Benign by design

It is important that strategies to prevent pollution and limit the potential harm of pharmaceuticals on the environment are developed. An important principle of green chemistry is designing chemicals and products to degrade at a reasonable rate after use, so that they do not accumulate in the environment and are inherently 'benign by design'. Designing drugs that are degradable is however not a straightforward issue as the biological activity of a pharmaceutical compound is dependent upon its precise chemical structure and must also have the correct level of stability and a reasonable shelf life. This module looks at this issue in more depth and explores the scope for minimising the environmental impact of APIs.

Learning Objectives

By the end of this module you should:

- Understand how the 10th principle of Green Chemistry (design for degradation) relates to APIs and why it can be problematic.

and be able to:

- Describe different strategies for reducing the persistance of APIs in the environment;
- Describe the pros and cons of these strategies.

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Scope for biodegradable API molecules

One solution put forward to reducing the burden of pharmaceuticals in the environment (PIE) is to design and market totally biodegradable API molecules. Vaccines, therapeutic enzymes, hormones and biological therapies (termed 'biologics') like monoclonal antibodies are not subject to ERA, or to as much scrutiny post-patient as small molecule APIs, as they are deemed to be 'natural' and rapidly breakdown in the patient and environment to form small non-toxic materials like amino acids.

This may not always be the case with 'hybrid molecules' such as PEGylated antibodies and antibody drug conjugates. While the number of biological medicines (biologics) in use has risen over the past 10 years, small molecule APIs are still heavily prevalent for treating many diseases, which suggests that biologics are unlikely to replace small molecules in the near future.[1]

Most pharmaceutical drug candidates fail at the R&D stage (93-96% failure rate), as shown in **Figure 1**. Early development failure arises from a range of factors such as inadequate pharmacokinetics, bioavailability and unacceptable toxicology profiles, in addition to lack of efficacy in man. Candidate drug properties, a consequence of chemistry design, are key to the success or failure of a proposed molecule. Hence an additional barrier in the form of designing biodegradable drugs would impact further still on what is already a very high attrition rate.

*Figure 1**: Reasons for the failure of candidate drugs [2]***

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1. Small molecules or biologics? (Last accessed:).
2. I. Kola and J. Landis, Can the pharmaceutical industry reduce attrition rates?, *Nat Rev Drug Discov*, 2004, **3**, 711-716.

Questions around green design

One solution to potential PIE issues with new pharmaceuticals is 'green design'; the concept of producing drugs with (near) zero environmental impact, i.e. to exhibit near-zero PBT. This poses a number of questions however:

- Could we implement 'green design' without compromising patient benefit?
- Could it apply to all or only some therapies?
- Would we want to 'design green'? Given the difficulty and large numbers of existing hurdles in getting new pharmaceuticals to market and hence the patient, why would medicinal chemists add further barriers such as designing molecules for degradation post patient?
- When would 'green benefit' emerge?

Developing general guidelines is difficult. Lipinski's famous rule of five describes the desirable 'drug like' properties of a molecule:[1]

- No more than 5 hydrogen bond donors;
- Not more than 10 hydrogen bond acceptors;
- A molecular mass less than 500 Da;
- An octanol/water partition coefficient log *P* of no greater than 5.

At present, a similar guideline for avoiding PBT properties in API molecules does not exist. It is also worth noting that guidelines are not rules – many successful API molecules do not conform to the Lipinski rule of five. Currently, whether or not an API molecule is PBT is generally down to chance, and not a factor of molecular design. A number of strategies to avoid PBT have been put forward for consideration during the molecular design phase, and these will be discussed further in this module.

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1. C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, *Advanced Drug Delivery Reviews*, 2012, **64, Supplement**, 4-17.

