Can drug delivery systems deliver value in the new pharmaceutical marketplace?

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Introduction

John Snow, pioneer in epidemiology and anaesthesiology, designed and built the first drug delivery system, to control the proportion of chloroform or ether in inspired air [1]. A century later, in the 1950s, work began on various means to retard release of drug from solid dosage forms, but the notion of achieving sustained control over the rate of drug release *in vivo* from dosage forms dates from about 1970 [2, 3]. Rate control brings the ability to specify duration of drug delivery, and a change in the definition of pharmacological strength from quantity of drug released to rate of drug release [4]. Not all delivery system-based pharmaceuticals have been so-labeled, but it is a natural evolution, paralleling the development of pharmacometrics [5].

My aim is to review the main medical and economic features of such products, all of which have been developed since the first delivery systems product for ambulatory care was approved in 1974 [6]. I do not consider delivery systems for localized drug delivery, or liposome-based products, which have just begun to reach the market.

Table 1 is a listing of delivery systems products, based on recent market research [7]. About four dozen products comprise the category. The size of the American market makes U.S. sales a convenient reference point, and an index of clinical use. As a pathway of innovation, delivery systems products can be compared with new chemical entities (NCEs). The 4 dozen delivery system products contrast with about 600 NCEs approved since the mid-1970s. Thus, delivery systems have been a smaller pathway of innovation than had been earlier projected [2–4].

Example 1 Prolonging the action of short-acting, parenterally administered peptides

An important application of delivery systems is to enable practical clinical use of exceptionally short-lived agents, exemplified by two peptide products, leuprolide [8] and goserelin [9], derivatives of gonadotropin-releasing hormone. These products are 3-monthly injectables, which release peptide continuously for gonadotropin suppression in the management of carcinoma of the prostate and other conditions benefited by suppression of endogenous androgens or oestrogens [8, 9].

Transforming the duration of action of a single dose of peptide from minutes to months is an important achievement that will undoubtedly be repeated with other peptides. The alternative is frequent re-injection, as with insulin, which

incurs many direct and indirect costs, with inevitable compliance problems in some patients. Thus, the ability to formulate a short-lived peptide into a long-acting product is a notable advance. The unattained holy grail remains, of course, insulin, whose delivery is complicated by widely fluctuating metabolic needs, a narrow therapeutic index, and difficult physical chemistry.

Controlling the delivery of 150–400 dalton organic molecules

Most of the delivery system developments have involved organic molecules in the 150–400 dalton range of most drugs. Three products in this category seem best to exemplify how drug delivery systems can usefully change the expressions of drug action. Duration of drug action is prolonged in all three, and, in two, rate-controlled drug delivery has improved the drug's usual side-effect profile.

To contrast conventional and delivery system formulations, I have relied mainly on labeling claims approved by the U.S. Food & Drug Administration (FDA). The FDA's judgments have three useful aspects: (a) they are based on review of a database the completeness of which is legally mandated; (b) the resulting claims are approved against a legal mandate for proof of efficacy in adequately controlled clinical trials; (c) the approved claims for efficacy and safety define the resulting product's promotional charter in the largest marketplace. These more or less guarantee rigor, but not, of course, omniscience. A concluding section considers whether new, inevitably more costly forms of older drugs have a role in a marketplace where cost-sensitivity looms larger than ever, eclipsing its more appealing sibling, value-sensitivity.

Example 2 The levonorgestrel implant (Norplant®): improved efficacy through radically prolonged duration of action

Among the oral steroidal contraceptives, once-daily levonorgestrel 'minipill' has the poorest record of contraceptive efficacy—see Table 2 and [10]. In contrast, levonorgestrel in a 5-year implant has the best record of contraceptive efficacy (Table 2; [10]). The implant radically changed both duration and reliability of the contraceptive action of levonorgestrel.

