



Reagent guides

A significant amount of effort has been dedicated by EFPIA members to develop in-house training material in the form of easily accessible tools that provide assessments early on in the drug discovery process and highlight potential sustainability issues. Reagent selection guides assist the user in selecting the 'greenest' reagent for a particular transformation. Whilst it is important to have a sound understanding of issues and the wider implications surrounding the reagents you use in your research, it is not necessarily practical to spend significant amounts of time analysing each individual substance. One of the advantages of using selection guides is that the data collection and analysis has already been performed. The individual ranking or grouping within the guides allows you to make an informed decision as to the most appropriate choice for your needs.

Learning Objectives

By the end of this module you should:

- Understand why reagent selection guides are needed in the pharmaceutical industry;
- Be able to describe the criteria used in devising such guides, and the resulting benefits and limitations;
- Be aware of the use of these guides in practice via specific case studies.

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GSK reagent selection guides

GSK has developed a number of in-house guides and tools for use by their staff in order to influence their employees in their choice of chemicals and to endeavour to embed sustainability into everyday practice.

Most recently GSK published reagent guides that rank commonly used reagents for fifteen different chemical transformations [1] (all of which are available in the [supplementary information of the journal article](#)). Each reagent was assessed on a number of criteria to provide an Environment, Health and Safety score, a Chemistry score (which assesses stoichiometry, work-up, co-reagents and other issues) and a resulting overall Greenness score. Although issues such as by-product formation and elemental sustainability are not incorporated, there are plans to include Reaction Mass Efficiency and other considerations in future to update these guides. The guides provide a sound and easy to access reference particularly for bench chemists to encourage use of greener reagents.

In this video Helen Sneddon gives us an insight into the GSK reagent guides and the assessment criteria.

1. J. P. Adams, C. M. Alder, I. Andrews, A. M. Bullion, M. Campbell-Crawford, M. G. Darcy, J. D. Hayler, R. K. Henderson, C. A. Oare, I. Pendrak, A. M. Redman, L. E. Shuster, H. F. Sneddon and M. D. Walker, [Development of GSK's reagent guides - embedding sustainability into reagent selection](#), *Green Chem.*, 2013, **15**, 1542-1549.



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Transcript

After considering solvents it is logical to move on to consider the Green Chemistry impacts of those reagents which are most commonly used.

At GSK we have been pleased by the uptake that our solvent guide had had in our

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laboratories.

We therefore decided to apply a similar approach to scoring and advertising our reagent guides.

Hence, we scored each reagent against a number of distinct Green Chemistry criteria and used a geometric mean of those scores to derive an overall score and colour classification.

We have published the full details of our methodology in Green Chemistry, 2013, Volume 15, pages 1542-1549 and 15 of our guides are fully available, with supporting information off that publication.

In short, however, we scored health, safety and environment categories based on the EU risk phrases associated with each reagent.

And, in some cases, by-product.

We considered different aspects of the chemistry, including work-up.

Whether the reaction produced toxic, or difficult to remove by-products.

Whether it involves a gas or was gas sensitive.

Whether an extractive work-up and/or column chromatography was required.

Or, in the best cases, if the product could simply be isolated by filtration or concentration of the reaction mixture or filtrate.

Whether or not a reagent needed a co-reagent was considered, with lowest scores being given to any co-reagent needed in excess, followed any co-reagents with zero CHS concerns, or used stoichiometrically.

Other issues taken into account: Whether a reaction is air or moisture sensitive.

Whether it may cause a stench or have to be operated at extremes of temperature or pressure.

In addition, the British Geological Survey risk factors were used to penalize those elements in danger of running out.

Atom efficiency was assessed using molecular weight of reagent as a crude surrogate.

And stoichiometry clearly benefits catalytic reagents over those used stoichiometrically, or in excess.

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Comparing all these factors we have produce guides as described for the majority of the most common transformations in discovery and development chemistry.

Multiple choice question

1. Which of these criteria would not generally be considered when assessing a reagent's green credentials?
 1. Flash point
 2. Molecular weight
 3. Stability
 4. Solubility
 5. Chemical formula

Answers on [last page](#)

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Pfizer reagent selection guide

Pfizer developed an educational tool in the form of an electronic in-house Reagent Selection guide for use by medicinal chemists to assess greenness of their chemistry. This tool provides rapidly accessible information to select efficient green transformations by grading reagents using three criteria: greenness, utility and scalability, and is visually represented in the form of Venn diagrams. The tool/guide was donated to the ACS GCIPR for further development and expansion. [1].

