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Towards a holistic approach to metrics for the 21st century pharmaceutical industry†

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A unified metrics toolkit has been developed to evaluate sustainability of reactions, encompassing a comprehensive and holistic range of criteria for measuring how green a reaction is, covering quantitative and qualitative criteria both upstream and downstream of the reaction itself. In addition, three new metrics are proposed, optimum efficiency (OE), renewable percentage (RP) and waste percentage (WP). The structure of the toolkit is tailored to give a level of detail and complexity commensurate with the stage of research, with an initial 'light-touch' appraisal at a few mg scale through to very in-depth analyses incorporating lifecycle considerations at large (multi-kg) scale. The toolkit additionally allows benchmarking of reactions against state-of-the-art in terms of their 'green credentials'. By promoting critical thinking in the user it also lends itself to being an educational tool, and its widespread adoption will support the training of a new generation of chemists to whom the use of greener and more sustainable techniques becomes second nature.

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Introduction

The CHEM21 project (Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries), is a consortium of academics, pharmaceutical companies and SMEs working together to develop a broad based portfolio of sustainable technologies for green chemical intermediate manufacture aimed at the pharmaceutical industry.¹

The project aims to create sustainable alternatives for a number of key transformations (*e.g.* amidation, C–X bond formation and C–H activation) utilising a wide range of chemical catalysis and synthetic methods, biocatalysis and synthetic biology techniques. Determining whether the new reactions or methodologies developed are genuinely superior to existing chemistries from an environmental standpoint requires detailed assessment of the metrics. The project also focuses on the education and training of existing and future generations of medicinal and process chemists *via* a dedicated Work Package (WP5), which is jointly led by the Green Chemistry Centre of Excellence at the University of York and Janssen Pharmaceutica NV. It consists of a blend of representatives from academia, the pharmaceutical industry and SMEs.

In order to assess how efficient a reaction is, a mechanism to measure success is required. The most common metric used by chemists is yield, closely followed by conversion and selectivity. These early metrics are useful but only capture the limiting reactant being transformed to desired product. With the publication of the 12 principles of green chemistry,² it became apparent that other metrics were needed to try to capture other inputs within a reaction to encompass as many of these principles as possible. This clearly cannot not be achieved by a standalone metric or guide.

Although many of the European Federation of Pharmaceutical Industries and Associations (EFPIA) partners already had their own favoured metrics, it was agreed that the Green Chemistry Centre of Excellence at the University of York would assess and compare green metrics from the pharmaceutical and other industries and the literature to make recommendations to the CHEM21 project for preferred methods for measuring sustainability.³ These recommendations were reviewed by members of WP5 and others involved in the project at both face-to-face meetings and teleconferences. Amendments and additional suggestions were incorporated following these discussions to reflect the needs and viewpoints of the consortium as a whole. This led to the creation of a unified 'Metrics Toolkit', which has been adopted by the consortium to allow them to monitor, measure, compare and evaluate new methodologies in terms of their 'green credentials'. Herein we describe the rationale behind this toolkit and explain how it has been designed to promote critical thinking

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†Electronic supplementary information (ESI) available: Appendix 1 survey of available Green Chemistry metrics and appendix 2 summary of Zero and First Pass Metrics Toolkit. See DOI: 10.1039/c5gc00340g



by incorporating a more holistic approach than traditional metrics assessments.

Rationale behind the toolkit

Objectives

The main objectives for the creation of the toolkit are to:

- Allow the current state of the art to be assessed for each class of transformation, reaction or pathway giving a baseline against which to compare new discoveries, *i.e.* to be an indicator of success.
- Clearly identify hot-spots and bottle-necks in current methodologies in order to aid chemists in targeting their research to areas where it will have greatest effect.
- Provide a means to ensure that removing/meliorating one problem does not give rise to others elsewhere in the process.
- Encourage continuous improvement.
- Train researchers to think critically about sustainability and environmental acceptability by analysing and making improvements to their synthetic routes.

As the CHEM21 consortium aims to develop transformations utilising chemo-catalytic, bio-catalytic and synthetic biology techniques, an objective method for making comparisons of the 'greenness' of the different approaches was required. This was essential for the validation of the green credentials of new reactions in order to guide innovation.

