The Impact of Off-Label, Compassionate and Unlicensed Use on Health Care Laws in preselected Countries

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Abstract

Objective

- To compare the effects of NDU on pharmaceutical legislation in selected industrial countries and to determine strategies brought forth by NDU.
- to develop a general regulatory approach to the management of NDU.

Methods

- Semi-structured qualitative interviews,
- comparison of laws, and
- Literature research

Setting

- Canada, the U.S., the U.K., Japan, France, Germany, Switzerland, Austria, and the transnational E.U.

Results

- there is a circumstantial need for off-label, unlicensed and compassionate use,
- but also isolated evidence suggesting intermittent non-rational NDU.
- evidence of legal obligations for physicians to perform off-label, unlicensed and compassionate drug use is found.
- a demand for information on NDU on behalf of HCPs was present.
- cross-liability for HCPs and MAH can be deduced.
- regulatory strategies include incentives for new indications (a) limited to one year or (b) restricted to (i) paediatrics or (ii) rare disorders.

Conclusion:

- Patient's needs and physician's requirements must be met, but patients must also be protected from marketing-induced malpractice.
- Well-balanced information from independent sources is necessary
- Coverage of claims must be transparent
- Immediate and long term solutions should be sought in order to ensure that patients needs are met without any gaps in supply
- Low administrative expenses should be aimed at
- Strategies for access to NDU must extend beyond paediatrics, rare disorders and must not be limited to a period of time

Background:

- Over half of the children (421; 67%) received an unlicensed or off label drug prescription during their stay in European, paediatric hospitals. [1]
- In 506 (25%) of 2013, prescriptions drugs were used in either an unlicensed (139) or off label manner (367) in paediatric units. [2]
- Unlicensed drugs in paediatric, out-patient care amounted to 16.6% (11 288) of the total prescriptions and were mainly dermatological and liquid preparations. [3] (figure 1)
- Among office-based physicians, most (575 million [79%]) were for FDA-approved indications, many drug mentions (150 million [21%]) lacked FDA approval for the condition they were used to treat. [4]

In commonly and widely studied settings nonlicensed drug use may be supervalued e.g. in children in comparison to less studied medicinal areas such as obstetrics.

Figure 1: Extemporaneous preparation is often referred to as 'off-label' or 'unlicensed' medicines.

Country \ Call	Initial [N]	Response [N]	Appointments [N]
Japan	7	1	2
Canada	10	8	2
U.S.	68	13	7
E.U.	9	6	5
Switzerland	7	7	4
U.K.	13	13	10
Germany	31	15	9
Austria	7	5	4
France	9	4	2
Total [N] (%)	161 (100)	98 (61)	45 (28)

Table 1: There was 61% interest in participating, of whom 46% took part in an interview

Documentation

- Philips Digital Voice Tracer 7680
- MAXQDA 2007 R270608-ENG (for Windows 2000, Windows XP, Windows Vista). Belous, I., n.p.

Validation

- (a) face validation, (b) piloting of the interview topic guide, and (c) content validation

Methods:

Semi-structured interviews were selected due to their circumstantial flexibility whilst enabling comparison of covered topics.

Triangulation (literature research, comparison of laws and expert survey) was chosen to address the research problem counterbalancing disadvantages of single approaches

Selection

- Inclusion criteria for participation in this survey were (a) affiliation to a stakeholder, (b) point of contact to NDUs, and (c) willingness to provide insightful information.
- in-depth interviews (t = 9 to 180 minutes) either face-to-face or by telephone survey

Determination

- (a) medical or pharmaceutical societies, self help groups, HCP associations, federations and confederations, (b) "regulatory" bodies, either a supreme or higher federal authority and federal state authorities, (c) MAHs denoting pharmaceutical companies or enterprises or their federal associations, (d) funding agencies including institutes for cost benefit analysis, and (e) "academia" including research professors, lawyers and authors of scientific papers

Table 1 on the upper left illustrates the recruitment procedure.