Duration

The implant's 5-year duration depends on two factors [11, 12]. First is the slow permeation, by solution diffusion, of levonorgestrel through the silicone rubber (dimethylsiloxane/methylvinylsiloxane copolymer) walls of tube-shaped capsules. Second is the high molar potency of the steroid: a delivery rate of 30–85 µg day⁻¹ is required for contraceptive action. Thus, about 110 mg of drug is delivered during a

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\$1250 million

Oral nifedipine controlled-release (Pfizer, Bayer; ALZA)

\$900–1000 million

Injectable LH-RH analogue (Takeda, TAP-Abbott)

Oral diltiazem controlled-release (HMR; Elan)

\$300–600 million

Injectable goserelin (Zeneca)

Transdermal estradiol (Novartis; ALZA)

Transdermal nitroglycerin (Novartis; ALZA)

\$100–200 million

NORPLANT implant of norgestrel (American Home; Population Council)**

Transdermal fentanyl (Janssen; ALZA)

Transdermal nitroglycerin (Schering-Plough)

Oral potassium chloride controlled-release (Schering-Plough)

Oral glipizide controlled-release (Pfizer; ALZA)

Oral ketoprofen controlled-release (American Home; Biovail)

Oral propranolol controlled-release (American Home; Forest)

Transdermal nicotine (HMR, SKB; ALZA)

Oral isosorbide mononitrate controlled-release (Schering-Plough)

Oral diltiazem controlled-release (RPR; Jago)

Oral verapamil controlled-release (American Home; Elan)

\$50–80 million

Transdermal nicotine (J&J; Cygnus)

Transdermal nicotine (Novartis; Lohmann)

Oral theophylline controlled-release (Schering-Plough)

Transdermal nitroglycerin (multi-source)

Oral naproxen controlled-release (American Home; Elan)

Transdermal clonidine (Boehringer-Ingelheim; ALZA)

\$20–45 million

Oral prazosin controlled-release (Pfizer; ALZA)

Oral verapamil controlled-release (Searle; ALZA)

Oral diltiazem controlled-release (Forest; Biovail)

Transdermal nicotine (American Home; Elan)

Oral salbutamol controlled-release (Glaxo; ALZA)

Under \$20 million

Transdermal scopolamine (Novartis; ALZA)***

Transdermal testosterone (SKB; Theratech)

Transdermal testosterone (ALZA)

Oral theophylline controlled-release (UNI-DUR, Schering-Plough)

The table is adapted from [7]. The authors overlooked NORPLANT, so those data come from a different source and may not be entirely comparable with the other figures. No products had sales in the gaps between the ranges.

Sales levels are for 1996, with exceptions as noted.

The company names in parentheses list the principal marketer first. The developer, if different from the principal marketer, is listed after the semicolon.

The total sales level of multi-source products were: oral diltiazem controlled-release, *circa* \$1070 million, transdermal nitroglycerin, *circa* \$580 million, transdermal nicotine, *circa* \$350 million.

**1993 figure; NORPLANT sales were over \$140 million in 1992, but then fell, as discussed in the text, to today's levels in the \$2–3 million range.

***1994 figure, prior to sales interruption due to manufacturing problems; manufacturing resumed in early 1997.

Table 1 Leading drug delivery systems products by estimated manufacturer-level sales* (US\$).

5-year period. Drug is released from six equally-sized tubes of 2.4 mm diameter and 34 mm length, each containing 36 mg of drug, for a total of 216 mg. The total volume of the implants is about 920 μ l, of which about a quarter is occupied by drug, which is released by solution diffusion, driven by residual drug within the reservoir. About half of the drug remains within the tubes after 5 years, providing

not only the motive force for continuing drug release but also an unspecified margin of safety against two kinds of variance: (a) units that exhaust soonest from a combination of lowest drug loading and highest release rate, and (b) delayed institution of follow-on contraception. As drug release continues, void space develops within the tubal lumens, and is a main factor in the gradual decline in release

Table 2 Rated efficacy of leading contraceptive modalities.

