Improving the drug selection and development process for combination devices

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Combination devices are at the interface of both pharmaceutical and medical device research. While there have been several notable successes in bringing combination devices to market there are drug selection criteria that both the pharmaceutical and medical device companies need to consider. A successful combination device creates a product that has efficacy greater than the sum of the parts. However, failure to address some aspects of the drug or biologic properties in enough detail could result in a suboptimal product, creating a challenging legacy for future iterations. This review addresses the many dimensions including opportunities and challenges of combination device development from both the device and pharmaceutical perspectives.

The past several years have witnessed combination devices, consisting of two or more regulated components such as a device that may contain a drug and/or biologic [1,2] (usually in a polymeric matrix), become multibillion dollar products as they are used in millions of patients. In contrast to the low success rate for drug development as described in this [3] and many other journals in recent years, medical devices have a higher success rate with drug-eluting stents suggested to have a development and launch success rate of about 1 in 6 [4], taking four to eight years and costing approximately $250 million [5]. This is partly because of the fact that the drugs involved have already gained regulatory approval. Although very recently there has been increasing scrutiny of combination devices such as drug-eluting cardiovascular stents due to late stage complications including late thrombosis compared with bare metal stents [6–8], there is considerable interest in developing combination devices such as peripheral stents, orthopedics, indwelling catheters, dental implants, surgical meshes, wound dressings, ophthalmic implants, sutures, and even artificial organs [2,9].

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A lot of attention in the literature has been paid to inert coatings and biodegradable polymers. By contrast, very little has been written about drug selection for combination devices, which in many ways could have a greater impact on the success of the device, both in the clinic and in the marketplace. From both the medical device and pharmaceutical perspective, there is an inadequate understanding of the requirements of such combination devices and the criteria for selecting the drug, even for large conglomerate companies. From the medical device side, engineers have considerable knowledge about processing and testing their particular kind and class of device. For example, most metallic implants require accelerated fatigue tests [10,11] and studies around corrosion properties [12], which would be completely foreign to a pharmaceutical company. From the pharmaceutical side, there is ample knowledge about systemic toxicity and oral pharmacokinetics and the like. However, when one considers the combination of a drug with a device, there may be issues, both engineering and toxicological [13], that are very little known by either the pharmaceutical or the medical device company that need thorough preclinical investigation, such as sterilization methods and biopharmaceutics of the coating mixture [14]. Clinically, the combination device may also behave differently than

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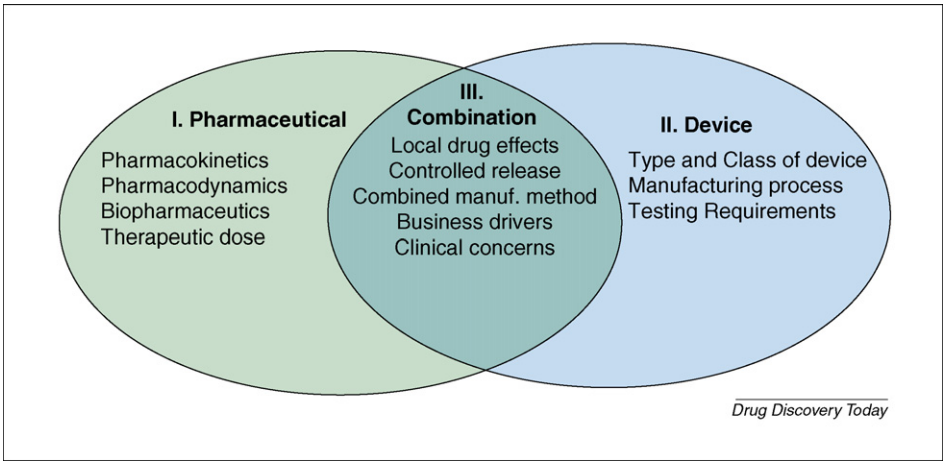

FIGURE 1

A Venn diagram presenting a high level view of combination device considerations discussed in this article.

would be predicted from the sum of the two parts, with possible concerns in local versus systemic toxicity and the pharmacodynamics and efficacy of the desired response [2].