Following donation of the initial guides to the ACS GCI Pharmaceutical Roundtable, the collaborative team have reviewed, updated and expanded the supporting information and number of transformations, which include, 'amide reduction', 'ester deprotection' and 'epoxidation'. The consistent approach which includes up to date references, scaled up examples and a 'green criteria' section educates the reader to make an informed choice – ideally towards the most sustainable reagent. In keeping with the original guides, they still include the Venn diagram and list of reagents. Importantly [the online tools](#) are searchable and linked to allow easy navigation to external references, internal reagents etc. (NB. It is necessary to register for an account with the ACS GCI to access the guides, however this is free of charge.)

1. K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, P. H. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, [Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation](#), *Green Chem.*, 2008, **10**, 31-36.

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GSK acid and base selection guides

A set of [Acid and Base Selection guides](#) have been developed by GlaxoSmithKline [1] using the same methodology that was applied to develop their reagent guides. Factors such as solubility, boiling point, ease of handling and EHS considerations should all be taken into account when selecting the correct acid or base to use for a particular transformation, and the user may sometimes be limited to a small number of options.

- Where a range of options for the choice of acid or base are available, these guides can direct the user to more sustainable alternatives. Importantly, these guides also include the pKa data for all of the individual acids and bases.
- Where choice is limited, the guides can also help the user to differentiate between a class of acids or bases based on their sustainability.

Scoring includes consideration of concerns arising from, for example, the generation of gaseous, flammable or toxic by-products or the disposal via incineration for halogenated acids, via incorporation in the 'Chemistry Score'. These issues have the potential to cause significant problems if the chemistry is to be performed on a larger scale. LCA and waste disposal may also need to be taken into consideration in the case of using an acid or a base as a solvent.

1. R. K. Henderson, A. P. Hill, A. M. Redman and H. F. Sneddon, [Development of GSK's acid and base selection guides](#), *Green Chem.*, 2015, **17**, 945-949.

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GSK example: oxidation to aldehydes and ketones

In this video Helen Sneddon describes the application of the [GSK reagent guides](#) to a case study on choosing greener reagents for the oxidation of an alcohol to a ketone.



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Transcript

Oxidation has long been noted as a transformation for which there is an urgent need for cleaner alternatives, especially ones which can be carried out in non-chlorinated solvents.

It is therefore not surprising that the GSK guide for oxidation of alcohols to aldehydes and ketones has very few options in the green section and most of those options are sadly limited in scope.

Some interesting new zeolites do permit oxidation with air as the terminal oxidant and these highlight the interplay between green chemistry and engineering, with engineering solutions such as flow chemistry being required to perform such operation safely on scale.

Likewise, enzymes such as laccase and ketoreductases highlight the role synthetic biochemistry can play in finding greener transformations.

But these enzymes are often highly substrate dependent.

Partner supported reagents such as PIPO and a co-oxidant can allow for easier work up and, in some cases, recycling of their non-supportive variant, such as TEMPO.

The amber category contains several classic oxidations such the Moffat oxidation, Oppenauer oxidation and Swern reaction.

The red category largely comprises oxidations relying on toxic metals or with serious safety implications.

The reverse of the oxidation guide, as always, gives more detail, including full names CAS Numbers, scores and comments as to why some of these reagents have been scored the way they have, such as highlighting the carcinogenic nature of the chromium and nickel containing the reagents.

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For transparency, we'd like to share an example where using the guides does not work.

Clearly, every reaction has its own challenges and there is no one-size-fits-all solution.

For the shown oxidation to a Cathepsin K inhibitor.

PIPO, polymer immobilized piperdinyloxyl radical, and bleach was highlighted as a potential replacement for the original Moffat oxidation.

Cheaper, greener and avoiding the issues of handling the dimethyl sulfide by-product.

Unfortunately emulsification prevented the application of PIPO on scale and the requirement for dichloromethane soon negated any sustainability improvements.

The original conditions were therefore optimized and we consider this yet another piece of evidence to support the need for further research into greener oxidation conditions..

Multiple choice question

1. Which of the following would be a green reason why copper might be preferred to ruthenium catalyst for a particular oxidation reaction, despite being ranked lower on the guide?
 1. Cost
 2. Toxicity
 3. Supply risk of ruthenium
 4. Available oxidation states

Answers on [last page](#)

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GSK example: reductive amination

In this video Helen Sneddon describes the application of the [GSK reagent guides](#) to a case study on choosing greener reagents for reductive aminations.



