Organic Process Research & Development

Article

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Sanofi's Solvent Selection Guide: A Step Toward More Sustainable Processes

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ABSTRACT: Sanofi's solvent selection guide helps chemists in early development select sustainable solvents that will be accepted in all production sites. Solvents are divided into four classes, from "recommended" to "banned". This ranking is derived from Safety, Health, Environmental, Quality, and Industrial constraints. Each solvent has its own ID card that indicates the overall ranking, H, S & E hazard bands, as well as its ICH limit, physical properties, cost, and substitution advice.

INTRODUCTION

Most pharmaceutical companies are making increasing efforts to limit waste and avoid pollution (air and water) and accidents, by applying the concept of "green chemistry", which has been defined by the well-known 12 principles.[1] The term "sustainable chemistry" is more appropriate, since these principles deal not only with the environment but also with the protection of people in the workplace. Despite all these efforts, the pharmaceutical industry still generates a lot of waste, half of it being organic solvents.[2] In a chemical process, solvents are used for the reaction itself (to achieve the desired selectivity, to ensure efficient mass transfer, to take up heat generated by the reaction, or to offer a safety barrier by refluxing), for the extractions, for the crystallization, and for the cleaning of the equipment train. In a multipurpose workshop, cleaning is often the main source of solvent consumption.

As solvents are the main materials in a process, they also provide the greatest opportunity for reducing waste and environmental impact.

GREEN SOLVENTS

The selection of a "green solvent" is often difficult because one must deal with constraints that are sometimes contradictory:[3] chemical efficiency (for the reaction), safety (flash point, resistivity, energy of decomposition, risk of peroxides), health (acute, long-term and single target organ toxicity), environment (biodegradability, ecotoxicity, solubility in water, volatility, odor, life cycle analysis), quality, industrial constraints (boiling point, freezing temperature, density, recyclability), and cost. Even water is not an ideal solvent as a result of its high freezing point (0 °C) and its high enthalpy of vaporization. Methanol is very inexpensive, has acceptable physical properties, is biodegradable, and has a low resistivity but is flammable, volatile, and harmful and is therefore subjected to regulatory constraints.[4]

In order to help chemists in the selection of more sustainable solvents, many pharmaceutical companies have elaborated solvent selection guides. Pfizer edited a simple two-page document targeted toward medicinal chemists.[5] On the recto, the most classical solvents are classified into three categories: preferred, usable, and undesirable. On the verso, a substitution table gives simple and useful advice. Astra Zeneca's guide consists of a table of solvents with 10 different criteria: two for safety (flammability, resistivity), one for health, and seven for environment, including life cycle analysis.[6] Each criterion is scored between 1 and 10, with a 3-color code (green, yellow, and red) to facilitate the analysis. Glaxo SmithKline has a similar guide, with two safety criteria, one health criterion, and three environment criteria, as well as additional red flags for high boiling solvents and solvents governed by regulations. Their guide presents 110 solvents.[7]

The American Chemical Society's Green Chemistry Institute Pharmaceutical Roundtable (GCI-PR)[8] was created in 2005 to encourage the integration of green chemistry and green engineering into the pharmaceutical industry. To this purpose, the Roundtable edited in 2010 a solvent selection guide using the same structure as the AZ and GSK guides: a table with one safety criterion, one health criterion, and three environmental criteria, with scores between 1 and 10 for each, and the same three-color code.[9] The philosophy of solvent guides based on different criteria is to offer a rich collection of data, from which chemists can make a choice depending on process considerations. On the other hand, as no overall recommendation is proposed, it is not

Received: September 17, 2013
Published: November 4, 2013

dx.doi.org/10.1021/op4002565 | *Org. Process Res. Dev.* 2013, 17, 1517−1525

Table 1. Alcohols

Solvents Guide	ALCOHOLS: OVERVIEW					SANOFI
Name	Overall ranking	ICH limit (ppm)	Occ. health	Safety	Environ-ment	Other concern
Methanol	Recommended	3000	OEBV3 Sk	SHB3	EHB1	VOC
Ethanol	Recommended	5000	OEBV2 G1	SHB3	EHB1	Taxes or denaturing agent
n-Propanol	Recommended	5000	OEBV2	SHB3	EHB1	Cost
i-Propanol	Recommended	5000	OEBV2	SHB3	EHB1	
n-Butanol	Recommended	5000	OEBV3	SHB2	EHB1	
2-Butanol	Recommended	5000	OEBV2	SHB2	EHB1	
i-Butanol	Recommended	5000	OEBV3	SHB3	EHB1	
t-Butanol	Substitution advisable	5000	OEBV3	SHB3	EHB1	High melting point, instability
t-Amyl alcohol	Substitution advisable	Not listed	OEBV2	SHB3	Not available	Odor, lack of data
Cyclohexanol	Substitution advisable	Not listed	OEBV3 Sk	SHB3	EHB1	High freezing point, cost
Benzyl alcohol	Substitution advisable	Not listed	OEBV3 Sk	SHB2	EHB1	High boiling point
Ethylene glycol	Substitution advisable	620	OEBV3 G1 Sk	SHB2	EHB1	High boiling point
1, 2-propane diol	Substitution advisable	Not listed	OEBV2	SHB2	EHB1	High boiling point
1, 3-propane diol	Substitution advisable	Not listed	OEBV2	SHB2	EHB1	High boiling point, cost