This article aims to address the drug selection criteria that both the pharmaceutical and medical device companies need to consider to successfully develop a combination device. The format we will take follows the Venn diagram shown in Figure 1 in dividing the important criteria to consider in combination device development into three groups: the pharmaceutical, the medical device, and the combination device perspective. We will now discuss the three sections and subtopics of this diagram in detail. We will not address drug delivery vehicles such as chemoembolization devices [15], nasal vaccine delivery, pulmonary insulin, transdermal delivery, or other drug delivery devices that incorporate microtechnologies or nanotechnologies that are beyond the scope of this present article [1].

Important criteria to consider in combination device development

Pharmaceutical

From the pharmaceutical perspective, there are several factors that should be considered when developing a drug, which are well known to many of those in the pharmaceutical industry, but possibly less well known to those in the medical device industry. The local pharmacokinetics (PK) and pharmacodynamics (PD) will need to be assessed to insure optimal efficacy. However, the animal models that are used *in vivo* for pharmaceuticals may not be the appropriate models for the device. For example, in coronary stent delivery the pig heart is commonly used for the anatomical similarities to humans, but this implies the model is limited to the porcine PK/PD, which may be a suboptimal predictor for human [13], and which may only be discovered in randomised clinical trials. An implant clearly is more akin to an intramuscular or intravenous dosage form, rather than an oral drug, hence the properties of these molecules need not be biased toward high oral bioavailability. Metabolism will certainly be different because of the non-systemic dosage and because of the variable expression of drug metabolizing enzymes in different tissues where the device resides. Depending on the implantation site, protein binding may be an important factor to consider, in order to maintain local concentrations of the drug [16]. There has been some pharmacokinetic modeling [17] of drugs used in devices and we envisage that this will be increasingly important in their future development.

The mechanism of action of the drug is a key consideration: which target or targets are the goal and whether they are present in the tissues in which the device is presented. Receptor subtype selectivity may be more critical in some tissues such as the heart, than in other tissues, such as other parts of the vasculature. Additional practical requirements are the targeted dose of the drug and its therapeutic range, which will dictate whether there is likely to be any local toxicity, compared with the known systemic activity of the molecule. Depending on the size and type of the device, dosages may be limited to several hundred micrograms (paclitaxel and sirolimus ~140 $\mu g/cm^2$ per device [2]) or less for the duration of the implant, compared with milligrams when given systemically (Table 1).

The biopharmaceutics of the drug are also important to evaluate, and again there are differences to note versus other dosage forms. For example, in most cases the drug will be in an amorphous, rather than crystalline state on the device, because of typical coating manufacturing methods; therefore, the stability of the drug at various temperatures (storage, room, and body) and humidities needs to be evaluated in the amorphous state [18]. Also, traditional methods of retarding absorption or dissolution using hydrophobic salt forms will be less relevant. Solubility and stability of the drug in the local body fluids and also in a variety of potential processing solvents, for example, organic solvents, will need to be evaluated [19].

Many small molecules have been evaluated for use in combination devices (Table 1; Figure 2) and most of these used and investigated so far have been in conjunction with coronary stents as anti-neoplastics, immunosuppressives, or anti-inflammatory agents [20]. While this table represents a fraction of the molecules evaluated as drug-eluting stents [21,22] there is perhaps a future need for a more extensive review of this area alone. Other classes of compounds used in combination devices include those with antibacterial or epithelial cell attachment or other mechanisms of action, for example, the orthopedic delivery of antibiotics [23–25]. As can be seen in the molecular structures (Figure 2) and their calculated molecular properties (Table 1) for these small mole-

TABLE 1

Molecular properties of a selection of the molecules used or evaluated for combination medical devices [21,22]