Key parameters

In order to achieve a holistic viewpoint, the toolkit needed to cover a wide variety of issues. A survey was carried out to identify all of the available green metrics in the literature, as well as those currently used by the EFPIA partners (see ESI Appendix 1†). The survey revealed a wide variety of metrics covering a large number of considerations. Recently, Roschangar, Sheldon and Senanayake have published a process performance metric for the pharmaceutical industry which assesses the relative greenness of a process in terms of waste, taking into consideration its complexity.⁴

A gap analysis was performed to compare current methods against the lifecycle of a typical active pharmaceutical ingredient (API). Subsequently, a number of 'key parameters' were identified which were chosen to cover a comprehensive range of relevant issues regarding the synthesis of chemical products. In this way, the focus was expanded significantly from simply adopting a traditional mass inputs/outputs approach. A summary of the key parameters is shown in Fig. 1. In order to be included in the toolkit, parameters needed to meet the criteria of being able to be practically and consistently measured/assessed in a laboratory based setting. Following an in-depth critical analysis, favoured quantitative metrics were selected to cover the key parameters. These were supplemented by additional qualitative parameters (where no straightforward calculation is possible).

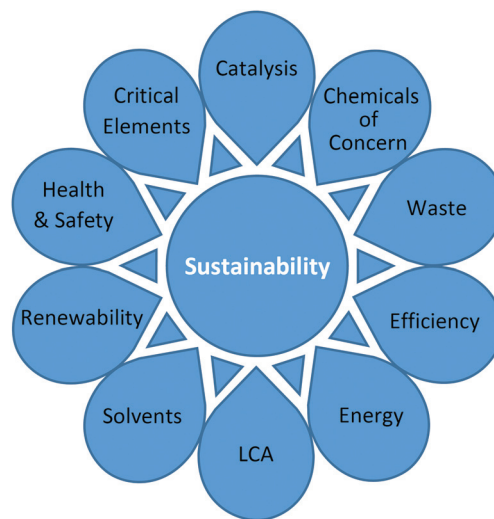


Fig. 1 Summary of the key parameters covered by the metrics toolkit.

The metrics within the toolkit needed to be universally recognised and agreed upon in order for widespread adoption and application. Of course the metrics toolkit was not able to cover everything, and to remain practical, compromises and assumptions had to be made. A delicate balance needed to be struck between the metrics toolkit being sufficiently complex to be comprehensive in order to cover all key parameters, while also being straightforward enough to be practical in terms of ease of use. Thus, the metrics adopted were chosen to be simple but not simplistic.

Scoring system

Tools for assessing greenness found in the literature vary widely in type and complexity, several of which include some form of scoring.⁵ Each approach was carefully considered for implementation in the metrics toolkit. A numerical scoring system for the metrics toolkit was discounted, as it was felt that although it would provide certain benefits, simply assigning an overall 'number' or score to a reaction or methodology may not be the most meaningful way of assessing its 'greenness'. This is because it does not easily allow one to identify areas of concern, or indeed aspects where improvements are being made. In order to provide a visual indicator of the acceptability of a given process or reaction step, a system of flags for the toolkit was decided upon. A green, amber or red 'flag' is assigned to each of the assessed criteria where green denotes 'preferred', amber is 'acceptable-some issues' and red is 'undesirable'. An amber or red flag acts as an alert to the user regarding existing issues surrounding that parameter.

Whilst a figure is produced for each of the numerical metrics, it is a fundamental principle of the toolkit that no parameter be viewed in isolation. Instead they should be considered holistically, and the impact of adjusting one parameter on the overall metrics should be examined in order to build a more complete picture.



Green Chem., 2015, 17, 3111–3121 | 3113

RME as certain types of chemistries are intrinsically atom or mass efficient, while others are not.

Green Chem., 2015, 17, 3111–3121 | 3115

performed in some cases by the use of biphasic systems, membrane technology, catalyst scavengers *etc.*²² Recovery helps the metrics of a system by allowing for catalyst reuse, retaining potential high value resources and allowing for reactions to be carried out in continuous as opposed to batch conditions where appropriate.²³ Finally as there are stringent guidelines on the amount of residual metals allowed in an API, easier recovery reduces purification demands which in turn should improve the metrics and reduce cost.²⁴

Critical elements

To our knowledge, there are currently no metrics in use that consider sustainability outside the carbon cycle. Simply employing a catalyst is not the only factor to be considered, most chemo-catalytic systems employ a metal centre and the sustainability of supply in terms of reserves and potential geo-political impacts need to be considered.²⁵ An element is defined by the EU to be critical if it is of high economic value coupled with a high risk of supply (in terms of abundance and/or geo-political issues).²⁶ If an element is used within the reaction which is considered to be at risk of depletion within the next 5–50 years then a red flag is given; if 50–500 years then an amber flag is given. If all elements within the reaction are judged to be widely available, a green flag is given. These categories are based on the remaining years until depletion of known reserves assuming consumption continues at the present rate and is based on data from the recent publication by Hunt *et al.* (Fig. 4).²⁵ This data does not however consider rates of recycling or discovery of new reserves, which vary widely for different elements.

