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ULLMANN'S

Fine Chemicals

Ullmann's Fine Chemicals

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Preface

This handbook features selected articles from the 7th edition of *ULLMANN'S Encyclopedia of Industrial Chemistry*, including newly written articles that have not been published in a printed edition before. True to the tradition of the ULLMANN'S Encyclopedia, products and processes are addressed from an industrial perspective, including production figures, quality standards and patent protection issues where appropriate. Safety and environmental aspects which are a key concern for modern process industries are likewise considered.

More content on related topics can be found in the complete edition of the ULLMANN'S Encyclopedia.

About ULLMANN'S

ULLMANN'S Encyclopedia is the world's largest reference in applied chemistry, industrial chemistry, and chemical engineering. In its current edition, the Encyclopedia contains more than 30,000 pages, 15,000 tables, 25,000 figures, and innumerable literature sources and cross-references, offering a wealth of comprehensive and well-structured information on all facets of industrial chemistry.

1,100 major articles cover the following main areas:

- Agrochemicals
- Analytical Techniques
- Biochemistry and Biotechnology
- Chemical Reactions
- Dyes and Pigments
- Energy
- Environmental Protection and Industrial Safety
- Fat, Oil, Food and Feed, Cosmetics
- Inorganic Chemicals
- Materials
- Metals and Alloys
- Organic Chemicals
- Pharmaceuticals
- Polymers and Plastics
- Processes and Process Engineering
- Renewable Resources
- Special Topics

First published in 1914 by Professor Fritz Ullmann in Berlin, the *Enzyklopädie der Technischen Chemie* (as the German title read) quickly became the standard reference work in industrial chemistry. Generations of chemists have since relied on ULLMANN'S as their prime reference source. Three further German editions followed in 1928–1932, 1951–1970, and in 1972–1984. From 1985 to 1996, the 5th edition of ULLMANN'S Encyclopedia of Industrial Chemistry was the first edition to be published in English rather than German language. So far, two more complete English editions have been published; the 6th edition of 40 volumes in 2002, and the 7th edition in 2011, again comprising 40 volumes. In addition, a number of smaller topic-oriented editions have been published.

Since 1997, *ULLMANN'S Encyclopedia of Industrial Chemistry* has also been available in electronic format, first in a CD-ROM edition and, since 2000, in an enhanced online edition. Both electronic editions feature powerful search and navigation functions as well as regular content updates.

Contents

Symbols and Units

Symbols and units agree with SI standards (for conversion factors see page XI). The following list gives the most important symbols used in the encyclopedia. Articles with many specific units and symbols have a similar list as front matter.

Symbol	Unit	Physical Quantity
a_B		activity of substance B
A_r		relative atomic mass (atomic weight)
A	m^2	area
c_B	mol/m^3, mol/L (M)	concentration of substance B
C	C/V	electric capacity
c_p, c_v	$J\,kg^{-1}\,K^{-1}$	specific heat capacity
d	cm, m	diameter
d		relative density (ϱ/ϱ_{water})
D	m^2/s	diffusion coefficient
D	Gy (=J/kg)	absorbed dose
e	C	elementary charge
E	J	energy
E	V/m	electric field strength
E	V	electromotive force
E_A	J	activation energy
f		activity coefficient
F	C/mol	Faraday constant
F	N	force
g	m/s^2	acceleration due to gravity
G	J	Gibbs free energy
h	m	height
$\hbar$	$W{\cdot}s^2$	Planck constant
H	J	enthalpy
I	A	electric current
I	cd	luminous intensity
k	(variable)	rate constant of a chemical reaction
k	J/K	Boltzmann constant
K	(variable)	equilibrium constant
l	m	length
m	g, kg, t	mass
M_r		relative molecular mass (molecular weight)
n_D^{20}		refractive index (sodium D-line, 20 °C)
n	mol	amount of substance
N_A	mol^{-1}	Avogadro constant ($6.023 \times 10^{23}\,mol^{-1}$)
P	Pa, bar*	pressure
Q	J	quantity of heat
r	m	radius
R	$JK^{-1}\,mol^{-1}$	gas constant
R	Ω	electric resistance
S	J/K	entropy
t	s, min, h, d, month, a	time
t	°C	temperature
T	K	absolute temperature
u	m/s	velocity
U	V	electric potential

Symbols and Units (Continued from p. IX)

Symbol	Unit	Physical Quantity
U	J	internal energy
V	m^3, L, mL, µL	volume
w		mass fraction
W	J	work
x_B		mole fraction of substance B
Z		proton number, atomic number
α		cubic expansion coefficient
α	$Wm^{-2}K^{-1}$	heat-transfer coefficient (heat-transfer number)
α		degree of dissociation of electrolyte
$[\alpha]$	10^{-2}deg cm^2g^{-1}	specific rotation
η	Pa·s	dynamic viscosity
θ	°C	temperature
$\varkappa$		c_p/c_v
λ	$Wm^{-1}K^{-1}$	thermal conductivity
λ	nm, m	wavelength
μ		chemical potential
ν	Hz, s^{-1}	frequency
ν	m^2/s	kinematic viscosity (η/ϱ)
π	Pa	osmotic pressure
ϱ	g/cm^3	density
σ	N/m	surface tension
τ	Pa (N/m^2)	shear stress
φ		volume fraction
χ	Pa^{-1} (m^2/N)	compressibility

*The official unit of pressure is the pascal (Pa).

Conversion Factors

SI unit	Non-SI unit	From SI to non-SI multiply by
Mass		
kg	pound (avoirdupois)	2.205
kg	ton (long)	9.842×10^{-4}
kg	ton (short)	1.102×10^{-3}
Volume		
m^3	cubic inch	6.102×10^{4}
m^3	cubic foot	35.315
m^3	gallon (U.S., liquid)	2.642×10^{2}
m^3	gallon (Imperial)	2.200×10^{2}
Temperature		
°C	°F	$°C \times 1.8 + 32$
Force		
N	dyne	1.0×10^{5}
Energy, Work		
J	Btu (int.)	9.480×10^{-4}
J	cal (int.)	2.389×10^{-1}
J	eV	6.242×10^{18}
J	erg	1.0×10^{7}
J	kW·h	2.778×10^{-7}
J	kp·m	1.020×10^{-1}
Pressure		
MPa	at	10.20
MPa	atm	9.869
MPa	bar	10
kPa	mbar	10
kPa	mm Hg	7.502
kPa	psi	0.145
kPa	torr	7.502

Powers of Ten

E (exa)	10^{18}	d (deci)	10^{-1}
P (peta)	10^{15}	c (centi)	10^{-2}
T (tera)	10^{12}	m (milli)	10^{-3}
G (giga)	10^{9}	μ (micro)	10^{-6}
M (mega)	10^{6}	n (nano)	10^{-9}
k (kilo)	10^{3}	p (pico)	10^{-12}
h (hecto)	10^{2}	f (femto)	10^{-15}
da (deca)	10	a (atto)	10^{-18}

