint as burdens can often, for example, be hidden in work-up and purification procedures.
* toolkit needed to be able toshow whether modifications were genuinely greener to a system overall or whether they had a detrimental effect elsewhere e.g. running a reaction at lower temperatures would have a positive effect on energy consumption but could have a negative impact on mass efficiencies.

Initiallyd. Gaps in existing available metrics were then identified e.g. elemental sustainability (which is particularly important in the area of metal catalysis) andnew parameters were identified to address these gaps. This work and the earlier identified concerns were amalgamated resulting in the development of a new, unified metrics toolkit which is described in more detail below.

The rationale behind the creation of the Toolkit and a description of the methodologies adopted is available as an open access publication. (McElroy et al. 2015) The Toolkit itself has been made freely available in the form of a user friendly [excel spreadsheet](http://www.rsc.org/suppdata/c5/gc/c5gc00340g/c5gc00340g1.xlsx) in the supplementary information of the publication to maximise uptake. ([http://www.rsc.org/suppdata/c5/gc/c5gc00340g/c5gc00340g1.xlsx)](http://www.rsc.org/suppdata/c5/gc/c5gc00340g/c5gc00340g1.xlsx%29),

To overcome a barrier to uptake amongst the CHEM21 consortium members, the Toolkit was embedded into a bespoke, combined Electronic Laboratory Notebook and Reaction Database (developed by the University of Leeds) to allow routine use and interpretation of data.

#### 5.1.2 Description of the CHEM21 Metrics Toolkit

The CHEM21 Metrics Toolkit facilitates the comprehensive evaluation of the sustainability of chemical and bio-chemical reactions based on a series of key parameters (see Figure 4). Moving beyond the use of ‘mass based metrics’ alone, the Toolkit uses a blend of both qualitative and quantitative criteria to assess how green a reaction is, as well as considering factors both upstream and downstream of the reaction itself. This ensures a truly holistic approach.



**Fig. 4**: Summary of the Key Parameters covered by the metrics toolkit [McElroy et al. 2015. Reproduced under license: Creative Commons Attribution 3.0 [http://creativecommons.org/licenses/by/3.0/]](http://creativecommons.org/licenses/by/3.0/)

The Toolkit allows the user to:

* **Assess/demonstrate** the ‘green credentials’ of their research – highlighting where research is performing well in terms of its ‘greenness’ and clearly identify hot-spots or areas of concern in current methodologies (in order to focus research to areas where it will have greatest effect).
* **Benchmark** against current state of the art for a particular reaction or pathway by giving a baseline against which new discoveries can be compared.
* **Monitor, measure and evaluate** new methodologies to ensure that solving one problem does not give rise to others elsewhere in the process.

The Toolkit is specifically structured with a series of ‘passes’ to cover everything from bench top research right through to industrial scale with increasing level of complexity (see Figure 5):

* **‘Zero Pass’**– an initial light tough appraisal for screening reactions (few mg scale)
* **‘First Pass’** – a more comprehensive evaluation of research that has shown potential at Zero Pass and has been further optimised and scaled up (ca. hundreds mg/g scale).
* **‘Second Pass’** *& ‘***Third Pass’** *–* thorough analyses of data gathered from pilot scale research and beyond (kg/multi kg scale)

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**Fig. 5**: Structure of the metrics toolkit showing the parameters covered at each Pass. [McElroy et al. 2015. Reproduced under license: Creative Commons Attribution 3.0 [http://creativecommons.org/licenses/by/3.0/]](http://creativecommons.org/licenses/by/3.0/)

The acceptability of a particular process or reaction step is shown by a system of flags. For each of the assessed criteria a green, amber or red ‘flag’ is assigned, where green denotes ‘preferred’, amber is ‘acceptable – some issues’ and red is ‘undesirable’. Whilst amber or red flags in the metrics analysis draw the user’s attention to issues or concerns, this does not necessarily indicate an outright ‘ban’. Instead it directs the user to seek further information, considering why the flag has been produced and what means can be taken to improve the issue. Information on how to interpret the metrics analysis from the Toolkit is available on the online learning platform (see section 5.3) (<http://learning.chem21.eu/methods-of-facilitating-change/metrics/chem21-metrics-toolkit/>)

### 5.2 Solvents selection guides

One of the key points that was highlighted in the survey and education and training workshop (see Section 2.1 and 2.2) was a strong desire for new tools and guides to be created, especially in the area of solvent selection. The development of a unified solvent selection guide was also critical to the development of the metrics toolkit, where an agreed set of criteria was required in order to generate ‘flags’ for preferred solvents and those to be avoided. Another key driver for the creation of a new solvent selection tool was that although there is a move towards increasing the uptake of bio-derived solvents, existing guides do not in general include these solvents. It is also important to assess them on a level playing field alongside classical solvents, as one cannot assume that just because something is bio-derived it is automatically green.