Table 2. Ketones

Solvents Guide	KETONES: OVERVIEW					SANOFI
Name	Overall ranking	ICH limit (ppm)	Occ. health	Safety	Environ-ment	Other concern
Acetone	Recommended	5000	OEBV2	SHB4	EHB1	VOC
Butanone (MEK)	Recommended	5000	OEBV2 Sk	SHB4	EHB1	
MIBUK	Recommended	5000	OEBV3	SHB3	EHB1	Strong odor
2-Hexanone	Substitution requested	50	Not available	SHB3	Not available	Availability, lack of data
Cyclopentanone	Substitution advisable	Not listed	OEBV3 Sk	SHB2	EHB1	Cost
Cyclohexanone	Substitution advisable	Not listed	OEBV3	SHB2	EHB1	Not commonly used

easy in the early development phases to make decisions, as many industrial constraints are still unknown.

GENESIS OF SANOFI'S SOLVENT SELECTION GUIDE

As Sanofi is a recent member of GCI-PR, we did not participate in the elaboration of the Roundtable guide. The basis of our own project is a Sanofi-Aventis HSE (Health, Safety & Environment) guide, which divides solvents into two categories: recommended (A list) and to be substituted (B list). During development work, chemists must carry out substitution studies and justify why a solvent on the B list is used during scale-up. This guide is not very user-friendly, as solvents are ranked in alphabetic order and not by chemical families. In addition, the B list is too long, and it is difficult to determine among the solvents to be substituted which ones are less undesirable.

A working group was created in 2009 in order to redesign and update this guide. It was all the more necessary as Sanofi is the result of several mergers of companies (Hoechst Marion Roussel, Rhône Poulenc Rorer, Sanofi Synthelabo, etc.) with industrial sites in different countries and with different cultures, and the working group's composition reflected this diversity. For example, some solvents were undesirable in some sites and not in others. An internal standard was thus necessary. Another objective was to promote solvents from renewable sources.

STRUCTURE OF THE GUIDE

Sanofi's new guide, available on the company intranet, consists of several Word or Excel documents offering multiple levels of lecture, from the overall view of all solvents with their ranking, to the details of each solvent including the main applications in synthesis and substitution advice. It contains an introduction, nine chapters dedicated to each family of solvents (alcohols, ketones, esters, ethers, hydrocarbons,[10] halogenated, aprotic polar, bifunctional,[11] miscellaneous[12]), tables of azeotropes, a table of physical properties (17 constants per solvent), and a chapter explaining the scale-up issues associated with the physical properties (for example, the boiling point). The solvent chapters

dx.doi.org/10.1021/op4002565 | Org. Process Res. Dev. 2013, 17, 1517−1525

Table 3. Esters

Solvents Guide	ESTERS: OVERVIEW					SANOFI
Name	Overall ranking	ICH limit (ppm)	Occ. health	Safety	Environ-ment	Other concern
Ethyl formate	Substitution advisable	3000	OEBV3	SHB4	EHB2	VOC
Methyl acetate	Substitution advisable	5000	OEBV2	SHB4	EHB1	Reactive, VOC
Ethyl acetate	Recommended	5000	OEBV2	SHB4	EHB1	
n-Propyl acetate	Recommended	5000	OEBV2	SHB3	EHB2	Not commonly used
i-Propyl acetate	Recommended	5000	OEBV2	SHB3	EHB1	
n-Butyl acetate	Recommended	5000	OEBV2	SHB2	Not available	
i-Butyl acetate	Substitution advisable	Not listed	OEBV2	SHB3	Not available	Not commonly used
Butyrolactone	Substitution requested	Not listed	OEBV2	SHB1	Not available	Aphorizing effects, high boiling point
Valerolactone	Substitution advisable	Not listed	Not available	Not available	Not available	High boiling point, lack of data
Glycol diacetate	Substitution advisable	Not listed	Not available	Not available	Not available	High boiling point, lack of data
Glycerol triacetate	Substitution advisable	Not listed	Not available	Not available	Not available	High boiling point, lack of data