An important implication of the use of critical elements is financial; the cost per kilo of critical metals is higher than those of more abundant alternatives. Additionally, as already mentioned, there are stringent controls of metal content within APIs, the permitted daily exposure (oral) of platinum or palladium is 100 µg; however if replaced with copper it increases to 3000 µg, or with iron, better still at 130 000 µg.²⁴ If the limits for metal content are higher, the level of purification

subsequently required is lower, improving the metrics and reducing cost.

Energy (First Pass)

Accurate and consistent measurement of energy use in a laboratory setting is inherently challenging and so a simple and universally applicable metric was required. Reactions carried out under relatively mild conditions, between 0 to 70 °C gives a green flag. A reaction run outside of these mild conditions, but within an industrially acceptable standard temperature range of –20 to 140 °C, results in a yellow flag, outside of this range gives a red flag.²⁷ The second simple consideration is based on whether the reaction is at reflux. Running a reaction at reflux results in a 6 fold increase in energy consumption as opposed to doing so at 5 °C below.²⁷ Therefore any reaction run at reflux results in a red flag, any reaction run 5 °C or more below the solvent boiling point gives a green flag.

Although the energy input required to run a reaction may be smaller than other areas such as the building energy requirements¹⁶ or that required to manufacture the solvent,²⁸ if the industry is to reduce energy usage in line with targets, all areas should be considered for improvement.

Batch/flow

In order to encourage researchers to adopt continuous processing methods as opposed to batch conditions for their reactions, a green flag is awarded for reactions performed in flow and an amber flag for those in batch. Growth in the uptake of continuous flow reactions has been significant in recent years, and the advantages over batch reactions are numerous, including the potential to avoid or minimise solvent use and improved energy management.²⁹ Such benefits would be captured by the holistic nature of the toolkit, with a system in flow compared against the benchmark of the same system in batch.

Work up

Although a mass based metric regarding work up is captured in the MI/PMI breakdown (solvents, quenching agents, drying agents, neutralisation *etc.*), this is a significant area that requires more in depth analysis. In line with the ease of usability of the First Pass toolkit, common workup techniques have been considered, grouped and assigned the relevant flag based on approximated environmental burden.

Green flag: quenching, filtration, centrifugation, crystallisation, low temperature distillation/evaporation/sublimation (<140 °C at atmospheric pressure).

Amber flag: solvent exchange, quenching into aqueous solvent.

Red flag: chromatography, high temperature distillation/evaporations/sublimation (>140 °C at atmospheric pressure), multiple recrystallisations, ion exchange.

Health and safety (First Pass)

As with the Zero Pass, H-statements are used to define reagents of concern, but with more strict guidelines as to what denotes a red or amber flag (see Table 2).

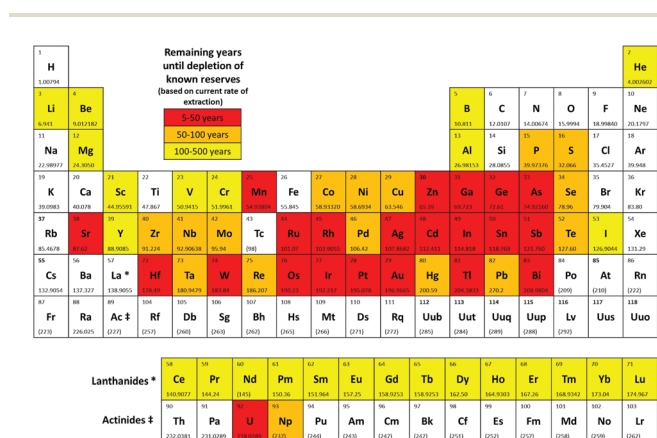


Fig. 4 Periodic table showing critical elements.²⁵



of a green flag should not necessarily discourage research using that substance.

	First Pass red flag	First Pass amber flag
Highly explosive	H200, H201, H202, H203	H205, H220, H224
Explosive thermal runaway	H230, H240, H250	H241
Toxic	H300, H310, H330	H301, H311, H331
Long term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373
Environmental implications	H400, H410, H411, H420	H401, H412

Applicability

This criteria refers to how widely applicable new reactions and transformations are likely to be within the pharmaceutical industry. If a transformation is shown to work on a wide range of reactants and could conceivably be applied to the synthesis of a wide range of APIs, a green flag is given. Similarly, if the reaction works for a limited set of reactants, an amber flag is given and finally if the transformation occurs only with a small number of reactants, a red flag is given. A green flag suggests the reaction class in question shows promise for inclusion into medicinal chemistry reaction sets, while a red flag indicates very narrow substrate specificity.