Method	Conception rate (% of women conceiving during first year of use)	
	Lowest expected*	Typical**
NORPLANT System	0.09	0.09
Male sterilization	0.1	0.15
Female sterilization	0.4	0.4
Injectable progestagen	0.3	0.3
Oral contraceptives		3
combined	0.1	N/A
progestin only	0.5	N/A
IUD		
progesterone	1.5	2.0
copper T 380A	0.6	0.8
Condom (male) without spermicide	3	12
(female) without spermicide	5	21
Cervical cap		
nulliparous women	9	18
parous women	26	36
Diaphragm with spermicide	6	18
Spermicides alone	6	21
No contraception	85	85

Slightly modified from [11]. *method effectiveness. **use effectiveness [16].

rate over time. All this adds up to reliable delivery from an implant small enough to create little distortion at the implant site.

Reliability in use

The implant's automaticity means that few demands are put on the patient to insure effectiveness: (a) at the 5 year point, to institute follow-on contraception to replace waning implants, which are recommended for removal at that time; (b) to take adequate precautions in the event of concomitant use of a few agents, e.g., phenytoin, carbamazepine, rifampicin, which increase the clearance of levonorgestrel, resulting in sub-contraceptive concentrations in plasma [11].

Minipill vs implant

The minipill loses contraceptive effectiveness at about the 27th hour after the last-taken dose [10]. Thus, patients must take the once-daily dose within an exceptionally narrow time interval of $24 \pm \text{circa } 2$ h. This brief margin for error in dose timing is the shortest of all once-daily products for which such limits are known. In contrast, the widely-used, combined oestrogen-progestin oral contraceptives have a 12–24 h margin for error—the British recommendation being 12 h [13], and the American being 24 h [14]. These timing requirements contrast with evidence that only about 15% of unselected patients maintain such punctuality in dosing [15]. Self-selection naturally plays a role in contracep-

tive choices, and probably accounts for the initial rush of patients to each new long-acting contraceptive.

Method- vs use-effectiveness

Unlike oral or barrier contraceptives, the implant functions without human intervention, except for replacement after 5 years, and attention to a few drug-drug interactions. Thus the implant's use-effectiveness is essentially equal to its method-effectiveness, the latter being the estimate of efficacy under conditions of correct use, the former being estimates of efficacy under various conditions of 'typical' use, which, with contraceptives, differ greatly with age, marital status, socio-economic factors, child-bearing plans, and so forth [16]. Table 2 reproduces the information provided in U.S. labeling of the various contraceptives on method and use effectiveness. The implant provides the lowest conception rate of any contraceptive product and a reference figure for method effectiveness, from which one can judge the extent to which compliance problems degrade outcomes of oral contraceptive use. Observations on contraceptive failure in everyday practice show, too, the prevalence and impact of compliance problems [17, 18], now beginning to be documented by objective methods for monitoring drug exposure in contraceptive trials [15–17].

Drop-outs

Early dropouts occur for many reasons; in clinical trials of the implant, about 20% dropped out within the first year,

with relatively few thereafter [8]—rates similar to those of other contraceptives. Mid-cycle spotting and irregular bleeding patterns are one reason. They appear to be about as common with the implant as with the minipill—a drug-related problem that the delivery system did not ‘fix’.

What is the comparator?

It is natural to compare implant and oral forms of norgestrel, but in the marketplace the implant’s advantages over the minipill have little impact because the latter is little-used. The implant competes with, and thus is compared with, all contraceptives, plus sterilization (Table 2).

Success factors

Norplant was initially very popular, but two types of adverse publicity soon arose: difficulties in removal of the implants, and alleged safety problems of silicone rubber. The latter gained official sanction in the FDA Commissioner’s declaration of a still-continuing moratorium on the sale of silicone rubber breast implants, aggravated by widely publicized but unsubstantiated claims made by self-styled expert witnesses in product liability court proceedings—so-called ‘junk science’—about adverse effects of silicone rubber implants [19]. From a high of nearly US\$200 million in 1993, the sales of levonorgestrel implants fell to under \$10 million in 1996, joining the intra-uterine devices in the category of long-acting contraceptives of short-lived popularity.