Molecule	Systemic dose of drug (route)[a]	C log *P*	TPSA	HBA	HBD	MWT	Rotatable bonds	Device coated	Mechanism of action
Sirolimus (rapamycin)	2 mg (po)	4.3	195.4	13	3	914.172	6	Stent (Cypher[b], Cordis)	Immunosuppressant
Paclitaxel	135–250 mg/m^2 (IV)	3	221.3	14	4	853.906	14	Stent (Taxus[b], Boston Scientific; MedStent, Conor Medsystems)	Anti-neoplastic
Everolimus	–	4.1	204.7	14	3	958.224	9	Stent (Xience, Guidant)	Immunosuppressant
Tacrolimus (FK506)	0.05–0.1 mg/kg/d (IV) 0.15–0.3 mg/kg/d (PO)	3.3	178.4	12	3	804.018	7	Stent (Janus, Sorin)	Immunosuppressant
Pimecrolimus	–	4.4	158.1	11	2	810.453	6	Stent	Immunosuppressant
Zotarolimus (ABT-578)	–	4.55[c]	218.8[c]	15[d]	2[d]	966.21[d]	7[c]	Stent (ZoMaxx, Abbott; Endeavor, Medtronic)	Immunosuppressant
Dexamethasone	0.5–0.75 mg/kg/d (PO)	1.1	94.8	6	3	392.461	2	Stent (Dexamet[b], Abbott)	Immunosuppressant
Estradiol	1–2 mg/d (oral)	4.2	40.5	2	2	272.382	0	Stent	Healing promoter
AM80	–	5.9	66.4	3	2	351.439	3	Stent	Inhibits neointima formation
Vinblastine	0.1–0.5 mg/kg/wk (IV)	3.9	154.1	13	3	810.974	10		Anti-neoplastic
Curcumin	–	2.3[c]	93.1	6	2	368.38	8	Stent	Anti-neoplastic
Flavopiridol	–	3.15	90.2	6	3	401.84	2	Stent	Anti-neoplastic
Vancomycin	2 g/d (IV), 0.5–2 g/d (PO)	0.129[c]	530.5	26	19	1449.25	13	In a biodegradeable carrier for treatment of bone infections.	Antibiotic
Minocycline	–	0.5	164.6	10	5	457.477	2	Surgical mesh (Pivit AB[b], TyRx Pharma), Silicone implants	Antibiotic
Rifampin	600 mg/d (PO)	2.7	216.7	15	6	822.94	5	Surgical mesh (Pivit AB[b], TyRx Pharma), Silicone implants	Antibiotic
Gentamycin	3–5 mg/kg/d (IV)	−3.1	199.7	12	8	477.596	7	Bone cement (DePuy 1[b], DePuy orthopedics), Metallic implants	Antibiotic
Tobramycin	1–2.5 mg/kg (IV)	−5.8	268	14	10	467.51	6	Bone cement (Simplex P[b], Stryker)	Antibiotic
Angiopeptin	-	2.4	355	13	13	1098.34	30	Stent	Anti-neoplastic

Structure property data retrieved from PubChem (http://pubchem.ncbi.nlm.nih.gov/) or calculated with web-based software. For additional molecules evaluated for use with stents see also references [21,22]. C log *P*, calculated log *P*; TPSA, total polar surface area; HBA, hydrogen bond acceptor; HBD, hydrogen bond donor; MWT, molecular weight.

[a] Dose data from [56].

[b] FDA approved.

[c] Data calculated from http://www.molinspiration.com.

[d] Data calculated with ChemDraw (CambridgeSoft Corp., Cambridge, MA).

cules, they are ironically generally very large and are not exclusively orally dosed drugs. This is reflected in the ranges for a selection of readily interpretable molecular properties for those that are very variable, with values for calculated log *P* ranging between −5.8 and 5.9 (very hydrophilic to hydrophobic) total polar surface area from 40.5 to 530.5 Å^3, hydrogen bond acceptor count from 2 to 26, hydrogen bond donor count from 2 to 30, molecular weight from 272.4 to 1449.3 Da, and rotatable bonds from 0 to 14. These values extend far beyond lead-like or drug-like molecular properties [26,27], appearing to be more like those in natural product or cancer medicinal space [28], which is not surprising as many of the molecules are used as anti-neoplastics. These molecular properties will obviously influence the release profile in the combination device in conjunction with the polymer coating (if used). The limited studies we are aware of in this regard have shown that log $P_{octanol/water}$ increases as the time to 90% release from phosphorylcholine-coated stents for a range of drugs also increases [29]. It was therefore suggested that release kinetics are influenced by drug–hydrophobic domain interactions in the polymer.