Abbreviations

The following is a list of the abbreviations used in the text. Common terms, the names of publications and institutions, and legal agreements are included along with their full identities. Other abbreviations will be defined wherever they first occur in an article. For further abbreviations, see page IX, Symbols and Units; page XVI, Frequently Cited Companies (Abbreviations), and page XVII, Country Codes in patent references. The names of periodical publications are abbreviated exactly as done by Chemical Abstracts Service.

abs.	absolute
a.c.	alternating current
ACGIH	American Conference of Governmental Industrial Hygienists
ACS	American Chemical Society
ADI	acceptable daily intake
ADN	accord européen relatif au transport international des marchandises dangereuses par voie de navigation interieure (European agreement concerning the international transportation of dangerous goods by inland waterways)
ADNR	ADN par le Rhin (regulation concerning the transportation of dangerous goods on the Rhine and all national waterways of the countries concerned)
ADP	adenosine 5′-diphosphate
ADR	accord européen relatif au transport international des marchandises dangereuses par route (European agreement concerning the international transportation of dangerous goods by road)
AEC	Atomic Energy Commission (United States)
a.i.	active ingredient
AIChE	American Institute of Chemical Engineers
AIME	American Institute of Mining, Metallurgical, and Petroleum Engineers
ANSI	American National Standards Institute
AMP	adenosine 5′-monophosphate
APhA	American Pharmaceutical Association
API	American Petroleum Institute
ASTM	American Society for Testing and Materials
ATP	adenosine 5′-triphosphate
BAM	Bundesanstalt für Materialprüfung (Federal Republic of Germany)
BAT	Biologischer Arbeitsstofftoleranzwert (biological tolerance value for a working material, established by MAK Commission, see MAK)
Beilstein	Beilstein's Handbook of Organic Chemistry, Springer, Berlin – Heidelberg – New York
BET	Brunauer – Emmett – Teller
BGA	Bundesgesundheitsamt (Federal Republic of Germany)
BGB1.	Bundesgesetzblatt (Federal Republic of Germany)
BIOS	British Intelligence Objectives Subcommittee Report (see also FIAT)
BOD	biological oxygen demand
bp	boiling point
B.P.	British Pharmacopeia
BS	British Standard
ca.	circa
calcd.	calculated
CAS	Chemical Abstracts Service
cat.	catalyst, catalyzed
CEN	Comité Européen de Normalisation
cf.	compare
CFR	Code of Federal Regulations (United States)
cfu	colony forming units
Chap.	chapter
ChemG	Chemikaliengesetz (Federal Republic of Germany)
C.I.	Colour Index
CIOS	Combined Intelligence Objectives Subcommitee Report (see also FIAT)
CLP	Classification, Labelling and Packaging
CNS	central nervous system
Co.	Company
COD	chemical oxygen demand
conc.	concentrated
const.	constant
Corp.	Corporation
crit.	critical
CSA	Chemical Safety Assessment according to REACH
CSR	Chemical Safety Report according to REACH
CTFA	The Cosmetic, Toiletry and Fragrance Association (United States)
DAB	Deutsches Arzneibuch, Deutscher Apotheker-Verlag, Stuttgart
d.c.	direct current
decomp.	decompose, decomposition
DFG	Deutsche Forschungsgemeinschaft (German Science Foundation)

dil.	dilute, diluted
DIN	Deutsche Industrienorm (Federal Republic of Germany)
DMF	dimethylformamide
DNA	deoxyribonucleic acid
DOE	Department of Energy (United States)
DOT	Department of Transportation – Materials Transportation Bureau (United States)
DTA	differential thermal analysis
EC	effective concentration
EC	European Community
ed.	editor, edition, edited
e.g.	for example
emf	electromotive force
EmS	Emergency Schedule
EN	European Standard (European Community)
EPA	Environmental Protection Agency (United States)
EPR	electron paramagnetic resonance
Eq.	equation
ESCA	electron spectroscopy for chemical analysis
esp.	especially
ESR	electron spin resonance
Et	ethyl substituent ($-C_2H_5$)
et al.	and others
etc.	et cetera
EVO	Eisenbahnverkehrsordnung (Federal Republic of Germany)
exp (...)	$e^{(...)}$, mathematical exponent
FAO	Food and Agriculture Organization (United Nations)
FDA	Food and Drug Administration (United States)
FD&C	Food, Drug and Cosmetic Act (United States)
FHSA	Federal Hazardous Substances Act (United States)
FIAT	Field Information Agency, Technical (United States reports on the chemical industry in Germany, 1945)
Fig.	figure
fp	freezing point
Friedländer	P. Friedländer, Fortschritte der Teerfarbenfabrikation und verwandter Industriezweige Vol. 1–25, Springer, Berlin 1888–1942
FT	Fourier transform
(g)	gas, gaseous
GC	gas chromatography
GefStoffV	Gefahrstoffverordnung (regulations in the Federal Republic of Germany concerning hazardous substances)
GGVE	Verordnung in der Bundesrepublik Deutschland über die Beförderung gefährlicher Güter mit der Eisenbahn (regulation in the Federal Republic of Germany concerning the transportation of dangerous goods by rail)
GGVS	Verordnung in der Bundesrepublik Deutschland über die Beförderung gefährlicher Güter auf der Straße (regulation in the Federal Republic of Germany concerning the transportation of dangerous goods by road)
GGVSee	Verordnung in der Bundesrepublik Deutschland über die Beförderung gefährlicher Güter mit Seeschiffen (regulation in the Federal Republic of Germany concerning the transportation of dangerous goods by sea-going vessels)
GHS	Globally Harmonised System of Chemicals (internationally agreed-upon system, created by the UN, designed to replace the various classification and labeling standards used in different countries by using consistent criteria for classification and labeling on a global level)
GLC	gas-liquid chromatography
Gmelin	Gmelin's Handbook of Inorganic Chemistry, 8th ed., Springer, Berlin – Heidelberg –New York
GRAS	generally recognized as safe
Hal	halogen substituent (−F, −Cl, −Br, −I)
Houben-Weyl	Methoden der organischen Chemie, 4th ed., Georg Thieme Verlag, Stuttgart
HPLC	high performance liquid chromatography
H statement	hazard statement in GHS
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer, Lyon, France
IATA-DGR	International Air Transport Association, Dangerous Goods Regulations
ICAO	International Civil Aviation Organization
i.e.	that is
i.m.	intramuscular
IMDG	International Maritime Dangerous Goods Code
IMO	Inter-Governmental Maritime Consultive Organization (in the past: IMCO)
Inst.	Institute
i.p.	intraperitoneal
IR	infrared
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry

i.v.	intravenous
Kirk-Othmer	Encyclopedia of Chemical Technology, 3rd ed., 1991–1998, 5th ed., 2004–2007, John Wiley & Sons, Hoboken
(l)	liquid
Landolt-Börnstein	Zahlenwerte u. Funktionen aus Physik, Chemie, Astronomie, Geophysik u. Technik, Springer, Heidelberg 1950–1980; Zahlenwerte und Funktionen aus Naturwissenschaften und Technik, Neue Serie, Springer, Heidelberg, since 1961
LC_{50}	lethal concentration for 50 % of the test animals
LCLo	lowest published lethal concentration
LD_{50}	lethal dose for 50 % of the test animals
LDLo	lowest published lethal dose
ln	logarithm (base e)
LNG	liquefied natural gas
log	logarithm (base 10)
LPG	liquefied petroleum gas
M	mol/L
M	metal (in chemical formulas)
MAK	Maximale Arbeitsplatzkonzentration (maximum concentration at the workplace in the Federal Republic of Germany); cf. Deutsche Forschungsgemeinschaft (ed.): Maximale Arbeitsplatzkonzentrationen (MAK) und Biologische Arbeitsstofftoleranzwerte (BAT), WILEY-VCH Verlag, Weinheim (published annually)
max.	maximum
MCA	Manufacturing Chemists Association (United States)
Me	methyl substituent ($-CH_3$)
Methodicum Chimicum	Methodicum Chimicum, Georg Thieme Verlag, Stuttgart
MFAG	Medical First Aid Guide for Use in Accidents Involving Dangerous Goods
MIK	maximale Immissionskonzentration (maximum immission concentration)
min.	minimum
mp	melting point
MS	mass spectrum, mass spectrometry
NAS	National Academy of Sciences (United States)
NASA	National Aeronautics and Space Administration (United States)
NBS	National Bureau of Standards (United States)
NCTC	National Collection of Type Cultures (United States)
NIH	National Institutes of Health (United States)
NIOSH	National Institute for Occupational Safety and Health (United States)
NMR	nuclear magnetic resonance
no.	number
NOEL	no observed effect level
NRC	Nuclear Regulatory Commission (United States)
NRDC	National Research Development Corporation (United States)
NSC	National Service Center (United States)
NSF	National Science Foundation (United States)
NTSB	National Transportation Safety Board (United States)
OECD	Organization for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration (United States)
p., pp.	page, pages
Patty	G.D. Clayton, F.E. Clayton (eds.): Patty's Industrial Hygiene and Toxicology, 3rd ed., Wiley Interscience, New York
PB report	Publication Board Report (U.S. Department of Commerce, Scientific and Industrial Reports)
PEL	permitted exposure limit
Ph	phenyl substituent ($—C_6H_5$)
Ph. Eur.	European Pharmacopoeia, Council of Europe, Strasbourg
phr	part per hundred rubber (resin)
PNS	peripheral nervous system
ppm	parts per million
P statement	precautionary statement in GHS
q.v.	which see (quod vide)
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (EU regulation addressing the production and use of chemical substances, and their potential impacts on both human health and the environment)
ref.	refer, reference
resp.	respectively
R_f	retention factor (TLC)
R.H.	relative humidity
RID	réglement international concernant le transport des marchandises dangereuses par chemin de fer (international convention concerning the transportation of dangerous goods by rail)
RNA	ribonucleic acid
R phrase (R-Satz)	risk phrase according to ChemG and GefStoffV (Federal Republic of Germany)
rpm	revolutions per minute
RTECS	Registry of Toxic Effects of Chemical Substances, edited by the

	National Institute of Occupational Safety and Health (United States)
(s)	solid
SAE	Society of Automotive Engineers (United States)
SAICM	Strategic Approach on International Chemicals Management (international framework to foster the sound management of chemicals)
s.c.	subcutaneous
SI	International System of Units
SIMS	secondary ion mass spectrometry
S phrase (S-Satz)	safety phrase according to ChemG and GefStoffV (Federal Republic of Germany)
STEL	Short Term Exposure Limit (see TLV)
STP	standard temperature and pressure (0°C, 101.325 kPa)
T_g	glass transition temperature
TA Luft	Technische Anleitung zur Reinhaltung der Luft (clean air regulation in Federal Republic of Germany)
TA Lärm	Technische Anleitung zum Schutz gegen Lärm (low noise regulation in Federal Republic of Germany)
TDLo	lowest published toxic dose
THF	tetrahydrofuran
TLC	thin layer chromatography
TLV	Threshold Limit Value (TWA and STEL); published annually by the American Conference of Governmental Industrial Hygienists (ACGIH), Cincinnati, Ohio
TOD	total oxygen demand
TRK	Technische Richtkonzentration (lowest technically feasible level)
TSCA	Toxic Substances Control Act (United States)
TÜV	Technischer Überwachungsverein (Technical Control Board of the Federal Republic of Germany)
TWA	Time Weighted Average
UBA	Umweltbundesamt (Federal Environmental Agency)
Ullmann	Ullmann's Encyclopedia of Industrial Chemistry, 6th ed., Wiley-VCH, Weinheim 2002; Ullmann's Encyclopedia of Industrial Chemistry, 5th ed., VCH Verlagsgesellschaft, Weinheim 1985–1996; Ullmanns Encyklopädie der Technischen Chemie, 4th ed., Verlag Chemie, Weinheim 1972–1984; 3rd ed., Urban und Schwarzenberg, München 1951–1970
USAEC	United States Atomic Energy Commission
USAN	United States Adopted Names
USD	United States Dispensatory
USDA	United States Department of Agriculture
U.S.P.	United States Pharmacopeia
UV	ultraviolet
UVV	Unfallverhütungsvorschriften der Berufsgenossenschaft (workplace safety regulations in the Federal Republic of Germany)
VbF	Verordnung in der Bundesrepublik Deutschland über die Errichtung und den Betrieb von Anlagen zur Lagerung, Abfüllung und Beförderung brennbarer Flüssigkeiten (regulation in the Federal Republic of Germany concerning the construction and operation of plants for storage, filling, and transportation of flammable liquids; classification according to the flash point of liquids, in accordance with the classification in the United States)
VDE	Verband Deutscher Elektroingenieure (Federal Republic of Germany)
VDI	Verein Deutscher Ingenieure (Federal Republic of Germany)
vol	volume
vol.	volume (of a series of books)
vs.	versus
WGK	Wassergefährdungsklasse (water hazard class)
WHO	World Health Organization (United Nations)
Winnacker-Küchler	Chemische Technologie, 4th ed., Carl Hanser Verlag, München, 1982-1986; Winnacker-Küchler, Chemische Technik: Prozesse und Produkte, Wiley-VCH, Weinheim, 2003–2006
wt	weight
$	U.S. dollar, unless otherwise stated