Example: Glufosfamide

Glufosfamide is often given as an example of a biodegradable version of ifosamide, a drug which is persistent in the environment; the structures of both are given in **Figure 1**.[1]

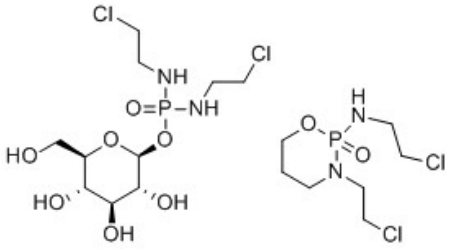

*Figure 1**: Antineoplastic drugs: glufosfamide and ifosfamide***

Whilst better environmental performance has been suggested in laboratory tests for glufosfamide (which has not so far been marketed), it was not designed to have a greener environmental profile. Ifosfamide has several detrimental issues as an API, including pharmacokinetic variability, resistance and severe host toxicity. Glufosfamide makes use of the normal cell glucose transport mechanism for its own transport into the cell. Glucose transport can be overexpressed and upregulated in certain cancer cell lines, so the ultimate design driver for glufosfamide was to achieve increased selectivity and efficacy in the patient. The better environmental profile was a bonus, as opposed to a design feature, but highlights that the inclusion of natural product-like fragments could result in a better environmental profile.[2]

1. K. Kümmerer, A. Al-Ahmad, B. Bertram and M. Wießler, Biodegradability of antineoplastic compounds in screening tests: influence of glucosidation and of

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stereochemistry, *Chemosphere*, 2000, **40**, 767-773.

2. J. Liang, M. Huang, W. Duan, X. - Q. Yu and S. Zhou, Design of New Oxazaphosphorine Anticancer Drugs, *Current Pharmaceutical Design*, 2007, **13**, 963-978.

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Minimising the chance of PBT properties

A number of suggestions to increase the chances that an API molecule will not be persistent have been put forward, including:

- Tagging molecules with an affinity marker to allow extraction onto solid supports in Effluent/Sewage Treatment Plants (ETP/STP).
- Tagging molecules with functionality known to be degraded by aerobic/anaerobic bacteria.
- Increasing the photosensitivity of molecules to natural sunlight; if the UV maxima is < 290 nm, direct photolysis would not be expected to occur (although indirect photolysis might).

However none of the above solutions would be practical or desirable as design options in medicinal chemistry. Probably the most practical solutions would be:

1) If possible, avoid molecules or fragments known to give rise to environmental problems like PBT.

2) If possible, choose functional groups that are more likely to be biologically degraded.

3) Use natural product or natural product-like scaffolds.

4) Get an early idea of possible PBT issues through screening – *in vivo* or *in vitro* or using animal/human toxicology data to 'read across' to other species.

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Groups likely to give rise to PBT properties

A number of literature sources and published data can show which molecular fragments are more likely to cause PBT issues in molecules that reach the environment, and wherever possible these should be avoided. They include both non-functionalised hydrocarbon-like structures and functionalised molecules, and are discussed in more detail in this lesson.

Non-functionalised hydrocarbon-like structures

Petroleum hydrocarbons can be divided into four classes: [1]

- Saturates;
- Aromatics;
- Asphaltenes (phenols, fatty acids, ketones, esters and porphyrins);
- Resins (pyridines, quinolines, carbazoles, suphoxides and amides).

These can be sub-divided and listed in order of ease of biotic breakdown, so if there is a choice of functionality, the groups with the best chance of biotic breakdown should be used: [1]

- *n*-alkanes > branched alkanes > low molecular weight aromatics > cyclic alkanes.
- Saturates > light aromatics > high molecular weight aromatics > polar compounds.
- Electron-rich aromatics > aromatics with electron withdrawing groups > heterocycles.
- Substituted aromatics: ortho > para > meta.

1. Understanding Biobased/Biodegradable and the Industry's Standardized Tests and Definitions (Last accessed: May, 2016).

Functionalised molecules

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Scheringer *et al*.[1] examined ~95,000 compounds for PBT properties with the thresholds defined under REACH. Some data was experimental but most was obtained by modelling (QSAR). Depending on which data set the chemicals were taken from, between 3-5% of the total were classified as potentially PBT. The most common structural motifs noted in the PBT set are listed below Table 1 alongside a comparison with common functionality found in pharmaceutical molecules.