In contrast to the numbers of small molecules, relatively few proteins and glycoproteins in the literature have been tested in combination with devices including the marketed products in Table 2. These include bone grafting materials, spinal fusion putty, and fibrin sealant. Other biologics studied preclinically include gene therapy with vascular endothelial growth factor [30] to enhance re-endothelialization [31]. The combination of IGF-1 and TGF-beta 1 or BMP-2 alone has been used in orthopedic titanium implants that were tested in sheep, and the growth factors were demonstrated to form a capsule on treated side of disc that may be advantageous [32,33]. Studies undertaken with stents loaded with oligonucleotides (15 and 32 base) of molecular weight 4700 and 10 000 showed that the larger molecule was released less rapidly from the stent [34]. The same

authors also identified different molecules from molecular weight 1096 to 3300 000 that had been loaded on stents, but they did not present any quantitative relationships with drug release.

In summary, drug candidates for combination devices may certainly have different physicochemical properties, pharmacokinetic and pharmacodynamic profiles, and exist in different physical states versus those that are commonly used orally or in other dosage forms.

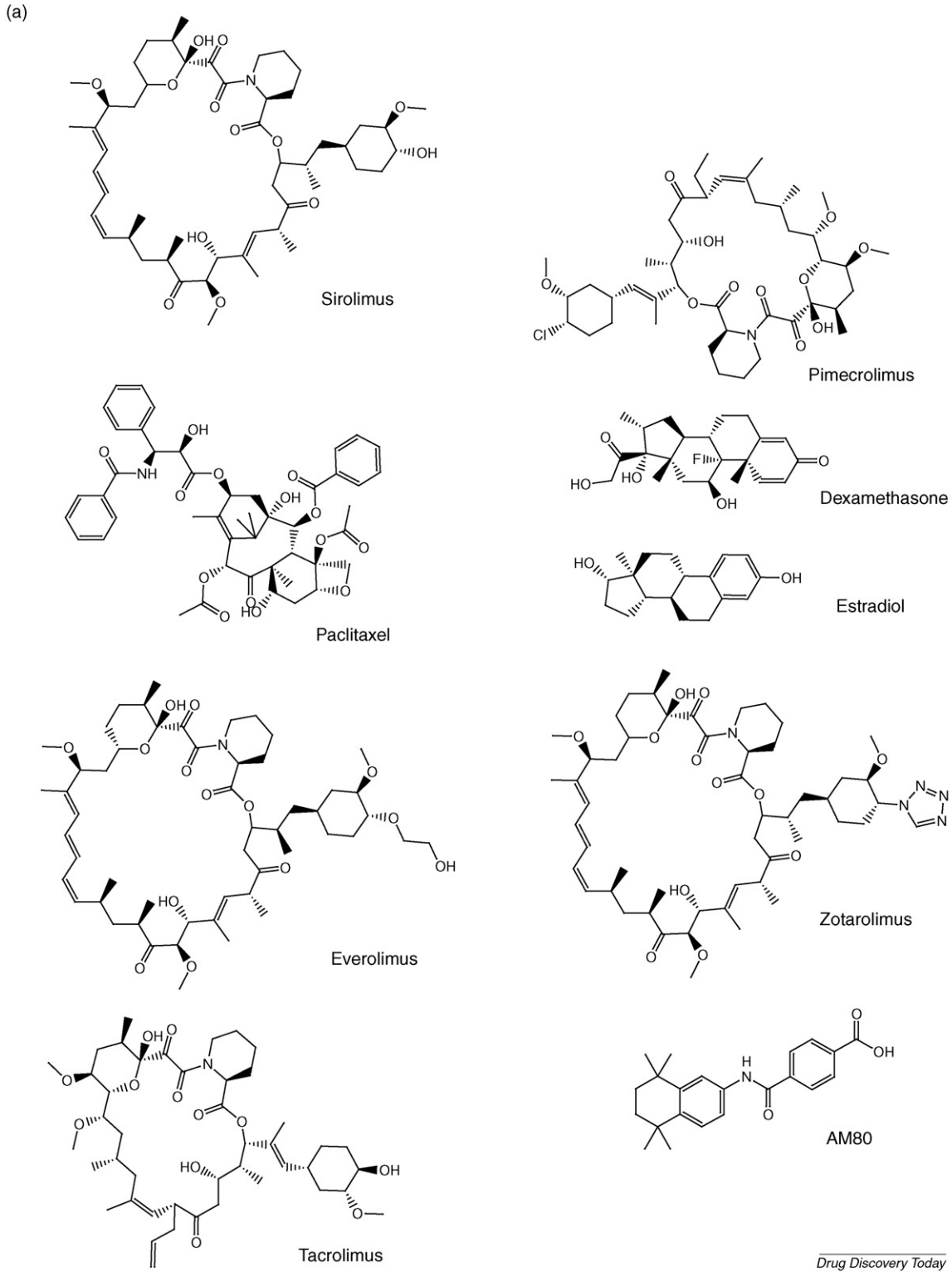

FIGURE 2

Molecule structures retrieved from PubChem (http://pubchem.ncbi.nlm.nih.gov/) that have been used or evaluated with combination devices as described in Table 1.