In order to develop this guidance, a working group - the Solvents Sub-committee - was set up comprising members from each EFPIA company and coordinated by the GGCE at York. The aim of the group was to establish a unified solvent selection guide promoting the use of sustainable solvents, including new bio-derived solvents. The first stage of this work was to survey existing selection guides (Pfizer, AZ, GSK, GCI-PR, Sanofi). (Prat, D. et al 2014) and align them to provide a ranked comparison. Of the 51 solvents considered, all bar 17 could be acceptably aligned into four categories: recommended, problematic, hazardous and highly hazardous. Expanding on this work, the committee then went on to create a new CHEM21 solvent selection guide that allowed ranking on an equal playing field for both classical and non-classical (bio-derived) solvents. Table 4 shows the rankings for classical solvents. In the guide these solvents are grouped into solvent families to make it easier to select ‘best in class’. The publication of this guide and the methodology behind it is open-access. (Prat, D. et al 2016)

The methodology is based upon a combination of Safety, Health and Environment criteria and physical properties, and in alignment with the Global Harmonised System (GHS) of chemical classification and European regulations. Uniquely for a solvent selection guide, and as with the CHEM21 Metrics Toolkit (see section 5.1), the guide itself is freely available allowing the user to rank any solvent of their choice via the same process. This takes the form of an excel spreadsheet and associated user guidance in the supplementary data of the publication. (<http://www.rsc.org/suppdata/c5/gc/c5gc01008j/c5gc01008j1.xlsx>)

|  |  |
| --- | --- |
| Recommended | Water, EtOH, *i*-PrOH, *n*-BuOH, *t*-BuOH, EtOAc, *i*-PrOAc, *n*-BuOAc, ethylene glycol, DMSOMEK, MIBK, cyclohexanone, acetonitrile, pyridine. |
| Problematic | THF, Me-THF, 1,4-dioxane,anisole, heptane, cyclohexane, Me-cyclohexane, toluene, xylenes, chlorobenzene, DMPU, benzyl alcohol, MeOAc, AcOH, Ac2O, acetone, chloroform, formic acid, TEA, MeOH |
| Hazardous | Diisopropyl ether, DME, pentane, hexane, DMF, DMAc, NMP, methoxy-ethanol, Diethyl ether, benzene, CCl4, DCE, nitromethane, MTBE, DCM, sulfolane, HMPA, carbon disulfide |

**Table 4: Solvent Selection Guidance for classical solvents created by the CHEM21** (Prat, D. et al 2016)

### 5.3 CHEM21 Online Learning Platform

A bespoke e-learning platform containing structured material for distance learning with resources in a variety of formats has been developed by the CHEM21 project. It was designed and built to bring together all the elements of the CHEM21 education and training activities in one place, make them open access and act as a repository for material to ensure its availability beyond the lifetime of the CHEM21 project.

The CHEM21 online learning platform [http://learning.chem21.eu](%20http%3A//learning.chem21.eu) , launched at the CHEM21 Summer School in June 2016 (see Section 5.5.5), comprises a range of **free**, **shareable** and **interactive** educational and training materials created to promote the uptake of green and sustainable methodologies, with a particular focus on the synthesis of pharmaceuticals. The online platform encapsulates the learning process undertaken by the young researchers during the project in a comprehensive menu of educational and training resources. The platform also showcases some of the novel research that has resulted from the CHEM21 project, exemplifying the benefits of adopting sustainable chemistry in medicinal and process chemistry.