Table 4. Ethers

Solvents Guide	ETHERS: OVERVIEW					SANOFI
Name	Overall ranking	ICH limit (ppm)	Occ. health	Safety	Environ-ment	Other concern
Diethyl ether	**Banned**	5000	OEBV2	SHB5	EHB2	Peroxides, VOC
Diisopropyl ether	Substitution advisable	Not listed	OEBV2	SHB5	EHB3	Peroxides
Dibutyl ether	Substitution advisable	Not listed	OEBV2	SHB5	EHB3	Peroxides, odor
THF	Substitution advisable	720	OEBV3 Sk	SHB4	EHB2	VOC, miscible with water, peroxides
Methyl-THF	Recommended	Not listed	OEBV2	SHB4	EHB3	Peroxides, cost
Dioxane	Substitution requested	380	OEBV3 Sk	SHB5	EHB2	Miscible with water, peroxides
Anisole	Recommended	5000	OEBV2	SHB3	EHB2	Odor
MTBE	Substitution advisable	5000	OEBV3 Sk	SHB5	EHB3	VOC
ETBE	Substitution requested	Not listed	OEBV4	SHB5	EHB3	Peroxides, lack of data
CPME	Substitution requested	Not listed	OEBV3	SHB5	EHB3	Peroxides, one supplier only
Dimethoxy ethane	Substitution requested	100	OEBV4 G2	SHB4	EHB2	CMR (R1B), peroxides
Diglyme	Substitution requested	Not listed	OEBV4 G2	SHB4	EHB2	CMR (R1B), peroxides
Diethoxymethane	Substitution requested	Not listed	OEBV4	SHB5	Not available	Reactive, considered as CMR

(Excel documents) contain an overview of the different solvents with their overall rankings, ICH limits,[13] internal Occupational Health (OEB), Safety (SHB), and Environmental (EHB) Hazard Bands, as well as other industrial or legal constraints (Tables 1−9), followed by an introductory text on the solvent family. At one glance, one can select the most desirable solvent in the family and see its Quality, Health, Safety, and Environment rankings. A click on the solvent's name in the table gives access to a paragraph dedicated to this solvent, which contains a color coded ID card giving the chemical formula, the CAS number, the GHS hazard symbols,[14] its reference in the Sanofi Safety Data Sheet base, the internal H, S & E bands, the ICH limit, its classification (A or B) in the HSE guide, the origin of the solvent, its relative cost with respect to methanol, and some of its physical properties (Figures 1−4). Color codes (green, yellow, red) are associated with some data. The frame of the card has the same color as the overall recommendation:

- Green: recommended solvent (most often these solvents are in the A list of the HSE guide)
- Yellow: substitution advisable. These can be used on an industrial scale with some constraints.
- Red: substitution requested. These can still be used in the pilot plant, but their use on industrial level for new processes has to be justified on the basis of unsuccessful substitution experiments.

dx.doi.org/10.1021/op4002565 | *Org. Process Res. Dev.* 2013, 17, 1517−1525

Table 5. Hydrocarbons

Solvents Guide	HYDROCARBONS: OVERVIEW					SANOFI
Name	Overall ranking	ICH limit (ppm)	Occ. health	Safety	Environ-ment	Other concern
n-Pentane	**Banned**	5000	OEBV2	SHB5	EHB4	Peroxides, VOC
n-Hexane	Substitution requested	290	OEBV3 G1 Sk	SHB5	EHB4	Isomers
n-Heptane	Substitution advisable	5000	OEBV2	SHB5	EHB5	Cost, or isomers
n-Octane	Substitution requested	Not listed	Not available	SHB4	EHB5	Cost, or isomers
Cyclohexane	Substitution advisable	3880	OEBV2	SHB5	EHB5	High freezing point
Me-Cyclohexane	Substitution requested	1180	OEBV2	SHB5	EHB4	
Benzene	**Banned**	2	OEBV5 G1 Sk	SHB5	EHB3	CMR, VOC
Toluene	Substitution advisable	890	OEBV3 G1 Sk	SHB4	EHB3	
Xylene	Substitution advisable	2170	OEBV3 G1 Sk	SHB3	EHB3	Isomers
Cumene	Substitution advisable	2000	OEBV3 Sk	SHB3	EHB4	Peroxides
Tetraline	Substitution requested	100	OEBV2 Sk	SHB3	EHB4	High boiling point
Limonene	Substitution advisable	Not listed	OEBV3 G1 Sk	SHB2	EHB5	Degradation over time
Turpentine	Substitution advisable	Not listed	Not available	Not available	Not available	Degradation over time