Industrial toolkits: Second and Third Pass

The Second and Third Pass toolkits depicted in Fig. 2 are for application with reactions/pathways at pilot scale and beyond. In both cases, reactions have already been shown to be highly promising and for that reason, a more thorough analysis of the green credentials of the route is warranted as investigations continue. Second and Third Passes include metrics covering the rest of the key parameters, those which were considered too time consuming to be performed earlier in the development process or were not appropriate on a smaller scale, such as Turnover number and Space time yield for catalysts/enzymes, Renewables Intensity, LCA and Waste. Second Pass is aimed at pilot scale research and requires input from data gathered conducting reactions on a 2 to 10 L scale if in batch, or producing in excess of 1 kg of product in less time than required to run the bench top reaction in First Pass, if in flow. Third Pass is envisaged as desk exercise to be carried out upon successful completion of pilot scale reactions when moving towards industrialisation. Due to the smaller number of reactions expected to reach Second/Third Pass, neither of these Pass levels have been incorporated in the automated CHEM21 reaction database at present.

Second Pass

This toolkit should be applied once a reaction/pathway has produced an intermediate/API which is industrially relevant, has potential commercial value and where the First Pass metrics have exceeded the state of the art. This will allow assessment of the scalability of a process and to determine if the pathway meets both green chemistry and financial goals.

MI/PMI (Second Pass)

As with First Pass, this key mass based metric will be repeated, but now with a focus on reducing the mass intensity still further, most likely through solvent reduction. Feasibility of recycling, recovery and reuse of inputs can also be properly assessed at this point, with this then taken into account when

Use of chemicals of environmental concern

In addition to the data collected under health and safety, acute and chronic toxicity data of chemicals is being gathered in response to legislation such as REACH. There are highly respected databases which have compiled such information, SINLIST³⁰ (substitute it now: consisting of chemicals ChemSec have identified as Substances of Very High Concern based on the criteria established by REACH) and SUBSPORT³¹ (the Substitution Support Portal, a database/search engine on hazardous substances that are legally or voluntarily restricted or subject to public debate).

These lists are however compiled for general use and include, for example substances which are not appropriate for inclusion in foodstuffs or consumer products, but may not represent the same level of risk when used in the synthesis of an API. As such, determination of which chemicals of concern are specific to pharmaceutical manufacture for this toolkit has to be performed manually by routine interrogation of the databases and cross-referencing with REACH legislation, SINLIST and SUBSPORT.

Availability

As the eventual goal of the research conducted by the CHEM21 consortium is to substitute current reaction pathways towards APIs and to produce synthetic routes to novel APIs using new greener methodologies, any new technologies developed have to be economically viable. Therefore any solvent, reagents, enzymes and catalysts should be commercially available. A simple method to assess this was devised. Any reaction/transformation in which all chemicals/biochemicals utilised are compounds available from two or more suppliers in greater than 100 g batches results in a green flag, otherwise no flag is given. If a novel chemical/catalyst has been employed, then feasibility of commercial production must be considered. Of course we want to encourage existing and new companies to produce greener chemicals especially in areas where REACH is having a major effect, such as solvents, and hence the absence



calculating the metric. Comparison of MI/PMI values generated when carrying out the process methodology at g and kilo scale gives an indication of the scalability of the reaction.

Catalyst/enzyme (Second Pass)

As the scale of reaction increases, the nature and efficiency of the catalyst/enzyme becomes more important and as such needs to be thoroughly investigated. When viewing a reaction holistically, the catalyst may work very well, but if the synthesis of the catalyst itself is energy and resource intensive and/or inefficient, the effect upon the metrics of the process may be significant. To determine this upstream effect, the catalyst/enzyme synthesis needs to be run through the First Pass metrics and compared with that used in state of the art processes as a baseline. This could also be further assessed by using a similar flagged system applied to catalytic aprotic imidazolium salts which also takes into account issues such as toxicity, biodegradation and number of synthetic steps.³² In turn, with regard to organocatalysts, they can also possibly be assessed using the 8 complementary environmental impact criteria laid out by Beadham *et al.*³³