Frequently Cited Companies (Abbreviations)

Air Products	Air Products and Chemicals
Akzo	Algemene Koninklijke Zout Organon
Alcoa	Aluminum Company of America
Allied	Allied Corporation
Amer. Cyanamid	American Cyanamid Company
BASF	BASF Aktiengesellschaft
Bayer	Bayer AG
BP	British Petroleum Company
Celanese	Celanese Corporation
Daicel	Daicel Chemical Industries
Dainippon	Dainippon Ink and Chemicals Inc.
Dow Chemical	The Dow Chemical Company
DSM	Dutch Staats Mijnen
Du Pont	E.I. du Pont de Nemours & Company
Exxon	Exxon Corporation
FMC	Food Machinery & Chemical Corporation
GAF	General Aniline & Film Corporation
W.R. Grace	W.R. Grace & Company
Hoechst	Hoechst Aktiengesellschaft
IBM	International Business Machines Corporation
ICI	Imperial Chemical Industries
IFP	Institut Français du Pétrole
INCO	International Nickel Company
3M	Minnesota Mining and Manufacturing Company
Mitsubishi Chemical	Mitsubishi Chemical Industries
Monsanto	Monsanto Company
Nippon Shokubai	Nippon Shokubai Kagaku Kogyo
PCUK	Pechiney Ugine Kuhlmann
PPG	Pittsburg Plate Glass Industries
Searle	G.D. Searle & Company
SKF	Smith Kline & French Laboratories
SNAM	Societá Nazionale Metandotti
Sohio	Standard Oil of Ohio
Stauffer	Stauffer Chemical Company
Sumitomo	Sumitomo Chemical Company
Toray	Toray Industries Inc.
UCB	Union Chimique Belge
Union Carbide	Union Carbide Corporation
UOP	Universal Oil Products Company
VEBA	Vereinigte Elektrizitäts- und Bergwerks-AG
Wacker	Wacker Chemie GmbH

Country Codes

The following list contains a selection of standard country codes used in the patent references.

AT	Austria
AU	Australia
BE	Belgium
BG	Bulgaria
BR	Brazil
CA	Canada
CH	Switzerland
CS	Czechoslovakia
DD	German Democratic Republic
DE	Federal Republic of Germany (and Germany before 1949)*
DK	Denmark
ES	Spain
FI	Finland
FR	France
GB	United Kingdom
GR	Greece
HU	Hungary
ID	Indonesia
IL	Israel
IT	Italy
JP	Japan*
LU	Luxembourg
MA	Morocco
NL	Netherlands*
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
SE	Sweden
SU	Soviet Union
US	United States of America
YU	Yugoslavia
ZA	South Africa
EP	European Patent Office*
WO	World Intellectual Property Organization

*For Europe, Federal Republic of Germany, Japan, and the Netherlands, the type of patent is specified: EP (patent), EP-A (application), DE (patent), DE-OS (Offenlegungsschrift), DE-AS (Auslegeschrift), JP (patent), JP-Kokai (Kokai tokkyo koho), NL (patent), and NL-A (application).

Periodic Table of Elements

element symbol, atomic number, and relative atomic mass (atomic weight)

1A "European" group designation and old IUPAC recommendation
1 group designation to 1986 IUPAC proposal
IA "American" group designation, also used by the Chemical Abstracts Service until the end of 1986

1 **H** 1.0079 IA	2A **2** IIA											3B **13** IIIA	4B **14** IVA	5B **15** VA	6B **16** VIA	7B **17** VIA	0 **18** VIIIA 2 **He** 4.0026
3 **Li** 6.941	4 **Be** 9.0122											5 **B** 10.811	6 **C** 12.011	7 **N** 14.007	8 **O** 15.999	9 **F** 18.998	10 **Ne** 20.180
11 **Na** 22.990	12 **Mg** 24.305	3A **3** IIIB	4A **4** IVB	5A **5** VB	6A **6** VIB	7A **7** VIIB	8 **8** VIII	8 **9** VIII	8 **10** VIII	1B **11** IB	2B **12** IIB	13 **Al** 26.982	14 **Si** 28.086	15 **P** 30.974	16 **S** 32.066	17 **Cl** 35.453	18 **Ar** 39.948
19 **K** 39.098	20 **Ca** 40.078	21 **Sc** 44.956	22 **Ti** 47.867	23 **V** 50.942	24 **Cr** 51.996	25 **Mn** 54.938	26 **Fe** 55.845	27 **Co** 58.933	28 **Ni** 58.693	29 **Cu** 63.546	30 **Zn** 65.409	31 **Ga** 69.723	32 **Ge** 72.61	33 **As** 74.922	34 **Se** 78.96	35 **Br** 79.904	36 **Kr** 83.80
37 **Rb** 85.468	38 **Sr** 87.62	39 **Y** 88.906	40 **Zr** 91.224	41 **Nb** 92.906	42 **Mo** 95.94	43 **Tc*** 98.906	44 **Ru** 101.07	45 **Rh** 102.91	46 **Pd** 106.42	47 **Ag** 107.87	48 **Cd** 112.41	49 **In** 114.82	50 **Sn** 118.71	51 **Sb** 121.76	52 **Te** 127.60	53 **I** 126.90	54 **Xe** 131.29
55 **Cs** 132.91	56 **Ba** 137.33		72 **Hf** 178.49	73 **Ta** 180.95	74 **W** 183.84	75 **Re** 186.21	76 **Os** 190.23	77 **Ir** 192.22	78 **Pt** 195.08	79 **Au** 196.97	80 **Hg** 200.59	81 **Tl** 204.38	82 **Pb** 207.2	83 **Bi** 208.98	84 **Po*** 208.98	85 **At*** 209.99	86 **Rn*** 222.02
87 **Fr*** 223.02	88 **Ra*** 226.03		104 **Rf*** 261.11	105 **Db*** 262.11	106 **Sg**	107 **Bh**	108 **Hs**	109 **Mt**	110 **Ds**	111 **Rg**	112 **Cn**	113 **Uut**[a]	114 **Fl**	115 **Uup**[a]	116 **Lv**		118 **Uuo**[a]

[a] provisional IUPAC symbol

57 **La** 138.91	58 **Ce** 140.12	59 **Pr** 140.91	60 **Nd** 144.24	61 **Pm*** 146.92	62 **Sm** 150.36	63 **Eu** 151.97	64 **Gd** 157.25	65 **Tb** 158.93	66 **Dy** 162.50	67 **Ho** 164.93	68 **Er** 167.26	69 **Tm** 168.93	70 **Yb** 173.04	71 **Lu** 174.97
89 **Ac*** 227.03	90 **Th*** 232.04	91 **Pa*** 231.04	92 **U*** 238.03	93 **Np*** 237.05	94 **Pu*** 244.06	95 **Am*** 243.06	96 **Cm*** 247.07	97 **Bk*** 247.07	98 **Cf*** 251.08	99 **Es*** 252.08	100 **Fm*** 257.10	101 **Md*** 258.10	102 **No*** 259.10	103 **Lr*** 260.11

* radioactive element; mass of most important isotope given.