Table 6. Halogenated solvents

Solvents Guide	HALOGENATED SOLVENTS: OVERVIEW					SANOFI
Name	Overall ranking	ICH limit (ppm)	Occ. health	Safety	Environ-ment	Other concern
Dichloromethane	Substitution advisable	600	OEBV3	SHB1	EHB3	VOC
Chloroform	**Banned**	60	OEBV4 G1 Sk	SHB1	EHB3	VOC
Carbon tetrachloride	**Banned**	4	OEBV4	SHB1	EHB5	Dangerous for ozone layer
1, 2-Dichloroethane	**Banned**	5	OEBV4 Sk	SHB3	EHB2	CMR (carcinogenic)
1, 1-dichloroethylene	**Banned**	8	Not available	Not available	Not available	Prone to polymerization; VOC
Cis-dichloroethylene	Substitution requested	1870	Not available	Not available	Not available	Availability, lack of data
Trans-dichloroethylene	Substitution requested	1870	Not available	Not available	Not available	VOC, availability, lack of data
1, 1, 2-trichloroethylene	**Banned**	80	OEBV4 G1 Sk	SHB1	EHB3	CMR (carcinogenic)
1, 1, 1-trichloroethane	**Banned**	1500	OEBV3	SHB1	EHB5	Dangerous for ozone layer
1-chlorobutane	Substitution advisable	Not listed	OEBV3	SHB5	EHB3	
Chlorobenzene	Substitution advisable	360	OEBV4	SHB3	EHB4	
Dichlorobenzene	Substitution requested	Not listed	OEBV3 Sk	SHB3	EHB5	Isomers

• Brown: banned solvent. These solvents must not be used in the kilolab and the pilot plant and sometimes not even in the laboratory, for safety (diethyl ether, nitromethane), health (chloroform, benzene, 1,2-dichloroethane), or environmental (tetrachloromethane) reasons. For the rare industrial processes still using such solvents for historical reasons, their substitution is studied.

At the bottom of the ID card, a take-home message is given. The ID card is followed by a full text paragraph consisting of an introduction to the solvent (its synthesis, its main applications outside the pharma industry, etc.) and subparagraphs on HSE, Quality, solubility, physical properties, and incompatibilities. The conclusion includes the solvents' main applications in organic chemistry, extraction, or purification processes, as well as recommendations (e.g., substitution proposals).

The guide can therefore be read at four levels:

• The table of physical constants, which also gives the overall ranking of each solvent.

• The table of each solvent family, with overall recommendation and main constraints.

• The ID card of each solvent, with the main data.

• A paragraph on each solvent with full details.

The overall ranking is based on safety, occupational health, environment, quality and industrial constraints.

dx.doi.org/10.1021/op4002565 | *Org. Process Res. Dev.* 2013, 17, 1517−1525

Table 7. Aprotic polar solvents

Solvents Guide	APROTIC POLAR SOLVENTS: OVERVIEW					SANOFI
Name	Overall ranking	ICH limit (ppm)	Occ. health	Safety	Environ-ment	Other concern
Acetonitrile	Recommended	410	OEBV3 Sk	SHB3	EHB1	Availability
Propionitrile	Substitution requested	Not listed	OEBV4	SHB3	Not available	Decomposition gives HCN
Dimethyl formamide	Substitution requested	880	OEBV4 G2 Sk	SHB2	EHB1	CMR (reprotoxic)
Dimethyl acetamide	Substitution requested	1090	OEBV4 G2 Sk	SHB2	EHB1	CMR (reprotoxic)
N-Methyl-pyrolidone	Substitution requested	530	OEBV4 G2 Sk	SHB3	EHB1	CMR (reprotoxic), high boiling point
Dimethyl-ethylene-urea	Substitution advisable	Not listed	OEBV2 G1	SHB2	EHB2	Hygroscopic, high boiling point
Dimethyl-propylene-urea	Substitution advisable	Not listed	OEBV3 G1	SHB3	EHB2	Hygroscopic, high boiling point, cost
Dimethylsulfoxide	Substitution advisable	5000	OEBV2 Sk	SHB4	EHB2	Many incompatibilities, odor
Sulfolane	Substitution advisable	160	OEBV2	SHB1	EHB2	High boiling and freezing points
Nitromethane	**Banned**	50	OEBV3	SHB5	EHB3	High energy of decomposition

Table 8. Bifunctional solvents

Solvents Guide	BIFUNCTIONAL SOLVENTS: OVERVIEW					SANOFI
Name	Overall ranking	ICH limit (ppm)	Occ. health	Safety	Environ-ment	Other concern
Methoxy-ethanol	Substitution requested	50	OEBV4 G2	SHB3	EHB1	CMR (reprotoxic)
Ethoxy-ethanol	Substitution requested	160	OEBV4 G2	SHB3	EHB1	CMR (reprotoxic)
1-Methoxy-propan-2-ol	Substitution advisable	Not listed	OEBV3	SHB3	Not available	May contain 2-methoxy-propane-1-ol (CMR)
Furfuryl alcohol	Substitution advisable	Not listed	Not available	Not available	Not available	Availability, lack of data
Tetrahydro-furfuryl alcohol	Substitution advisable	Not listed	OEBV3 Sk	SHB3	Not available	Availability, lack of data
Ethyl lactate	Substitution advisable	Not listed	Not available	SHB2	EHB1	Availability, lack of data