We anticipate that the resources on the platform will be used by a wide audience to enhance their training and practice. To achieve this, the platform has been designed specifically to have the following key features:

* **Open:** the site requires no payment or log-in to access, and has been designed for ease of use and accessibility.
* **Flexible:** each learning module stands alone, so the user can pick and choose from a wealth of resources to create a learning path appropriate to their needs.
* **Shareable:**  the majority of the content on the site is under a Creative Commons license, allowing the user to reuse and reproduce material in their own courses (with acknowledgement)
* **Interactive:** learning resources are provided in a variety of formats including text, video, charts and diagrams, interactive tools, multiple choice quizzes, and in-depth study exercises.

The platform covers a broad range of topics, both at an introductory level and in-depth under the following topics:

* Foundation
* Guides and Metrics
* Solvents
* Synthetic Toolbox
* Process Design
* Life Cycle Impacts and the Environmental Fate of Pharmaceuticals

The blended nature of the platform content has been specifically designed to maintain the user’s interest. It also benefits from rapid feedback questions and more detailed exercises requiring deeper comprehension and application to test knowledge and understanding. Embedded references and further reading allow easy access to more information for those that are interested in learning more on a particular subject area.

Another key benefit of the online platform is the incorporation of new cutting-edge methodologies for greening the synthesis of APIs (active pharmaceutical ingredients) and intermediates, with associated case studies arising from CHEM21 research. This information encompasses the ‘Synthetic Toolbox’ module, which describes a range of synthetic approaches that are more sustainable and efficient than existing ones including:

* [Base metal catalysis](http://learning.chem21.eu/synthetic-toolbox/base-metal-catalysis/);
* [Biocatalysis](http://learning.chem21.eu/synthetic-toolbox/biocatalysis/);
* [Multicomponent reactions](http://learning.chem21.eu/synthetic-toolbox/multicomponent-reactions/);
* [C-H activation](http://learning.chem21.eu/synthetic-toolbox/c-h-activation/);
* [Carbonylation](http://learning.chem21.eu/synthetic-toolbox/carbonylation/);
* [C-F bond formation](http://learning.chem21.eu/synthetic-toolbox/c-x-bond-formation/);
* [Flow chemistry](http://learning.chem21.eu/synthetic-toolbox/flow-chemistry/);
* [Amidation](http://learning.chem21.eu/synthetic-toolbox/amidation/);
* [Synthetic biology](http://learning.chem21.eu/synthetic-toolbox/synthetic-biology/).

As mentioned previously, the online learning platform can be readily used both for personal study and for teaching purposes, and has been specifically organised to allow the user to ‘pick and choose’ material tailored to their specific needs. Unless stated otherwise, material can be embedded (with acknowledgement) into in-house training/taught courses, including everything from power point presentations/videos through to in-depth assessment exercises with associated answer sheets. This can provide opportunities to incorporate cutting edge research into teaching; cover core concepts; extend learning; or even facilitate delivery of so-called ‘flipped’ lectures, whereby students study material in advance and contact time is used for more interactive engagement with the tutor and/or peer group. Work is ongoing to make the resources on the platform even more accessible in future (see Section 5.3.1).

#### 5.3.1 Learning platform development

A bespoke content generation tool was developed at the University of York that allows non-technical users to quickly and easily create new or update existing material for the platform. Innovative features of this tool include:

* Features for generating and uploading video, quizzes, PDF and other media material;
* Ability to automatically add references from EndNote / RIS format files and easily include them into text;
* Ability to add and render .mol files for chemical visualisation.

Rather than running the public website in a high-maintenance web framework or Content Management System, which can quickly become unsecure or poorly functioning if left without specialist technical maintenance for a period of time, the tool exports to simple HTML/CSS files and folders with accompanying media resources. This makes the site much more maintainable, a requirement for its intended very long lifespan.

In future, we hope that the full range of material will be available in additional downloadable delivery formats, including:

* SCORM sharable objects for embedding into institutions’ Learning Management Systems;
* Printable PDF for classroom / lecture room teaching (where applicable)
* MP4 format video (where applicable)

### 5.4 CHEM21 themed book

The online learning platform is supported by a complementary CHEM21 themed book, 'Green and sustainable medicinal chemistry: Methods, Tools and Strategies for the 21st century pharmaceutical industry', was published by the Royal Society of Chemistry in March 2016 in both hard-copy and e-book format. (Clark et al. 2016) The book contains 17 chapters of material covering 'Green Processes, Strategies and Tools' and 'Green Chemistries'. The majority of the contributing authors are members of the CHEM21 consortium or external expert network. The topics for the chapters were based around the ‘key topics’ of the education and training workplan (see Figure 3) and CHEM21 methodologies. With RSC agreement, some parts of the book have been adapted for use on the online learning platform, which has led to the creation of a more comprehensive and interactive training resource.