Fine Chemicals

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ULLMANN'S ENCYCLOPEDIA OF INDUSTRIAL CHEMISTRY

1. Introduction

1.1. History

The roots of both the term "fine chemicals" and the emergence of the fine chemical industry as a distinct entity date back to the second half of the 1970s. As an illustrative example, the US/UK pharmaceutical company Smith, Kline & French (now GlaxoSmithKline) was overwhelmed by the success of its new anti-ulcer drug Tagamet (cimetidine), the first representative of a new therapeutic class, namely, H2 receptor antagonists, which inhibit gastric acid secretion and prevent stomach ulcer. As the demand by far exceeded SKF's in-house production capacity, third-party chemical companies with capabilities in organic intermediates manufacture were approached for custom manufacturing parts of the cimetidine active ingredient. Lonza, Switzerland, became the main supplier of precursor fine chemicals. In a similar way, Fine Organics, UK became the supplier of the thioethyl-*N*′-methyl-2-nitro-1,1-ethenediamine moiety of ranitidine, the second H2 receptor antagonist, marketed as Zantac by Glaxo. Other pharmaceutical and agrochemical companies gradually followed suit and also started outsourcing the procurement of fine chemicals.

In the 1980s the fine chemical industry developed rapidly. The first multipurpose plants designed purposely for custom manufacturing came on-stream. In the case of important projects, engineering and financial support by the customers was not unusual. The latter often were Anglo-Saxon pharmaceutical and agrochemical companies, which both had a

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large demand for fine chemicals and were prone to outsourcing.

In the 1990s the industry benefited from strong demand. The pharmaceutical industry launched a large number of new proprietary drugs. The record year was 1997 with 53 new drug launches. The emergence of generics expanded the customer base. The agrochemical industry launched a new category of highly active, low-volume products. Lacking in-house production capabilities for the production of these sophisticated compounds, it turned to outsourcing. Management had to cope with rapidly increasing regulatory requirements. In production, tight operating guidelines, the so-called Good Manufacturing Practices (GMP), were imposed by the U.S. FDA. As a result, a kind of standard, cross-contamination-proof, multipurpose plant for the production of complex pharmaceutical fine chemicals (PFCs) with molecular weight up to 500 became the state of the art. The observance of more severe legislation regarding safety, health, and environment necessitated infrastructure expansions, e.g., for waste incinerators and water-treatment plants.

In the early 2000s the "irrational exuberance of the nineties" came to a sudden halt. An unfortunate coincidence of sluggish demand and the emergence of many new plants, particularly in China and India, led to overcapacity, which, in turn, impaired the profitability of the whole industry.

In terms of process technology, *biotechnology* unlocked promising new opportunities. In conventional small-molecule synthesis, *biocatalysis* enables both more economical and more ecological production processes. For active ingredients for the emerging biopharmaceuticals, demanding *mammalian cell culture* technology is needed. The production of these very expensive ($> \$10^6$/kg) high molecular weight fine chemicals requires special high-containment plants.

1.2. Definition

Fine chemicals are complex, single, pure chemical substances. They are produced mainly by traditional organic synthesis in multipurpose plants in limited volumes (< 1000 t/a) and at relatively high prices ($> \$10$/kg) according to exacting specifications (see Table 1). Biotechnical processes are gaining ground. Whereas the delineations between commodities and both fine and specialty chemicals are clear-cut, the transition between commodities and fine chemicals is gradual (see [1, p. 4]). Fine chemicals are used as starting materials for specialty chemicals, particularly pharmaceuticals and agrochemicals. Custom manufacturing for the life sciences industry plays a big role.

The class of fine chemicals is further subdivided on the basis of

1. The *added value* or degree of sophistication. It extends all the way from small or low molecular weight (LMW) to big or high molecular weight (HMW) substances. The former are conventionally called building blocks, unregulated and regulated intermediates, and active ingredients. The latter comprise inter alia proteins and nucleotides (see Section 3.2).
2. The pharmaceutical industry distinguishes between *drug substance*, which is the active ingredient, a fine chemical, and *drug product*, which is the formulated, finished drug, a specialty.
3. The *type of business transaction*, namely, standard or exclusive products (see Section 6.1).

Table 1. Definition of fine chemicals

	Commodities	Fine chemicals	Specialties
Identity	single pure chemical substances		mixtures
Characteristic	specifications		performance
Total production value	$\approx \$10^{12}$	$\approx \$90 \times 10^9$	$\approx \$1.4 \times 10^9$
Production volume per product	>1000 t/a	<1000 t/a	undifferentiated
Plant type	dedicated, continuous	multipurpose, batch	formulation (dissolution, mixing)
Sales channel	business to business	business to business, captive use	business-to-consumer

2. The Fine Chemical Industry

2.1. Overview

Within the chemical universe, the fine chemical industry is positioned between the commodity and specialty chemical industries, which are their suppliers and customers, respectively. Among the customers, life sciences, especially the pharmaceutical industry, prevail (see Chap. 6). Fine chemical companies represent a wide variety of several 1000 enterprises offering mainly products and services along the drug supply chain (see Fig. 1). They extend from small, privately owned laboratories all the way to large, publicly owned manufacturing companies. Large Western fine chemical companies still dominate in sales revenues. Most of the small ones are located in Asia, particularly in China and India.

A comprehensive list of about 1400 fine chemical companies (including traders) can be found in the "event catalogue" of the CPhI exhibition [2].

The main raison d'être of the fine chemical industry is to satisfy the product and process development needs of the life sciences, primarily pharmaceutical and agrochemical industries, and other specialty chemical firms. It has its own characteristics with regard to finance, R&D, production, and marketing. The R&D expenditure is highest within the industry. Its main task is process development ("small r, big D"). Production takes place in asset-intense multipurpose plants.

Depending on their specific activities, one distinguishes three types of fine chemical companies, namely fine chemical/custom manufacturing companies (CM or CMO), contract research organizations (CRO), and laboratory chemical suppliers.

2.2. Fine Chemical/Custom Manufacturing Companies

Fine chemical/custom manufacturing companies are active in process development, scale up, pilot plant (trial) production, industrial-scale manufacture, and marketing. Custom manufacturing or its counterpart, outsourcing, has remained the most important discipline of the Western firms (see Chap. 6). Due to their advantage of low costs, the Asian companies have a strong position in active ingredients for generics [3].