Table 9. Water, acids, and amines

Solvents Guide	WATER, ACIDS AND AMINES: OVERVIEW					SANOFI
Name	Overall ranking	ICH limit (ppm)	Occ. health	Safety	Environ-ment	Other concern
Water	Recommended	none	OEBV1	SHB1	EHB1	High freezing point, high enthalpy of vaporization
Formic acid	Substitution requested	5000	OEBV4 Cor	SHB3	EHB2	Thermal decomposition; reducing agent
Acetic acid	Substitution advisable	5000	OEBV4 Cor	SHB3	EHB2	Odor, high freezing point
Propionic acid	Substitution advisable	Not listed	OEBV4 Cor	SHB2	EHB2	Odor, hygroscopic
Trifluoro-acetic acid	Substitution advisable	Not listed	OEBV4 Cor	SHB1	EHB3	Corrosion; decomposes into HCF3
Methane-sulfonic acid	Substitution requested	Not listed	OEBV3 Cor	SHB1	EHB3	Corrosion; forms GTI mesyl esters
Triflic acid	Substitution requested	Not listed	OEBV4 Cor	SHB2	Not available	Highly corrosive, cost
Acetic anhydride	Substitution advisable	Not listed	OEBV4 Cor	SHB2	EHB2	Exothermic reaction with water
Ammonia	Substitution advisable	Not listed	OEBV4 Cor	SHB2	EHB4	Odor, water solubility
Pyridine	Substitution advisable	200	OEBV4	SHB3	EHB3	Odor, water solubility
Triethylamine	Substitution requested	Not listed	OEBV4 G1 Sr Cor	SHB5	EHB3	Odor, water solubility, low AIT

dx.doi.org/10.1021/op4002565 | *Org. Process Res. Dev.* 2013, 17, 1517−1525

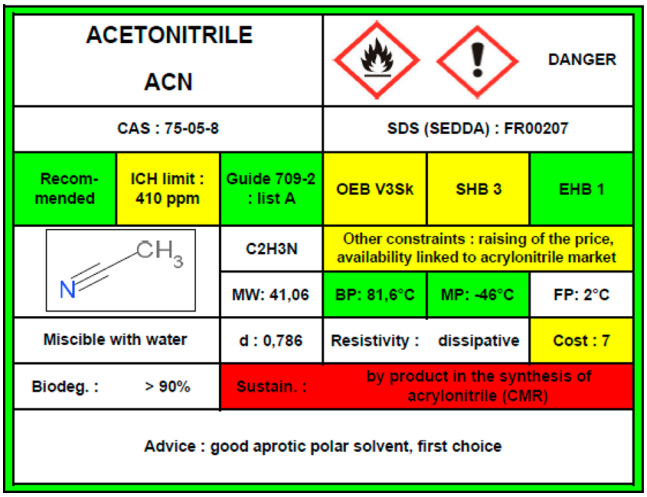

Figure 1. ID card of acetonitrile.

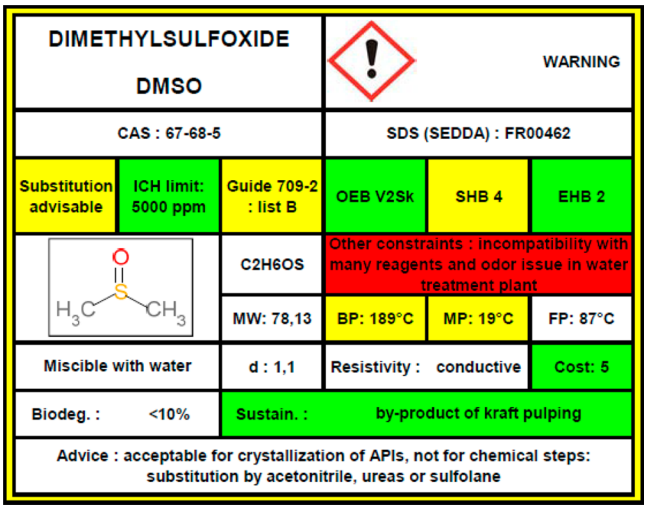

Figure 2. ID card of dimethylsulfoxide.

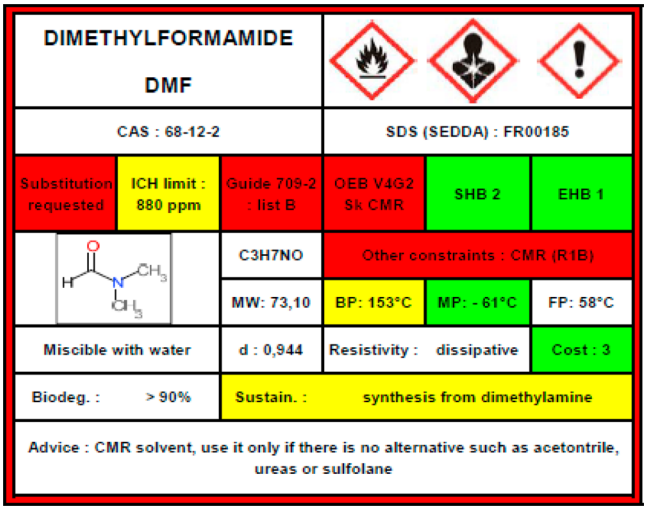

Figure 3. ID card of *N*,*N*′-dimethyl formamide.