### 5.5 CHEM21 Education and Training Events

Since its inception, CHEM21 has organised and delivered a series of education and training events to embed sustainable chemistry concepts in graduate training and in continuing professional development for those currently employed in industry. At first these events were solely developed for the YRN (see Section 4), however since 2015 they have been opened out to all and have been very well received.

Material delivered at these face-to-face events, including question and answer sheets, has been adapted to allow them to be used for distance learning and will are available as downloadable resources on the online learning platform to allow the workshops to be run by others.

#### 5.5.1 ‘Retrosynthetic Analysis using Biocatalysis’ workshop

In April 2015, the GCCE in partnership with the Institute of Technical Biochemistry, University of Stuttgart, ran a 1 day workshop on *‘Retrosynthetic Analysis using Biocatalysis’* in York, UK.

This course was designed to highlight the potential as well as applicability of enzyme catalysts to offer assistance in synthetic chemistry, inspired by the concept of retrosynthesis Corey (1988) pioneered retrosynthetic analysis in organic molecules, the process of ‘deconstructing’ a target molecule into readily available starting materials. Now, with biocatalysis surging and rightly staking a claim to be a viable option for chemical synthesis, we need to rethink the way in which target molecules can be constructed with the assistance of enzymes. ‘Biocatalytic retrosynthesis’ has potential as a construction and optimization methodology and is becoming increasingly important for biochemical pathway design and generation. The workshop facilitators delivered an engaging and interactive day which was attended by 48 delegates including both CHEM21 members and externals. The workshop consisted of seminars and group work using a broad range of cutting-edge case studies and applied examples. The course was specifically designed to be suitable for chemistry and biochemistry graduate students and early career researchers from the pharmaceutical and wider chemical manufacturing industries. Feedback from the day was very positive and the material was also incorporated into the 2nd European Summer School on Industrial Biotechnology (ESSIB2015) (held in Stuttgart in August 2015).

#### 5.5.2 ‘Greener pharmaceuticals: From discovery to launch’ workshop

Also in April 2015, another one day CHEM21 workshop was held in York entitled ‘*Greener pharmaceut*icals: *From discovery to launch’*. The event was delivered by a blend of CHEM21 partners, from final year PhD students to EFPIA members. The content of the workshop consisted of a blend of research presentations, seminars, group work and problem solving exercises using a range of cutting-edge case studies and industrial examples. Final year CHEM21 PhD students provided highlights of their research projects to date, which was complemented by a more industrial perspective provided in the form of two workshops on ‘Pharmaceutical development: Discovery and launch of Nexium – a $5 billion blockbuster’ and ‘the T2 Incident - Reactive hazards in scaling up chemical reactions’. 39 delegates attended the workshop and again, feedback from the day was positive with delegates particularly appreciating the blend of both academic and industrial perspectives.

#### 5.5.3 ‘Chemistry as an Enabler for a Sustainable Society’ event

In May 2015 the GCCE and GlaxoSmithKline delivered a Green Chemistry workshop at the University of Antwerp, as part of a series of events under the banner of ‘Chemistry as an Enabler for a Sustainable Society’ coordinated that week by Prof. Bert Maes and colleagues. The workshop provided an exciting opportunity to learn about new approaches for critically assessing synthetic methodologies and working towards greener and more sustainable solutions. The session was highly interactive with lectures being broken up by group work and problem solving exercises, using real-life examples from the scientific literature and industrial case studies (see programme below). 93 delegates attended from a range of different backgrounds including students, academics and industrialists from the pharmaceutical, fine chemical and the wider chemical manufacturing industries. Topics covered by the workshop included:

* Route analysis and interpretation: real life case studies, critical thinking and considerations
* Green Metrics - Using a holistic approach to drive forward the development of greener and more efficient routes and sustainable alternatives
* Identification of ‘hot-spots’ and bottlenecks in current synthetic routes
* Solvent and reagent selection (including bio-derived solvents) using industry guides
* Reducing our dependence on ‘critical’ elements – smarter solutions
* Renewable feedstocks and platform molecules
* Upstream and downstream considerations

The workshop generated a lot of discussion and debate and the delegates noted that the balance of theory and practice worked well.