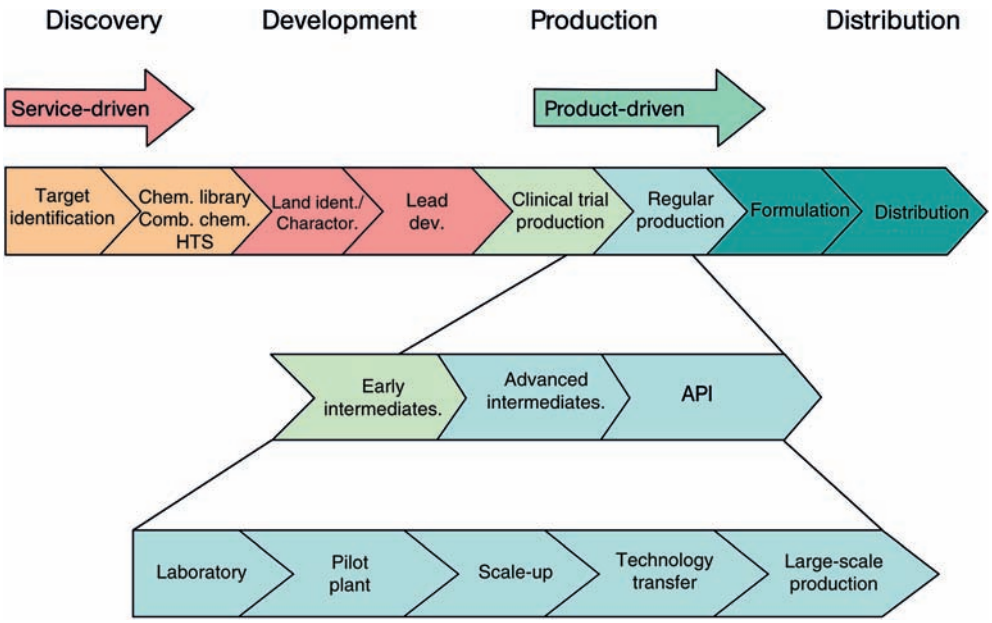


Figure 1. Drug development stages (HTS: high-throughput synthesis) Source: Lonza

Table 2. Top ten fine chemical companies or units (Sources: Company Annual Reports 2011,* author's estimate)

Company		Fine chemicals unit		
Name	Sales[a]	Name	Sales[a]	Notes
Lonza, Switzerland	2900	Custom Manufacturing	1440	HMW/LMW ≈55/45
Sumitomo Chem., Japan	24 300	Fine Chemicals	1090	includes some polymer additives
DSM, The Netherlands	18 300	DPP[b], DSP[c]	890	joint venture for β-lactam APIs
Boehringer-Ingelheim, Germany	17 100	Industrial Customers[d]	800	HMW/LMW ≈85/15
Sigma-Aldrich, USA	2500	SAFC[e]	730	custom cell engineering, HPAIs
BASF, Germany	97 750	P.I.&S[f]	660	includes excipients
Lanxess, Germany	11 700	Saltigo	550*	ex Bayer Fine Chemicals
CSPC[g], P.R. China	1500	Pharma F.C.'s	550[E]	mainly APIs for antibiotics
Evonik-Degussa, Germany	18 900	Exclusive Synthesis[h]	500	amino acids
Dr. Reddy's, India	2 000	PSAI[i]	492	

[a] 10^6 (2011).
[b] DSM Pharmaceutical Products.
[c] DSM Sinochem Pharmaceuticals.
[d] Biopharmaceuticals and Pharmaceutical Production.
[e] Sigma Aldrich Fine Chemicals.
[f] Pharmaceutical Ingredients & Services, business unit of Care Chemicals.
[g] Shijiazhuang Pharmaceutical Group, PRC.
[h] Next higher level is Consumer, Health & Nutrition Div.; sales $\$6.4 \times 10^9$.
[i] Pharmaceutical Services & Active Ingredients.

Despite some consolidation, mainly among the Western players, the fine chemical industry is still fragmented. The *top ten companies* have a combined market share of 25%. In comparison the top ten pharmaceutical companies have more than 40%. The top ten individually have sales of $\$(0.5–1.5) \times 10^9$ per year (see Table 2). Most are divisions of large, diversified chemical companies. Six are headquartered in Europe, and one each in China, India, Japan, and the USA. All are active both in standard products (especially API-for-Generics) and custom manufacturing. They have extensive resources in terms of specialists, plants, process knowledge, backwards integration, international presence, etc. The manufacturing plants spread over many different locations. Many have grown to their present size through massive acquisitions.

The portfolios of the *midsized companies* also comprise both exclusive synthesis and API-for-Generics. Sales are in the range of $\$100–500 \times 10^6$ per annum. They include both subsidiaries of major public companies and family owned independents. Examples of the latter are Bachem, Switzerland; Dishman, India; F.I.S. and SIMS, Italy; Hikal, India; and Hovione, Portugal. Most of the midsized fine chemical companies are located in Europe, particularly in France, Germany, Italy, the UK, and Switzerland. Italy and Spain, where international drug patent laws were not recognized until 1978 and 1992, respectively, are strongholds of API-for-Generics (see Section 6.1). Because of a lack of *economy in size*, the large fine chemical companies traditionally do not perform better than the midsized ones. As most fine chemicals are produced in quantities of not more than a few tens of tonnes per annum in multipurpose plants (see Section 5.1), the production trains are similar in size throughout the industry. Their main constituents, the reaction vessels, have a median size of 4–6 m^3. Various products are made throughout a year in campaigns. Therefore, the unit cost per cubic meter per hour (see Section 5.2) hardly depends on the size of the company. Last but not least, the large fine chemical companies operate many small rather sites than one big one. An example in case is Lonza. The Custom Manufacturing division alone operates 11 sites worldwide.

Finally, there are hundreds of *small independents* with sales below $100 million per annum. Most of them are located in Asia. They have only limited capabilities and often specialize in niche technologies, such as reactions with hazardous gases (e.g., ammonia/amines, diazomethane, ethylene oxide, halogens, hydrogen cyanide, hydrogen sulfide, mercaptans, ozone, nitrous oxides, and phosgene).

The plants of big and medium-size fine chemical companies comply with *current good manufacturing practice* (cGMP) regulations governing the production of pharmaceutical fine chemicals (see Chap. 7). With the exception of biopharmaceuticals, which are manufactured by only a few, the technology toolboxes of all these companies are similar. This means that they can carry out most types of chemical reactions. They differ in the breadth and quality of the offered service.