Structural Motif	Frequency in API Molecules
Polybrominated aromatic systems (benzenes, naphthalenes, biphenyls, diphenylethers, dibenzodioxins, and -furans)	
Polychlorinated and brominated cycloaliphatic compounds, including, for example, the chlorinated norbornene structure of the hexachloro cyclopentadiene insecticides.	
Highly branched alkylsubstances and aromatic compounds (often phenols and phenylamines) with several highly branched alkyl, ether, or tertiary amine groups as substituents.	
Triphenylmethyl substances.	
Spiro compounds.	
Per- and polyfluorinated alkyl substances of different chain lengths.	
Compounds with trifluoromethyl substituents.	
Nitroaromatic compounds.	
Tertiary amines with highly branched alkyl groups.	
Polycyclic aromatic hydrocarbons.	

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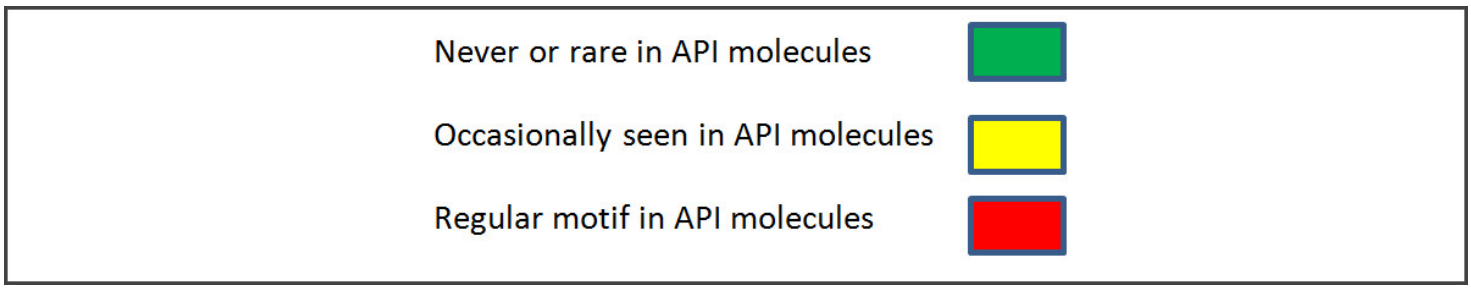

It can be seen from the above analysis that some motifs with high alert for PBT are never or rarely seen in APIs, but some are very common, like aliphatic branched amines and ethers. Generally, if there is a choice, in the case of amines, ethers and alcohols, the biotic degradation will favour: primary > secondary > tertiary, and steric hindrance and branching around heteroatom centres are liable to greatly reduce the rates of breakdown.

Two further areas of commonality are fluorinated compounds and spiro compounds. Looking at the percentage of halogens introduced into aromatic rings during API synthesis* nearly all fluorine and some chlorine are retained in the final API molecule. Traditionally, all bromine and iodine that is introduced is later removed in the synthesis as these elements are only used as a synthetic handles. This picture is beginning to change somewhat, with a few more brominated and iodinated aryl APIs being launched. Generally biotic degradation follows the trend: I > Br > Cl > F, with organoiodides also being prone to photo-degradation. Fluorinated compounds are very common and fluorine is often chosen for the specific beneficial properties it lends to API molecules and hence is unlikely to disappear from small molecule API portfolios in the near future, if ever. Typically organofluorine compounds are resistant to biotic breakdown and polyfluorination leads to highly hydrophobic molecules that have a tendency to bioaccumulate. CF_3-containing molecules may generate the persistent molecule CF_3CO_2H if mineralisation occurs.

In addition, whilst spiro compounds are not common in API molecules at present, there is a growing interest in using more spiro fragments and as such spiro compounds may therefore become more prevalent in the future.[2][3]

* This information was provided via a CHEM21 member study of in-house chemistries.

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1. S. Strempel, M. Scheringer, C. A. Ng and K. Hungerbühler, Screening for PBT Chemicals among the “Existing” and “New” Chemicals of the EU, *Environmental Science & Technology*, 2012, **46**, 5680-5687.
2. E. M. Carreira and T. C. Fessard, Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities, *Chemical Reviews*, 2014, **114**, 8257-8322.
3. Y. Zheng, C. M. Tice and S. B. Singh, The use of spirocyclic scaffolds in drug discovery, *Bioorganic & Medicinal Chemistry Letters*, 2014, **24**, 3673-3682.