Overview

The levonorgestrel implant radically transformed an agent that, in oral form, is so demanding of punctual compliance as to be a reliable contraceptive for only a small minority. The gap in efficacy between the oral and implant forms of the same drug highlights how imperfect compliance can undermine effectiveness. The implant is not a panacea, for it has the undesirable bleeding patterns that are seemingly inherent in progestin-only contraception. The implant’s superior efficacy is noteworthy, but bad publicity regarding difficulties with removal and hysteria about hazards of silicone implants ended its initial popularity.

Example 3 The oral osmotic delivery system form of nifedipine (Procardi-XL®; Adalat-Oros®)

The most common side-effect of nifedipine in the conventional, immediate-release dosage form is ‘reflex tachycardia’ (RT)—flushing, heat sensation, dizziness, light-headedness, giddiness, and palpitations. Labeling indicates that 25–27% of patients experience some combination of these symptoms, against an incidence in placebo recipients of 8–15%, and describes them as ‘expected consequences of the vasodilator actions of nifedipine’ [20]. The data come from trials involving patients with coronary heart disease and angina, the principal indication for immediate-release nifedipine.

Stimulus for a delivery system for nifedipine came from a small pharmacodynamic study, which indicated that the trigger for RT is a high rate of increase of the plasma concentration of nifedipine [21], supporting the inference

that constant-rate oral delivery of nifedipine could avoid RT by avoiding high rates of increase in the concentration of drug in plasma [22]. When developed and tested, the rate-controlled oral form of nifedipine was found to effect smooth reductions in arterial pressure with a <3% incidence of RT [23]. These features allowed rate-controlled nifedipine to be registered for use in mild-moderate hypertension [23].

The product’s most common side-effect is peripheral oedema, occurring in about 10% of treated patients—no different from that with the immediate-release form [20, 23]. As with levonorgestrel, the delivery system did not ‘fix’ all drug-related problems.

The delivery system releases its content of nifedipine by an osmotic mechanism at an essentially constant rate over an 18-h period—long-enough to qualify the product for once-daily administration (23) *vs* thrice-daily for the immediate-release form [20]. While both rate-controlled and immediate-release forms lower blood pressure, this action is inconsistent with the immediate-release form, which is labeled with a caution against its use for hypertension [20]. Both forms are indicated for vasospastic and chronic stable angina pectoris [20, 23].

Rate-controlled nifedipine entered the U.S. market in the midst of a major shift in initial therapy for hypertension, away from β -adrenoceptor antagonists and thiazide diuretics, toward angiotensin converting enzyme inhibitors and calcium channel antagonists [24]. At that time, diltiazem was the leading calcium channel antagonist for first-use in uncomplicated hypertension. Rate-controlled nifedipine soon captured that position, and, for a variety of reasons, the relative importance of which is uncertain, grew rapidly in sales to become by the early 1990s the largest-selling cardiovascular product in the history of the U.S. marketplace.

Success factors

Causal inferences about market success are as uncertain as those about other aspects of therapeutics, so let the reader be wary about the accuracy of what follows. First, the timing of the product’s introduction was undoubtedly crucial. It seems that nifedipine in conventional form was appealing enough to gain wide usage, embodying and popularizing the concept of calcium channel blockade, but still troublesome enough, mainly because of RT, to create good opportunity for calcium antagonists without RT. Diltiazem represents a molecular design solution to the RT problem; rate-controlled nifedipine, a pharmaceutical solution, allowing nifedipine to have a second, very successful course in the marketplace. As Table 1 shows, controlled-release forms of diltiazem run a close second in sales, an echoing success unrelated to changes in RT, which was never a problem with diltiazem.

Conversion from a thrice- to a once-daily dosing regimen undoubtedly played some role. Strong conviction prevails, notwithstanding contrary data and analysis [25–28] that once-daily dosing is best in hypertension and other chronic conditions. Probably more important contributors to success, however, were the product’s indication for use in hypertension, the virtual elimination of RT, and the timing of its market entry.