#### 5.5.4 ‘Sustainability in Industrial Chemistry’ workshop

In November 2015 Durham University, in partnership with the GCCE, GlaxoSmithKline and CTC Ltd, ran a two day symposium and workshop on ‘Sustainability in Industrial Chemistry’. The symposium aimed to expose students to new chemistry and industrial case studies, and to provide them with an opportunity not only to learn about advances in sustainable chemistry, but also to apply it to real-life problems within the workshop activities. The event was attended by 51 delegates and consisted of seminars and group work via workshops using a broad range of cutting-edge case studies and applied examples. There was also a poster session in the evening of the first day to further promote networking at the event. Feedback from the day was very positive with significant praise given to the quality of the interactive workshop sessions on route selection, metrics and process safety.

#### 5.5.5 CHEM21 Summer School & Launch of the CHEM21 online training platform

The CHEM21 summer school entitled ‘Practical Aspects of Green Chemistry in the Pharmaceutical Industry’ was held in June 2016 at Burlington House, London, UK, home of the Royal Society of Chemistry. The event was designed primarily for young researchers (Graduates and Post-Doctoral Researchers) as well as academics and industrialists seeking to incorporate more aspects of Green Chemistry into their work. The aims of the event were to:

* Showcase key outputs of the CHEM21 project
* Deliver a selection of the education and training material that has been developed over the lifetime of the project.
* Raise awareness of sustainability issues and technologies, and the methodologies that are being used to address them within the pharmaceutical industry.
* Provide methods and tools for working towards greener and more sustainable solutions.
* Promote critical thinking.

The event was also the ideal mechanism to launch the CHEM21 online learning platform (<http://learning.chem21.eu>) in order to increase uptake of the site and implementation of the material therein. (For more information on the online platform see section 5.3).

The main workshop/symposium was preceded by an evening networking event to launch the platform and allow the delegates to get to know each other in advance of the small group, interactive activities on the following days. This included a keynote speech entitled ‘Green Chemistry and Sustainability for the 21st Century’ from Professor James Clark, University of York. This was followed by a day and half of lectures and training workshops where new learning was tested and applied. The event was delivered by a blend of key researchers across all Work Packages. The key themes of the event were: *‘Metrics and Route Selection’; ‘Solvents’; ‘Fluorination’; ‘C-H activation’; ‘Biocatalytic Retrosynthesis’; ‘Flow Chemistry; ‘Biocatalysis’* and *‘Synthetic Biology’.*

The event was restricted to 40 places, which was decided to the be the optimum number from previous experience at past CHEM21 events to enable the small group/workshop style activities to be successful and allowed for optimum interaction with the workshop facilitators. The delegates were from a range of backgrounds with graduate and post-doctoral researchers making up the majority of the attendees.

The level of engagement from the delegates was very high, with a large amount of discussion and interaction throughout the event. The feedback from the event was overwhelmingly positive and it is hoped that the materials produced will build a foundation for a regular European summer school to be held annually.

## 6. Conclusion

There has been a considerable investment by the CHEM21 consortium into the creation of an extensive suite of education and training resources led by the GCCE at York, for which the priority now is to ensure their widespread use and longevity. The online learning platform contains a number of distinct training packages that can be readily used to embed the principles of sustainable manufacture in the education of future scientists, both in existing courses and the development of new courses, and for continuing professional development purposes. Partner organisations within CHEM21, both academic and EFPIA, are already taking advantage of these resources by incorporating them in their in-house education and training programmes. The flexible nature of the CHEM21 education and training outputs means that individuals are free to use, adapt and tailor them to meet their own requirements (with appropriate acknowledgement). We hope in future, through a focus on dissemination activities and through building strategic partnerships with relevant stakeholders, to maximise uptake of these resources and raise their profile internationally.

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1. IMI (Innovative Medicines Initiative) (<https://www.imi.europa.eu/>) is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients. IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe. It is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA. [↑](#footnote-ref-1)