Results:

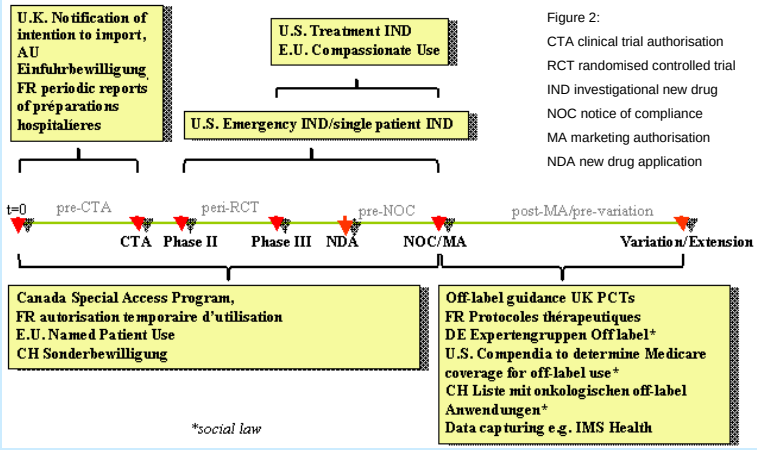

Figure 2:
CTA clinical trial authorisation
RCT randomised controlled trial
IND investigational new drug
NOC notice of compliance
MA marketing authorisation
NDA new drug application

Program	Number (y)		Σ	PID		
EU Compassionate Use	1 (2010)	X	n	IND	-	m/H
U.S. treatment IND	4.6/y (1997-2004)	√	n	IND	30d	m
FR ATU products	~ 200 (2008)	√	1/n	B	>48h	m/p
U.S. e/sp IND	659/y (1997-2004)	√	1	B	2d	H
AU Einfuhrbewilligung	925 (2006)	√	1/n	IMP	2w	m/p
CH Sonderbewilligung	3197 (2002)	√	1	B	-	H/p
FR ATUn	~ 20 000 (2008)	√	1	B	>48h	p
CA SA- requests	~ 30 000 (2007)	√	1	B	5d	H
UK Notif. of import intention	~117 000/y (2002-2008)	√	1	IMP	28d	W

Table 2: y=year, g=group, IND= investigational new drug, m=sponsor, h=physician, d=day, s=single, b=both, p=pharmacist, IMP=Imported medicinal product, W=wholesaler, PID=product identity, Quan=quantity

Table 2, above: Data illustrating the demand and use made of selected programs

Figure 2, left: Selected programs on a time axis of pharmaceutical development

Table 3, below: Characteristics of selected programs

Table 4, bottom left: Merger of all observed solutions to a proposed comprehensive approach

	EU	USA	Ca	FR	CH	AU	DE	JP	UK
Program (y)	Compassionate use (2004), NPU (2001)	Treatment / single patient / emergency IND (mid 80s)	Special access programme (mid 60s)	ATUn&c (1986)	Sonderbewilligung (2002)	Einfuhrbewilligung (2002)	Härtefallregelung (2010)	Planned	Intention to import (2005)
Product	IND	IND	HMP, VMP, HerMP	MP	HMP, VMP	MP	MP	N/a	MP
Applicant	Sponsor	Sponsor/practitioner	Practitioner	Sponsor, hospital pharmacist	HCP	Sponsor, pharmacist	Proposed	N/a	Wholesaler
Form	At MS level	Protocol, phone, rapid request	Rapid request	Form	Form	Form	Application	N/a	Form
N° of patients	Group/individual	Group/individual	Individual	Group/individual	Individual	Group/individual	Group	N/a	Individual
Timetable	At MS level	30 / 1-2days	5 business days	24-48h	No data	2w	N/a	N/a	28d proh. right

Table 3: As-is state of June 2009 (updated in 2010) as regards NDU programmes

[t]/ NDU	Compassionate use		Unlicensed use		Off label use
	Expanded access	*Named patient use*	*Imports*	*Extemporaneous preparation*	
Short term	**Approval procedure**	**Notification subject to prohibition**		**Data capturing**	
Long term	**MA**		**Standard MA**		**Data driven templates**
	Non approval				

Table 4: Proposed solutions merging the observed approaches to an overall management of NDU

Discussion:

Proposed solutions are

- the amendment of templates for patient information leaflets by competent authorities to include scientifically validated off-label use,
- full development/suspension of medicinal products used compassionately, and
- modelled on German procedure, a modified standard MAA for essential unlicensed drugs.

Recent developments:

- UK
  - scheme to provide earlier access to investigational medicines (Phase II) approved by ministerial group
  - under NHS up to one year
  - MHRA to review application within 75 days
- DE
  - Compassionate use regulation drafted for supply of critically ill patients
  - notification of competent authority / detailed documentation

References

[1] Conroy S et al; Survey of unlicensed and off-label drug use in paediatric wards in European countries. BMJ 2000;320;79-82.

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[3] Schirm E, Tobi H, de Jong-van den Berg LTW. Unlicensed and off label drug use by children in the community: cross sectional study. BMJ 2002;324:1312-1313.

[4] Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based *physicians. Arch Intern Med. 2006;166:1021-1026.*

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