If the catalyst is stated as being recoverable, this is more thoroughly investigated. This entails an investigation into the mode of recovery, recovery rate, metal leaching, catalyst activity, number of repeat reactions before significant loss of activity and catalyst regeneration. Relating to this, the efficiency of a catalyst is measured by turnover number (TON) which reflects the number of reactions each catalyst can perform before losing activity.³⁴

$$\text{Turnover number} = \frac{\text{moles of limiting reactant}}{\text{moles of catalyst}} \times \text{yield}$$

Space-time yield is a classic industrial metric which allows for the calculation of the maximum mass of product obtainable from a reactor over a given time period, usually in the form $\text{kg m}^{-3} \text{ h}^{-1}$.³⁵ This allows for an assessment of whether the cost of materials combined with plant time and other associated costs required to produce a given mass of API is economically viable or not.

$$\text{Space time yield} = \frac{\text{mass of product}}{\text{volume of reactor used} \times \text{reaction time}}$$

Renewables intensity

The use of bio-derived organic reagents and solvents is an important step towards improving the sustainability of a given process. The number of bio-platform molecules available is ever increasing, especially with the concept of the bio-refinery, utilising second and third generation biomass.³⁶ There are also a wide range of renewable chemicals from primary biomass, but these need to be assessed within a lifecycle context, as potential trade-offs are inevitable in terms of, for example, land use. These issues are likely to be resolved through new European Standards for bio-based products currently being prepared.³⁷

There are a number of metrics available to assess how renewable a reaction is, with the most comprehensive coverage achieved by converting all inputs into energy to allow for direct comparison.³⁸ These metrics however are not easy to implement and are more suited to life cycle assessment (LCA). A more straightforward and mass based metric would be that of renewables intensity (RI).¹⁶ Again this may well be improved as part of the new Standards "package".

$$\text{Renewables intensity} = \frac{\text{mass of all renewably derivable materials used}}{\text{mass of product}}$$

Comparison of RI to PMI then allows for a renewables percentage (RP) by mass to be calculated, on the condition that the same boundaries are applied. Additionally RI can be broken down in the same manner as PMI and subsequently RP calculated for reactants, reagents, solvents *etc.*

$$\text{Renewables percentage} = \frac{\text{RI}}{\text{PMI}} \times 100$$

Reagent and reactant preparation

As the upstream considerations of catalysts and solvents have been considered, the same must be applied to reagents and reactants. Therefore in a similar manner, reagents and reactants should be investigated by the First Pass toolkit to assess their impact on the overall metrics of the process. The production of synthesis trees for reagents and reactants also indicates the number of steps required to go from raw material (petrochemical/biomass feedstock) to the desired chemical. The overall aim being to identify whether chemicals that carry a high environmental footprint are being utilised in a reaction.

Appropriate safety study

Before scaling up a chemical reaction the appropriate basis of safe operation must be defined by appropriate safety testing relevant to the scale of operation. The primary responsibility for this is the organisation/company running the scale-up operation. The CHEM21 consortium have agreed to adopt the Stoessel method, a 5-band process safety ranking, adopted by a number of pharmaceutical companies.³⁹

It is based on the comparison of MTSR (maximum temperature attainable by the synthesis reaction) with the boiling point of the mixture and the estimated temperature of decomposition of the reaction mixture.

LCA

To gain a comprehensive view of the true environmental impacts of products and processes requires life cycle assessment (LCA) studies to be performed. Parameters that are measured as part of a LCA include: total cradle mass (amount of materials taken from the earth), energy requirements, greenhouse gas emissions (GHG), photochemical ozone creation (POCP), eutrophication, acidification, and total organic carbon (TOC).⁴⁰ Full LCA is extremely time-consuming and life cycle inventory (LCI) data is often difficult to acquire, in particular for bioprocesses in terms of substrates and enzymes.⁴¹



Green Chem., 2015, 17, 3111–3121 | 3119

mental effects elsewhere in the supply chain. We are also able to make direct comparisons between synthetic methods to achieve a particular transformation (*e.g.* different methods of esterification), and highlight reactions of promise as well as so-called ‘hot spots’ or areas of concern. The toolkit does not state if new chemistries are green or not as this is not a facile distinction to make, but rather it states if new chemistries are greener than those currently in use.

Another key outcome of the metric toolkit is in its use as an educational tool. By working through the iterative process of analysing their chemistries, finding hot spots and making improvements, researchers are encouraged to develop a new way of thinking and gain an increased knowledge and awareness of environmental issues which might not otherwise be at the forefront of their mind when focused on the task of synthesising target molecules. It is hoped that use of the toolkit will help to train a new generation of chemists to whom the use of greener and more sustainable techniques becomes second nature, allowing us to move away from the more outdated thinking and methodologies of the past.

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Notes and references

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