Example 4 Transdermal scopolamine for motion sickness (Transderm-scop®)

Scopolamine and atropine are the prototypical anticholinergics, with four pages of description in a leading pharmacology text [29]—probably the highest ratio of textbook ink to actual use of any drugs. When given by injection or rapid-release oral forms, these drugs elicit a panoply of dose-dependent effects, mostly unpleasant at low doses, and toxic or lethal at high doses [29]. In contrast, delivery of scopolamine continuously at low rates avoids or minimizes many of the 'classical' parasympatholytic effects [30].

In vivo, the product produces an initial, small surge of drug release, followed by an essentially constant rate of scopolamine delivery for 3 days, gradually tapering thereafter. Drug release occurs by diffusion from a central reservoir across a microporous membrane, which has a permeability to scopolamine that is about a fifth that of the average permeability of human skin to the drug, thus minimizing the influence of variations in skin permeability [31]. The reservoir contains an excess of drug, needed to maintain drug release for the claimed duration. The selected, low rate of scopolamine delivery prevents motion sickness in about three out of four patients; about two-thirds experience a sensation of dry mouth, and about one-sixth experience drowsiness [30], comparing favourably with diphenhydramine, a widely-used, over-the-counter inhibitor of motion sickness, with a high incidence of drowsiness. With repeated use, transdermal scopolamine causes changes in ocular accommodation, consistent with its anticholinergic actions, but the essential constancy of this effect facilitates optical correction, if needed [31]. Drowsiness is both a side-effect of scopolamine and part of the motion sickness syndrome, so can represent either.

Before the advent of the histamine H₂-receptor antagonists, anticholinergics were used to inhibit gastric acid secretion in peptic ulcer disease, with major efforts to find anticholinergics with greater selectivity of acid-inhibitory action. Transdermal scopolamine also inhibits gastric acid secretion [32], which is a relatively selective effect because it is accompanied by the few actions described above. No label claims are made for this effect, which had lost its importance after the advent of H₂-receptor antagonists.

As the product came into relatively wide usage, it appeared that a tiny fraction of treated patients—in the order of 1 in 25000—experience classical CNS effects of scopolamine, with memory disturbance or hallucinations [30]. The basis for these exceptional responses is not known.

In summary, one can say that the delivery system succeeded in attaining a novel and useful degree of selectivity of action from an agent of great pharmacological interest, but so unselective in conventional dosage forms as to have had very limited therapeutic utility. It conforms to a model of drug action, called 'steady-state pharmacology', resembling the Gillespie scheme for the actions of ether at varying concentrations in inspired air [33–35]. The rate-controlled ophthalmic form of the parasympathomimetic agent, pilocarpine, has an analogous story of enhanced selectivity of action [6]. These products illustrate why rapid-release formulations should not be the automatic standard of reference for basic pharmacologic characterization.

Success factors

Transderm-Scop was the first transdermal delivery system product, followed by transdermal forms of other agents (Table 1). It entered the U.S. market just as the FDA was finishing a long effort to rid over-the-counter cough-cold products of traditionally present anticholinergics for which no need could be demonstrated. Thus, timing was wrong for the product to achieve early over-the-counter status, so it has remained prescription-only, making it more difficult and costly to obtain than its main competitor, over-the-counter diphenhydramine. Intermittent manufacturing difficulties have made supplies irregular, but the product has a strong following among boaters, and has found off-label use in some patients with persistent vertigo, though it remains a relatively small product (Table 1).

Looking back, looking ahead

The examples illustrate the main ways in which value can be added by the use of a delivery system—prolonged action, curtailment of some troublesome side-effects, and/or enhanced selectivity of action. Each of the products listed in Table 1 has its own mix of these attributes.

Price vs value

Missing, though, is solid evidence on the economic impact of using delivery systems. As widely-used agents lose their patent protection and gain multiple manufacturers, competition brings the pricing of conventional forms down to pennies/day, *vs* \$1–2/day pricing for delivery system forms.