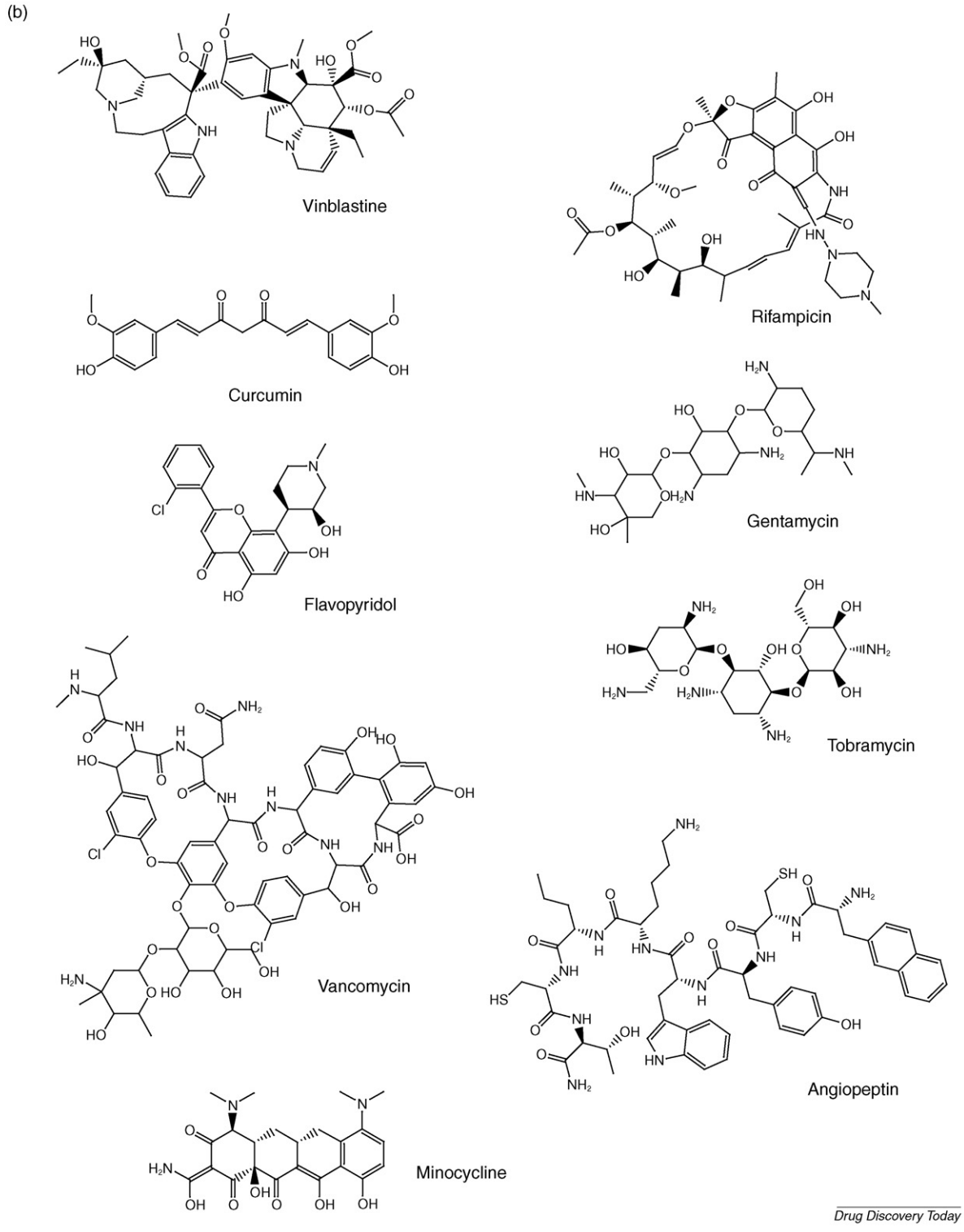

FIGURE 2 (*Continued*)