The minimum economical size of a fine chemical company depends on the availability of infrastructure. If a company is located in an industrial park, where analytical services; utilities, safety, health, and environmental (SHE) services, and warehousing are readily available, there is practically no lower limit.

Several large pharmaceutical companies market fine chemicals by themselves as subsidiary activity to their production for captive use, e.g., Abbott, USA; Bayer Schering Pharma, Boehringer-Ingelheim, Germany; Daiichi-Sankyo (after the takeover of Ranbaxy), Japan; Johnson & Johnson, USA; and Merck KGaA, Germany; and Pfizer (formerly Upjohn), USA.

Whereas the pharmaceutical industry is the dominant customer base for most fine chemical companies, some have a significant share of products and services for the agrochemical industry. Examples are Archimica, Saltigo (both Germany), DSM (The Netherlands), Pyosa (Mexico), and Hikal, India.

2.3. Contract Research Organizations

Contract research organizations (CROs) concentrate on research and process development, providing laboratory-scale process development and bench-scale synthesis services to the specialty chemical industry along product development. There are more than 2000 CROs operating worldwide, representing revenues of more than $\$20 \times 10^9$. One distinguishes between "patient" CROs and "product" CROs.

Product CROs, a.k.a. chemical CROs, provide primarily process research and development services. An overlap with CMOs exists with regard to pilot plants (100 kg quantities), which are part of the arsenal of both CMOs and product CROs. Their tasks are described in Table 3. Companies offering both contract research and manufacturing services (CRAMS), a.k.a. one-stop shops, also exist.

The offerings of *patient CROs*, a.k.a. clinical CROs, comprise more than 30 tasks addressing the clinical part of pharmaceutical development at the interface between drugs, physicians, hos-

Table 3. Tasks of "product" contract research organizations[*]

Task	Description
Sample preparation	
Synthetic PFCs	laboratory preparation of PFCs, impurities, metabolites, etc.
Natural products	product extraction, purification, and characterization
Process development	
General	upgrading of laboratory procedures to economically and ecologically viable industrial-scale manufacturing processes (including examination of process parameters)
Route screening	evaluation of the most suitable synthetic or biotechnological route (mostly by literature search)
Proof of principle	confirmation of selected route based upon economic and quality criteria, equipment specifications, etc.
Sample preparation	reference & impurity standards of PFCs
Safety and toxicology studies	hazard and toxicological (including genotoxicity) tests required for industrial-scale manufacture
Analytics	analytical method development and validation
Process research	process optimization, definition of the parameters for industrial-scale manufacture, method validation, stability studies
Regulatory affairs	production permits, API submissions (IND, NDA support)
Scale-up (kg laboratory/pilot and industrial-scale plant production)	confirmatory testing of the process, preclinical and clinical trial quantities, validation manufacturing (Phase III and beyond)

[*] Source: Jan Oudenes, Alphora Research, Mississauga, Canada (personal communication).

Table 4. Pros and cons of the one-stop-shop concept

Pros	Cons
Fine chemical/custom manufacturing company	
• Chance to establish a relationship with a drug company early on	• In >90% of cases, projects are stopped at the lab-sample stage
• Higher overall added value	• Need to master two different skills. "quick and dirty" lab scale vs. economically viable and ecologically safe large-scale production
Pharmaceutical company	
• Reduction of number of suppliers	• In contrast to the policy of selecting specialists for each step of drug development
	• Overdependence on one supplier

pitals, and patients. Only in a few cases (e.g., Aptuit, Cardinal Health, and Charles River Laboratories) do they also provide chemical R&D services.

There are about 50–100 product CROs in developed countries, either standalone companies or divisions of larger chemical companies, with a widely differing degree of width and depth of their offerings. Major customers for CRO services are the large global pharmaceutical companies. Half a dozen "Big Pharmas" (Pfizer, GlaxoSmithKline, Sanofi-Aventis, AstraZeneca, Johnson & Johnson, and Merck) alone absorb about one-third of all CRO spending. As for CMOs and also for CROs, biotech start-up companies with their dichotomy between ambitious drug development programs and limited resources are the second most promising prospects after Big Pharma. Contrary to manufacturing companies, the "currency" of CROs is not the unit product price, but *full-time equivalents* (FTEs), that is, the cost of a scientist working one year on a given customer assignment. Asian, especially Chinese and Indian, companies are emerging as low-cost contract research providers. The largest Chinese chemical CRO is WuXi AppTec, Shanghai WaiGaoQiao Free Trade Zone. Set up in the year 2001 and led by 50 returnees. 4500 employees generated sales of $\$334 \times 10^6$ in 2011.

Contract research and manufacturing organizations (CRAMs) are hybrids combining the activities of CROs and CMOs [4]. Their history is either a forward integration of a CRO, which adds industrial-scale capabilities (an early example is Suven, India; recent ones are AMRI Global and Cambridge Major in the USA), or backwards integration of a CMO. It is questionable, though, whether one-stop shops really fulfill a need. The pros and cons are summarized in Table 4.

The first pro entry in Table 4, "chance to establish..." is particularly noteworthy. Most new drugs fail in early-stage development. The situation has worsened over the years. Nowadays, even for developmental drugs in phase II, the probability of reaching the market is less than 10%. Furthermore, as there is little repeat business, and as in Big Pharma different functions are in charge of placing orders, CRO projects only rarely evolve to industrial-scale supplies. Actually, the large fine chemical companies consider the preparation of samples more as a marketing tool (and expense) rather than a profit contributor.

2.4. Laboratory Chemical Suppliers

Before the life sciences industry, colleges and universities, medical research institutions, hospital research labs, government agencies, and other facilities can initiate any chemical research activity they need chemicals (a.k.a. reagents), solvents, and laboratory equipment. The laboratory chemical suppliers offer a large number (tens of thousands) of fine chemicals in small quantities for research purposes. Their combined revenues are about $\$10 \times 10^9$. Major companies or business units are listed in Table 5. Online ordering is possible from all these companies.

Apart from the top five, there are many laboratory chemical suppliers with smaller catalogues geared to specific needs, such as Honeywell Riedel-de-Haën for inorganic chemicals, BioCatalytics, which offers a ketoreductase kit with

Table 5. Laboratory chemical suppliers

	Company		Laboratory chemicals			
	Name	Sales*	Business unit	Sales*	Products	Notes
1	Sigma-Aldrich	2505	Research Specialties	924	167 000	chemicals
2	VWR International	4100	Chemicals	820	750 000	including equipment
3	Thermo-Fisher Scientific	11 790	Laboratory Products Group	578	15 000	fine organic chemicals
5	Johnson Matthey	18 800	Alfa Aesar	124	18 000	research chemicals
4	Tokyo Chemical Industries (TCI)	N/A	Fine Chemicals	N/A	22 000	organic chemicals

* $\$ \times 10^6$ (2011).