Multiple choice questions

1. Which of these are barriers to ‘green design’ APIs?
    1. Failure rate for APIs is already extremely high without adding an additional criterion
    2. There are no legislative drivers to encourage greener design
    3. Some known persistent moieties (e.g. -CF_3) are extremely common in APIs and are hard to replace
    4. PBT properties can be very hard to predict in advance
    5. There is no demand for green pharmaceuticals
2. Which of the following can help minimise the chance of PBT properties of an API?
    1. Only using natural products as building blocks for the API
    2. Using natural-product like moieties known to biodegrade as part of an API
    3. Use of enzymes rather than reagents in synthetic steps
    4. Early (in vivo/in vitro) screening of APIs in manufacture to pre-empt problems
    5. Only using molecules with no known PBT properties to synthesise the API
    6. Avoiding moieties known to give rise to PBT properties

Answers on last page

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Predictive tools

A selection of tools that have been developed to provide guidance in predicting the environmental performance of chemicals are listed below. Some are collections or suites of publically available tools. The tools listed below are representative and not a comprehensive list of what is available.

ECOSAR

The Ecological Structure Activity Relationships (ECOSAR) class program is a predictive software program system that estimates aquatic toxicity.

EPA Sustainable Futures

A suite of links to free tools and training materials

Estimation Program Interface (EPI) Suite

The EPI (Estimation Programs Interface) Suite™ is a suite of physical/chemical property and environmental fate estimation programs – basically a single interface to a wide range of publically available tools.

PBT Profiler

OECD QSAR Toolbox

ETH Biocatalysis / biodegradation database

Predicts biotic (aerobic and anaerobic) decompostion pathways.

Of course, many commercial modelling packages can also be accessed if desired. It is also important to note that the molecule tested should fall within the applicability domain of the model used.

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Summary and further reading

To summarise, some steps that can be taken to minimise PBT issues with candidate drugs are listed below:

- Avoid polyhalogenated fragments (F, Cl, Br);
- Avoid fluorine if at all possible;
- Avoid large numbers of fused aromatic rings;
- If possible, the use of aliphatic rings is preferable to benzene/heteroaromatic rings;
- Highly substituted aromatic rings can be problematic;
- Avoid highly branched aliphatics;
- Avoid highly hindered/quaternary carbons if possible;
- Spiro compounds – be alert;
- Esters are preferable to amides;
- For amides, primary > secondary > tertiary;
- Ureas are preferable to sulphonamides;
- High aqueous solubility;
- Log P as low as possible (although most APIs should fall between -0.4 and 5.6 [1])
- Aim for as low a molecular weight as possible;
- It is beneficial if the compound has a UV/Vis maxima > 290 nm;
- Use ecotoxicity testing earlier on in the development pipeline to highlight potential environmental issues;
- Use predictive tools, but understand their limitations – probably quite good for P and B, not reliable for T (for quantitative measures of ecotoxicity);
- Look for structural similarity with compounds known to have PBT issues;
- Look for plausible degradation pathways that lead to known PBT fragments;
- Make use of 'read across' data but understand the associated risks and limitations.

Recommended reading:

K. Kümmerer, Benign by Design, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, The Royal Society of Chemistry, 2016, ch. 7, pp. 73-81.

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C. Leder, T. Rastogi and K. Kümmerer, Putting benign by design into practice-novel concepts for green and sustainable pharmacy: Designing green drug derivatives by non-targeted synthesis and screening for biodegradability, *Sustainable Chemistry and Pharmacy*, 2015, **2**, 31-36.

C. Rucker and K. Kümmerer, Modeling and predicting aquatic aerobic biodegradation - a review from a user's perspective, *Green Chemistry*, 2012, **14**, 875-887.

1. A. K. Ghose, V. N. Viswanadhan and J. J. Wendoloski, A Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery. 1. A Qualitative and Quantitative Characterization of Known Drug Databases, *Journal of Combinatorial Chemistry*, 1999, **1**, 55-68.

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