SAFETY

An internal 5-band safety ranking (Safety Hazard Band) is given by Central HSE Direction for most solvents, based on the boiling point, the flash point, the autoignition temperature, the resistivity, and the energy of decomposition (table 10).

A SHB5 solvent is not necessarily ranked as "banned" or "substitution requested". We do not consider a low flash point or autoignition temperature as a major concern for the solvent selection. As all operations are run in an inert atmosphere in closed equipment, for both safety and occupational health reasons, the risk of an explosion is very limited. Besides, our HSE policy imposes an in-depth risk analysis before any scale-up (already at the kilolab scale) and requires specific management of the rare situations where explosive atmospheres can occur (transfers from or into drums, discharge of filters, etc.) by minimizing spark sources from electrical equipment and electrostatic discharge. When ethers are used, peroxides content is always checked. Diethyl ether is banned because it cumulates many safety issues: low boiling point, low flash point, low autoignition temperature (180 °C), and ability to form peroxides. Nitromethane is banned as a result of its very high energy of decomposition (3.92 kJ/g).[15]

We do not generally take into account the reactivity of the solvent in the ranking, because it is very arbitrary. However, in each solvent paragraph, a subparagraph is dedicated to interaction issues with some reactants.

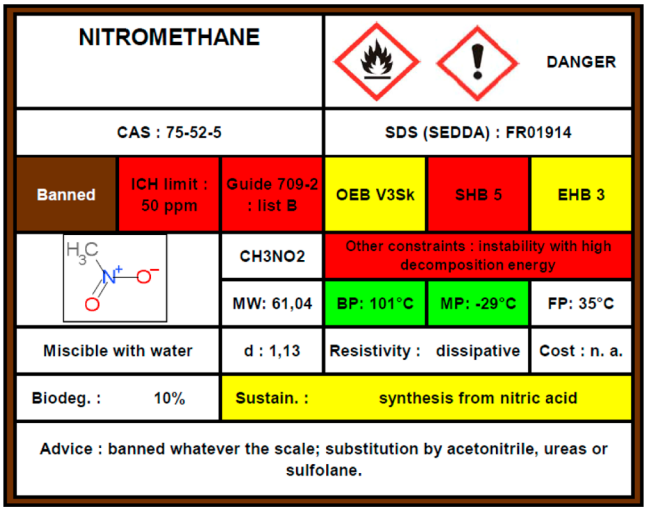

Figure 4. ID card of nitromethane.

OCCUPATIONAL HEALTH

In Sanofi, the Product Stewardship Department analyzes substances in terms of toxicity and ranks them according to a 5-band system, the Occupational Exposure Band (OEB). Solid substances ranked OEB5, for instance, can be handled only in full containment in the workshops: the airborne dust in the workplace must be lower than 1 μg per cubic meter. Suffixes complete this classification: Sk means that the product is sensitizing for the skin, G1 or G2 means that it may have effects on the foetus, and so on. For liquids, a similar OEBV (V for vapor) classification has been established (table 11). Carcinogenic solvents (H350) are ranked OEBV4 or 5. Reprotoxic solvents (H360) are most often ranked OEBV4G2.

The guide is aligned with European regulations on Carcinogenic, Mutagenic, and Reprotoxic (CMR) compounds. CMR compounds of category 1A or 1B (H340, H350, or H360) are subjected to substitution or justification and necessitate declaration of the workers involved as well as monitoring in the workplace.[16] Sanofi's guide is quite consistent with this:

dx.doi.org/10.1021/op4002565 | *Org. Process Res. Dev.* 2013, 17, 1517−1525

Table 10. Safety Hazard Bands for liquids[a]

SHB	GHS symbol	GHS hazard statement	Flash Point (°C)	Auto-ignition Temp. (°C)	Decomposition energy (J/g)
1	None	None	> 60	> 450	< 100
2		H226	24-60	301-450	101-200
3		H224 or H225	0-23	201-300	201-350
4			< 0	135-200	351-500
5			-	< 135	> 500

[a]The SHB is imposed by the most stringent safety criterion and is increased by 1 if the resistivity is higher than 10^8 ohm.m.