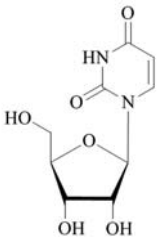
about 100 enzymes, or Chiral Technologies, a division of Daicel, Japan, which offers a range of 175 immobilized and coated polysaccharide chiral stationary phases for use with high-pressure liquid chromatography (HPLC), supercritical fluid (SCF), and simulated moving-bed (SMB) equipment. A selection of *N*-heterocyclic compounds, especially azaindoles, naphthyridines, pyridines, and pyrrolidines, is offered by Adesis, USA. Peptide building blocks are offered by Bachem, Switzerland (9000 products).

3. Products

In terms of molecular structure, one distinguishes first between *low molecular weight* (LMW) and *high molecular weight* (HMW) products. The generally accepted threshold between LMW and HMW is a molecular weight of about 700. The LMW fine chemicals, also designated small molecules, are produced by traditional chemical synthesis, by white biotechnology (see Section 4.2.1), or by extraction from plants and animals. In the production of modern life sciences products, total synthesis from petrochemicals prevails. The HMW fine chemicals, a.k.a. big molecules, are obtained mainly by red biotechnology processes. Peptides and proteins are the most important product categories.

3.1. Small Molecules

Many natural or synthetic LMW fine chemicals contain heterocyclic moieties. Widely occurring natural products are chlorophyll, hemoglobin, nucleosides (e.g., uridine), and the vitamins biotin (H), folic acid, niacin (PP), pyridoxine HCl (B_6), riboflavin (B_2), and thiamine (B_1).



Uridine (1-β-D-ribofuranosyluracil)

In life sciences, eight out of the top ten small-molecule proprietary pharmaceuticals contain one or more heterocyclic moieties; six of them contain an N heterocycle, one an S heterocycle, and one both an N and an S heterocycle (see Table 12). The same 8/10 share of molecules with a heterocyclic moiety is found within the top ten agrochemicals (see [1, Table 11.7, p. 118]. Further examples of pharmaceuticals are the β-lactam and quinolone antibiotics, the benzodiazepine antidepressants and the "-vir" antivirals. Widely used heterocyclic agrochemicals are the dipyridyl and triazine herbicides, the neonicotinoid, pyrazole, and anthranilic diamide insecticides and triazole "conazole" and aminopyrimidine and benzimidazole fungicides.

Even modern pigments, such as diphenylpyrazolopyrazoles, quinacridones, and engineering plastics, such as polybenzimidazoles, polyimides, and triazine resins, exhibit an *N*-heterocyclic structure.

3.2. Big Molecules

Big molecules are mostly oligomers or polymers of small molecules or chains of amino acids. Thus, within pharmaceutical sciences, peptides,

proteins, and oligonucleotides constitute the major categories.

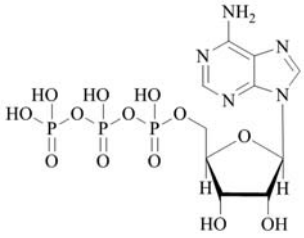
Peptides and *proteins* are oligomers or polycondensates of amino acid residues linked together by a carboxamide group. The threshold between the two is as at about 50 amino acid residues. Because of their unique biological functions, a significant and growing part of new drug discovery and development is focused on this class of biomolecules.

For the synthesis of *peptides*, four categories of fine chemicals, commonly referred to as peptide building blocks (PBBs), are used. In order of increasing sophistication they are amino acids (= starting materials), protected amino acids, peptide fragments, and peptides themselves [5] (see also Section 4.1). Along the way, the molecular weights increase from about 10^2 up to 10^4 and the unit prices from about $\$10^0$ up to $\$10^5$ per kilogram. However, only a small part of the total amino acid production is used for peptide synthesis. In fact, L-glutamic acid, D,L-methionine, L-aspartic acid, and L-phenylalanine are used in large quantities as food and feed additives. Nowadays, about 50 peptide drugs are commercialized. The number of amino acid residues that make up a specific peptide varies widely. At the low end are the dipeptides. The most important drugs with a dipeptide (L-alanyl-L-proline) moiety are the "-pril" cardiovascular drugs, such as enalapril, captopril, imidapril, and lysinopril. Also the artificial sweetener Aspartame (*N*-L-α-aspartyl-L-phenylanaline 1-methyl ester) is a dipeptide. At the high end there is the anticoagulant hirudin (MW ≈ 7000), which is composed of 65 amino acids.

The total production volume (excluding Aspartame) of chemically synthesized, pure peptides is about 1500 kg and sales approach $\$500 \times 10^6$ on the API level and $\$10 \times 10^9$ on the finished drug level. The numbers would be much higher, about 10% of total pharma sales, if also peptidomimetics and APIs which contain peptide sequences as part of a molecule were included, such as the above mentioned "-prils" or the first generation anti-AIDS drugs, the "-navirs". The bulk of the production of peptide drugs is outsourced to a few specialized contract manufacturers, such as Bachem Switzerland; Chengu GT Biochem, China; Chinese Peptide Company, China; Lonza, Switzerland; and Polypeptide, Denmark.

Proteins are very high molecular weight ($M >$ 100 000) fine chemicals consisting of amino acid sequences linked by peptide bonds. They are essential to the structure and function of all living cells and viruses and are among the most actively studied molecules in biochemistry. They can be made only by advanced biotechnological processes, primarily mammalian cell cultures (see Section 4.2.2). Monoclonal antibodies (mAb) prevail among human-made proteins. About a dozen of them are approved as pharmaceuticals, of which five rank among the top ten drugs (see Table 6).

Oligonucleotides are a third category of big molecules. They are oligomers of nucleotides, which in turn are composed of a five-carbon sugar (either ribose or desoxyribose), a nitrogenous base (a pyrimidine or a purine), and 1–3 phosphate groups. The best known representative of the nucleotides is the coenzyme adenosine triphosphate (ATP, $M = 507.2$). The maximum length of synthetic oligonucleotides hardly exceeds 200 nucleotide components.



Adenosine triphosphate

Peptides and *oligonucleotides* are now often summarized under the heading "tides". They are used in a variety of pharmaceutical applications including antisense agents, which inhibit undesirable cellular protein production, antiviral agents, and protein binding agents. An antisense drug in advanced (phase III) development is Genzyme's cholesterol-lowering drug Kynamro (mipomersen).

Antibody–drug conjugates (ADC) are a combination between small and big molecules. The small-molecule parts, up to four different APIs, are highly potent cytotoxic drugs. They are linked with a monoclonal antibody, a big molecule which is of little or no therapeutic value in itself but extremely discriminating for its targets, the cancer cells. The first commercialized ADCs were Isis's Formivirisen and, more recently,