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Transcript

Reductive amination is a very common transformation in drug discovery and development and one for which there are reasonable number of green reagent choices.

Enzyme approaches include the use of Omega transaminases for enantio-selective conversions of ketones to primary amines.

Imine reductases, for the preparation of secondary and tertiary amines, are rare but some isolated examples do exist.

And amine dehydrogenases have also been used to prepare chiral amines from ketones.

Imine reduction with hydrogen over a precious metal catalyst is clearly a preferred procedure, as is the use of formic acid for standalone reductive amination of aldehydes and amines.

So it should be noted that when this reagent is combined with formaldehyde, for amine methylation, in the standard Eschweiler–Clarke reaction the risk phrases of formaldehyde is such that this becomes non-preferred.

Picoline borane and acetic acid has a wide range of reactivity and avoids many of the concerns of using borane-pyridine.

The reverse of the guide again gives full names, CAS-numbers and scores and, in many cases, a brief rationale for the scoring.

This can include practical tips, such as granular sodium tri-acetoxoborohydride being preferred over powdered on scale for ease of transfer, or highlighting the risks of potential hydrogen cyanide formation when using sodium cyanoborohydride.

We can share a case study here which has been carried out with over 30 different amine examples reacting with this aldehyde core.

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The reaction conditions initially involved sodium triacetoxoborohydride in chloroform, but swapping to picoline-borane, not only allowed the use of a greener reagent, but also facilitated swapping to a more preferred solvent, methanol, and all amine choices still reacted successfully..

Multiple choice question

1. Despite being the greenest reagent in the reductive amination guide, which potentially non-green trade off might a chemist have to make when using enzyme as a reagent?
 1. Harsh conditions
 2. Is used up during the reaction
 3. Non-renewable
 4. Requires dilute conditions

Answers on [last page](#)

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Study exercise

When you have finished the [below exercise](#), you can compare your answers to the [model answer sheet](#).

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Summary and further reading

This page reproduces content from H. F. Sneddon, [Tools for Facilitating More Sustainable Medicinal Chemistry](#), in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, L. Summerton, H. F. Sneddon, L. C. Jones and J. H. Clark, Royal Society of Chemistry, Cambridge, UK, 2016, ch. 2, pp. 12-27.

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Reagent selection guides can provide assistance in a variety of ways. They can identify alternatives to reagents whose use may be becoming increasingly restricted by legislation; or constrained by individual company targets surrounding reducing usage of materials of concern. They can also assist with the identification of reagents with more benign risk phrases that hence have lower EHS implications as well as those with fewer operational complexities. They also highlight reagents /procedures which are more atom efficient and can signpoint chemists to reagents that can be used in more benign solvents. Reagent guides provide generalised advice on common reaction classes. More in-depth advice on the scope and utility of specific reagents is beginning to improve and can be accessed through databases and publications exploring the strengths and limitations of reagents.

Recommended reading:

H. F. Sneddon, [Tools for Facilitating More Sustainable Medicinal Chemistry](#), in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, L. Summerton, H. F. Sneddon, L. C. Jones and J. H. Clark, Royal Society of Chemistry, Cambridge, UK, 2016, ch. 2, pp. 12-27.

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31-36.

R. K. Henderson, A. P. Hill, A. M. Redman and H. F. Sneddon, **Development of GSK's acid and base selection guides**, *Green Chem.*, 2015, **17**, 945-949.

F. I. McGonagle, D. S. MacMillan, J. Murray, H. F. Sneddon, C. Jamieson and A. J. B. Watson, **Development of a solvent selection guide for aldehyde-based direct reductive amination processes**, *Green Chem.*, 2013, **15**, 1159-1165.

D. S. MacMillan, J. Murray, H. F. Sneddon, C. Jamieson and A. J. B. Watson, **Evaluation of alternative solvents in common amide coupling reactions: replacement of dichloromethane and N,N-dimethylformamide**, *Green Chem.*, 2013, **15**, 596-600.

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Quiz answers

GSK reagent selection guides - Multiple choice question

1. Which of these criteria would not generally be considered when assessing a reagent's green credentials?

Correct answer: *Chemical formula*

GSK example: oxidation to aldehydes and ketones - Multiple choice question

1. Which of the following would be a green reason why copper might be preferred to ruthenium catalyst for a particular oxidation reaction, despite being ranked lower on the guide?

Correct answers:

- (*u'Toxicity',*)
- (*u'Supply risk of ruthenium',*)

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