Table 11. Occupational Evaluation Bands (by default) for liquids

	occupational level (ppm)				
	>1000	100−1000	10−100	1−10	<1
OEBV	1	2	3	4	5

- All reprotoxic solvents (H360) are labeled as "substitution requested" by default.
- The guide is even more stringent with carcinogenic solvents (H350) such as benzene and 1, 2-dichloroethane, which are banned.

Also in alignment with regulations, CMR solvents of category 2 (H341, H351, or H361) are labeled only as "substitution advisable" by default.

In summary, Occupational Hygiene has a strong impact on the overall recommendation: the substitution of OEBV4 solvents is most often requested, and OEBV5 solvents are systematically banned.

■ ENVIRONMENT

Most solvents are classified with respect to their environmental toxicity and biodegradability, in an Environmental Hazard Band system (Table 12). As there are many EHB5 solvents (especially hydrocarbons), not all of them are classified as "substitution requested". On the other hand, no EHB4 solvent is recommended, and only one EHB3 (Me-THF) is recommended. Solvents that are dangerous for the ozone layer (H420) are banned (carbon tetrachloride, trichloroethane). This is also consistent with European regulations, which impose a strong limitation on such compounds.[17]

We did not perform a life cycle analysis of the solvents. In the box "sustainability" of the ID cards, the origin of the solvent is mentioned, and a very qualitative ranking (3-color flag) is given. While this is a weakness of our guide, there are other tools available to carry out this analysis.[18]

■ QUALITY

In the family tables and in the ID cards, the ICH limits are given (in ppm). This value is very useful for the selection of the solvents to be used in the last stage of the synthesis and particularly for the crystallization of a Drug Substance. In the solvent paragraph, more information is given, such as the presence of peroxides scavengers, dehydrating agents in alcohols, or traces of benzene in acetone produced from cumene.

■ INDUSTRIAL CONSTRAINTS

The ranking of a solvent is also influenced by industrial issues. In the alcohol and ester families, the difference between recommended solvents and usable solvents (substitution advisable) is often based on such constraints. Some examples of these constraints are high cost, boiling point below 50 °C or above 140 °C, freezing point above 0 °C, lack of data, or regulatory constraints linked to CMR solvents.

A chapter of the guide is dedicated to physical properties, as a complement to the table of physical constants. The purpose is to educate lab chemists on the physical constraints placed on plant engineers. The chemist being made aware of some issue on the industrial level (e.g., the difficulty to dehydrate a solvent) may thus try a similar solvent with fewer drawbacks. In this chapter, the physical properties are classified as intrinsic ones (density, boiling point, etc.), those linked to interaction with water or other solvents (polarity, solubility, azeotropes, etc.), or those linked to safety (flash point, specific heat capacity, resistivity, etc.). For each property, a definition is given, followed by a short presentation and a take-home message.

■ COST AND RECYCLABILITY

Cost and ease of recycling are progressively being updated. The cost is given as the relative cost with respect to methanol (RCM), rounded up or down, to minimize the need to frequently update the database. Cost is not always an issue; it depends on

Table 12. Environment Hazard Bands for solvents[a]

EHB	PNEC (μg/L)	GHS hazard statement	EU risk phrase	ecotoxicity (acute EC50)/ biodegradability/bioaccumulation
1	>1000	none	none	ecotox > 100 mg/L AND biodegradable AND nonbioaccumulable
2	100−1000	H402 or H413	R52 or R53	ecotox between 10 and 100 mg/L OR nonbiodegradable nor bioaccumulable
3	10−100	H401 or H412	R51 or R52/53	ecotox between 1 and 10 mg/L OR harmful for aquatic organisms AND nonbiodegradable nor bioaccumulable
4	1−10	H400 or H411	R50 or R51/53	ecotox < 1 mg/L OR toxic for aquatic organisms AND nonbiodegradable nor bioaccumulable
5	<1	H410, H420, or EUH059	R50/53 or R59	ecotox < 1 mg/L AND nonbiodegradable nor bioaccumulable, OR hazardous for the ozone layer

[a]EHB should first be based on Predictive No Effect Concentration (PNEC) data. EHB is imposed by the most stringent criterion.

dx.doi.org/10.1021/op4002565 | Org. Process Res. Dev. 2013, 17, 1517−1525

Table 13. Example of sustainability improvement during Drug Candidate development

STEP	Discovery	Study batch	GMP1 batch
Triflatation	DMF	THF	THF
Suzuki coupling	Dioxane	Dioxane	Acetonitrile
N-arylation	DMF	DMF	Acetonitrile
Purification of API	Diethyl ether	DCM	Isopropanol

the application. An expensive solvent is acceptable at the end of the synthesis or if it can easily be recycled. This is why we do not take into account the relative cost in the overall ranking of the solvent. As a matter of fact, recycling a waste solvent limits the pollution and often reduces the process cost. This is particularly true for Drug Substances with expired patents for which processes must be as inexpensive as possible.