For some people, value is inversely related to price, with no contest between pennies and dollars pricing. For a few, value is directly related to price, making the delivery system an easy choice. For the rest, the key issue is whether use of the delivery system, *vs* the conventional form, can result in aggregate savings in care costs which exceed the difference in the acquisition costs of the two products. Potential bases for such savings are described in [36], but specifics are lacking.

Compliance claims

A recurring claim for drug delivery systems is their ability to 'improve patient compliance', mostly based on extrapolation from an old study [37] that has been thoroughly discredited [25]. Long-acting implants, as we have seen, achieve uniform effectiveness by automatic drug delivery, without human intervention, but it is not clear whether the reductions in dosing frequency with oral or transdermal forms make material improvements to the usual goal of continuity in drug exposure. 'Better compliance' certainly can be a means to better outcomes, but it is not an end in itself, and may be a poor surrogate for better outcomes, because some recommended regimens are suboptimal [38]. Indeed, one of the benefits of work to develop a delivery system product is its inevitable challenge to the original regimen, which may end up considerably changed. Recent advances in measurement and understanding of drug regimen compliance highlight the importance of assessing drug exposure, rather than just counting doses taken/untaken,

and of designing regimens that afford patients reasonable latitude for errors in dose timing without loss of therapeutic drug action [39]. Pushing a drug regimen to unrealistically narrow limits on dose timing is likely to result in lapses in drug exposure, because strict punctuality in dosing is a relatively infrequent virtue [39].

Chemistry vs delivery systems

Delivery systems both complement and compete with medicinal chemistry to achieve pharmaceuticals that act selectively for a therapeutically apt length of time. The membrane technologies involved began as a sharp departure from conventional means of drug formulation, but the distinction is fading as concepts mature, patents expire, and the range of technologies available to drug formulators broadens. This evolution will inevitably broaden the usage and lower the prices of delivery systems-based products.

Market changes

The pharmaceutical market is undergoing unprecedented changes, driven by its transition from a few, low-cost products of proven efficacy, to many, high-cost products of proven efficacy. This transition is the triumphant dividend of the huge public and private investments in biomedical research that began during World War II and continued to grow thereafter. It also reflects the special economics of health care, in which prices rise, rather than fall, with increasing competition.

Since the early 1960s, product registration in most countries has required prior proof of efficacy, conventionally achieved by rejection of the null hypothesis (NH) in placebo-controlled trials. Taken literally, rejection of the NH supports a claim that the new product is 'not no better than nothing'—a good claim for value of the first product with a given therapeutic indication, but insufficient for subsequent, like-indicated products, except for those who find value in novelty *per se*. The perceived value of novelty is waning, most rapidly in marketplaces where formulary committees or other institutional bodies make the purchase decisions.

Price vs value in purchase decisions

Purchasing lowest-priced pharmaceuticals is the simplest decision rule in a crowded marketplace, but it does not guarantee the best value, which is defined by comparative costs of overall treatment and clinical outcomes. Such evaluation is difficult because these are multi-faceted issues, occurring on widely differing time scales from one medical situation to another. Thus, comparative value is often difficult to assess, so the transition will probably be slow from a cost-sensitive to a value-sensitive market. Meanwhile, the company that has invested in developing a delivery system-based form of a generic drug can expect difficulty in competing with a conventional form of the same agent priced at pennies per day.

In a rational marketplace, one might expect the higher-priced product to prevail if it can be shown to deliver both superior clinical benefits and saving in overall care costs,

with due allowances for the time-value of money and the time needed to recoup the savings. Yet obstacles exist, even in systems of managed care, e.g., when the higher-priced, higher-value choice is rejected because costs and savings show up in different budgetary categories that are not easily integrated. This problem is endemic in large organizations and is not peculiar to health care. It is heightened when prices of different forms of the same drug substance differ widely. Implicit in this problem is a challenge to the information technology that underpins healthcare accounting.

The need is clear for demonstrations that delivery systems-based forms of established pharmaceuticals do indeed deliver genuine value; even so, they will probably face difficulties in the marketplace until value can be confidently reckoned and take precedence over price.

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