IMI1 Final Project Report Public Summary

Project Acronym: CHEM21

Project Title: Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries

Grant Agreement: 115360
Project Duration: 01/10/2012 - 30/06/2017

1. Executive summary

1.1. Project rationale and overall objectives of the project

In order to ensure the cost-effective and environmentally responsible delivery of medicines to patients in Europe, and also to enhance European R&D and manufacturing competitiveness, it is critical to develop more sustainable synthetic and manufacturing processes for Active Pharmaceutical Ingredients (APIs). Methodologies which offer 'green' alternatives, such as the use of enzymes, synthetic biology, less toxic and non-stoichiometric metal catalysts, improved and efficient catalytic methods, and technological solutions such as flow chemistry, will provide significant improvements but also require a long term commitment and investment to develop. The CHEM21 project has been specifically conceived and designed to meet these important objectives and will do so by addressing two fundamental challenges;

1. The identification of reactions and methodologies that address current bottlenecks in the sustainability of processes applied to synthesize APIs.
2. The development of new reactions or methodologies with improved green metrics to demonstrate superiority to existing tools.

1.2. Overall deliverables of the project

1. To develop and make generally available more sustainable new catalytic methodologies for discovering and developing medicines.
2. To train a future generation of pharmaceutical chemists, engineers, and biologists, in the principles of green and sustainable manufacture of Active Pharmaceutical Ingredients (APIs).

The CHEM21 consortium is organised into 6 individual work packages, designed to ensure the successfully delivery of the following targets:

1. An evaluation of the current status of the field, to identify and choose the right targets, reactions, and methodologies for sustainability improvements for the synthetic design of APIs in the pharmaceutical industry (WP1)
2. Major development and innovation efforts in fast growing technologies supporting greener approaches for new and existing APIs based on catalysis, flow processes, biotransformations and synthetic biology (WP2-4)
3. The elaboration of an educational program to train graduate students and chemists from the pharmaceutical industry in sustainable chemistry, taking advantage of the input from the EFPIA experience and the benefits from the outcomes of this CHEM21 consortium (WP5)
4. A well managed project operating within the agreed budget and operating rules which meets or exceeds its deliverables and milestones, while disseminating results publicly (WP6).

1.3. Summary of progress versus plan since last period

The fifth reporting period progressed in accordance with plan and delivered all the deliverables agreed in the final amended Description of Work (Annex1)

1.4. Significant achievements since last report

The fifth reporting period was mostly resourced by Sanofi with many partners having completed their activities in the preceding report. Significant achievements were:

- producing purified flucytosine as per US pharmacopeia grade
- defining industrial feasiblity of NCA process for producing peptides and making dipeptides at 3kg/day
- improvements in yeast strain processes to produce (*S*)-2-aminobutanol as an intermediate *en route* to Ethambutol
- scale up of the synthetic biology cascade to produce 3-methylpiperidine to 20 L bioreactor scale
- adoption of the eLearning platform by ACS GCIPR to ensure its longevity

1.5. Scientific and technical results/foregrounds of the project

Consistent with the aim to develop tools and methodologies that have broad freedom to operate in pre-competitive areas few patents have been filed. The vast majority of the significant findings have been published in peer-reviewed literature enabling industries and academics alike to benefit from and build upon the results. These publications have been listed in full in this and preceding interim reports.

1.6. Potential impact and main dissemination activities and exploitation of results

The project scientific/technical outputs contribute to the overall IMI objectives:

- to provide socio-economic benefits for European citizens, ○ by enhancing the sustainability of pharmaceutical manufacturing in Europe
- to contribute to the health of European citizens, ○ by providing greater cost-effective access to medicines by reducing costs of goods and reducing environmental impact of manufacturing
- to increase the competitiveness of Europe and help to establish Europe as the most attractive place for biopharmaceutical research and development.
    - ○ By developing technologies for more efficient pharmaceutical manufacturing and encouraging research and development of cleaner chemical processes and future bioprocesses for a knowledge based bio-economy

The project outputs have the potential to be rapidly and broadly spread via the scientific literature and as a result of dissemination at conference. Technologoes have already been taken up within the scientific/industrial community as indicated by both consortium members and groups/companies outside of Chem21 working on many of the methodologies developed within Chem21.

1.7. Lessons learned and further opportunities for research

Collaboration in a public private partnership (PPP) has been an added value to achieve the objectives of the project via the exchange of ideas, materials and people between the public institutions and companies leading to significant advances. For example Orion and Janssen had little or no experience of biocatalysis and were able to rapidly develop capability by secondments between them and

academic labs and by using biocatalysts developed in Chem21. Access to chemo-catalyst technology from SME's and academic expertise allowed companies to evaluate methodologies which would otherwise have been out of reach as was also the case with flow chemistry. Synthetic Biology is an emerging science of interest to pharmaceutical manufacturing but with little internal expertise, Chem21 included world leading academic Synthetic Biology labs which enabled companies to progress much more rapidly in this field. The training and education components would not have been possible without a synergy between the academic experts and the real world experience of industrialists.

From your experience, please propose any recommendations/ solutions which could be useful for a PPP.

Continuity of projects beyond the funding period is a significant issue with support of even low cost online platforms not being available. Chem21 were able to find a sponsor for the educational platform but not for the reaction database nor project website. It would be helpful to have some limited funds available to maintain informatics resources beyond the lifetime of the projects.

In view of your project achievements, please provide your views on potential new research to further advance the field.

WP2: C-H activation and safe aerobic oxidations at scale; further exploitation of fluorine gas as a green fluorinating agent, further development of continuous manufacturing processes, more sustainable use of precious metal catalysts and replacement with base/sustainable catalysts

WP3: Further development of imine reductases, further exploration of amide bond forming biocatalysts, research into use of biocatalysts in continuous manufacturing for pharma, development of industrialy useful bio-oxidations

WP4: Further development of tools and protocols for developing synthetic biology in industrially relevant chassis

WP5: Dissemination and embedding of sustainable metrics, broader distribution of educational materials to wider audiences