On the basis of the cost criterion alone, Me-THF would be undesirable (RCM = 18). Yet on the positive site, it is easy to recycle. The case of *n*-heptane is also interesting. Pure *n*-heptane at 99% is very expensive (RCM = 18) due to the energy expended during its purification. Nevertheless, the purer quality of linear alkanes is generally preferred for the ease of analysis. A change in the lab chemist's mindset is sometimes necessary, and for this reason, advice on solvent cost is given in the guide. How many know that *n*-propanol is expensive (RCM = 14) and that isobutanol (RCM = 3) is cheaper than *n*-butanol (RCM = 7)?

RELATIVE RANKING

Establishing an overall ranking is not an easy task. This was sometimes the cause of vivid discussions in the working group. The ranking is relatively easy within one family: the substitution of ethyl formate and methyl acetate is advisable as a result of their low boiling point, and the same applies for high boiling esters. In this family it is very easy to make substitutions. In the family of alkanes, pentane is banned, and as the substitution of hexane is requested, the chemist is oriented to the use of heptane, cyclohexane, or methyl-cyclohexane. Thus, the ranking is consistent within one family, but not always from one family to another. We also tried to recommend at least one solvent per family, when possible, for instance, acetonitrile for aprotic polar solvents, 2-methyl-tetrahydrofurane and anisole for ethers, etc. We classified 2-methyl-tetrahydrofurane as "recommended" on the basis of its moderate water solubility, boiling point, and natural origin.[19] On the other hand, we considered that the substitution of cyclopentyl methyl ether[20] was requested, as it is a fully synthetic solvent with a low autoignition temperature (180 °C). The ranking of dimethyl sulfoxide (DMSO) was difficult. Its disadvantages include hazardous reactions with strong bases and oxidizing agents,[15] a high boiling point, miscibility with water, and the formation of dimethylsulfide in water treatment plants. On the other hand, it has a low toxicity (ICH class 3) and is suitable for purification of Drug Substances. In the end, we ranked it in the category "substitution advisable", with the appropriate recommendation: "acceptable for purification of Drug Substances and not for chemical steps".

GUIDE UPDATE

The guide is regularly updated. It has recently been reshaped, with the new GHS hazard pictograms, and the internal Safety Hazard Bands have been modified to be consistent with the GHS flammability classes. It contains 96 solvents. More solvents could be added after deliberation within the solvents working group. We try however to restrain the enthusiasm of lab chemists towards the so-called "neoteric solvents", on which we do not have full data. The general rule is to rank such solvents as "substitution advisable" by default. This is the case of ethyl lactate,[21] a renewable solvent that is an alternative to the reprotoxic 2-alcohoxy-ethanols and that may be recommended in the future.

CONCLUSION

Sanofi's guide provides useful advice, data, and clear recommendations to process research chemists for the selection of suitable solvents for scale-up. It can either be used in a very superficial way, to check if a solvent is recommended, or read more deeply, in order to get all data and advice on a solvent.

One of the advantages with respect to other guides is the existence of a category of "banned" solvents, which must not be used, even in the laboratory. This distinction between banned and undesirable solvents is very useful and is aligned with the policy of OPRD to discourage scientists' use of "strongly undesirable solvents".[22]

The guide is notably in alignment with the European regulations and Global Harmonized System.

Sanofi's solvent selection guide is available in all sites, from Zentiva, our generics subsidiary, to Vitry, which is dedicated to small scale syntheses of high activity products such as docetaxel. The tables of azeotropes and solvent physical properties are available on the desktop of most chemists' computers. The process safety reports and the Safety Hazard Analysis & Risk Evaluations before scale-up include the solvents' ranking. We did not follow in detail the solvent consumption in the company's pilot plants but could see through process safety studies on the Sanofi Vitry site that dioxane and DMF have often been substituted by acetonitrile and that 2-methyl-tetrahydrofurane is now very commonly used in processes. *n*-Butanol and 2-butanol are also common for Suzuki's coupling reactions. The example in Table 13 illustrates the efforts made by the process research chemists to select more sustainable solvents in the early development of a Drug Candidate. The full implementation of the guide for existing industrial processes will be challenging, since a solvent substitution is not always possible and must have no impact on the impurity profile of the Drug Substance. Nevertheless, the guide permits one to set up priorities for these substitution studies.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Many contributors worked on this guide, who are now retired or have taken new opportunities. We would particularly like to acknowledge Michel Mulhauser, Christian Hoff, Guy Rossey and Virginie Laigneau. We are also very grateful to Jeanne Leroux, the Solvent Guide Webmaster.

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(10) Aliphatic, ethylenic, or aromatic hydrocarbons together.
(11) Bifunctional solvents bear two distinct functions, e.g., ether and alcohol, whereas glycols (two alcohol functions) can be found in the alcohols chapter.
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