Device

From the medical device perspective, the first criterion is to determine what kind of device is being developed, which should be obvious to the device company, but may require exploratory analysis by the pharmaceutical company, possibly with the aid of medical device consultants. Medical devices have been subdivided into numbered classes by the FDA and other foreign regulatory authorities, which roughly correlate with the safety requirements and complexity of the device (http://www.fda.gov/cdrh/devadvice/313.html). For example, coronary and vascular stents require more significant preclinical and clinical studies than surgical meshes, which require very little by comparison. The kind of

TABLE 2

Biologics examples used in commercially available combination devices

Biologic	Device	Company
Human platelet derived growth factor	GEM 21S bone grafting material	BioMimetic Therapeutics
Recombinant human bone morphogenetic protein 2	INFUSE bone graft and lumbar fusion device	Medtronic
Recombinant human osteogenic protein, Type 1	OP-1 spinal fusion putty	Stryker
Fibrin	Fibrin sealant	OMRIX Biopharmaceuticals, Ltd.

device also indicates rough boundaries of manufacturing methods and limitations on coating methods. For example, while metallic orthopedic implants could potentially use a variety of organic solvent or evaporative deposition methods, as they are not likely to damage the metal, an indwelling polymeric extruded catheter, or polyethylene hip implant components would be more limited. Although there have been attempts at direct coating of devices without a polymeric matrix with small molecules, to date they have not made it onto the market because of poor efficacy. Therefore, the most typical coating method is a solvent solution sprayed, cast, or dip coated onto the surface followed by solvent evaporation. Materials used in medical devices include ceramics; metals and metallic alloys such as titanium, stainless steel, nitinol (NiTi), and cobalt chromium; a wide variety of plastics [35] such as polyamides, polyethylenes, polyurethanes, silicones, bioabsorbable polyesters, adhesives; and, finally, in some instances human tissues such as bone, cartilage, and collagen [36]. Some complex medical devices, such as pacemakers, can use multiple combinations of the above. On the basis of the type of device, there are usually guidance documents available from the FDA for preclinical physical testing requirements (http://www.fda.gov/opacom/morechoices/industry/guidedc.htm), in addition to any testing prescribed for the drug content and drug elution. Most implants require accelerated fatigue testing, including tests for coating durability, particulates, and corrosion, as well as physical property testing such as tensile or compressive strength. The majority of devices, in general, also require simulated surgical use tests, such as successful deployment and friction characterization [37]. Clearly, a urethral catheter needs to have a low friction coating [2] to minimize patient irritation!

Combined device

The combination of a drug with a medical device is more complex than the sum of the parts. There are various considerations that need to be evaluated carefully before, during, and after the development of such a combination device. Indeed, in our experience some factors unique to the combination device may only surface during development.

Combined manufacturing method and controlled release

In order to develop a combination device, one must, of course, meld the manufacturing methods from both perspectives. After extensive searching of the literature much of this information is in patents rather than scientific literature and the reader is referred to these for more detail. The primary method to be developed is the drug coating method, to insure a uniform durable coating that degrades neither the properties of the device nor the drug. In particular, the shelf life of the device may be limited by the amount of oxidation or other degradation of the drug during manufacture. Since sterilization methods for medical devices tend to be limited to gamma irradiation or ethylene oxide gas, the impact of these procedures need to be evaluated for their effects on the combination device, as it is difficult to create a sterile or aseptic process as would be used for pharmaceuticals. Another consideration is the length of device use *in situ* (days to years) and the required time scale of elution (hours to months). Different drug release profiles are possible by using several polymers for controlling release and the diffusion process [1,38] as well as varying drug loading on the device. Other important factors include the time scale of healing and/or the disease process. For example, drug-coated stents can be considered better than bare metal stents because they improve quality of life [4] as the rate of restenosis is greatly reduced [31], though there may be increased risk with off label use [6,7] that is a common occurrence in the life cycle of new devices as they reach the market [5]. Therefore, in the case of drug-eluting stents, dosage of drug and release kinetics must be optimal so as to balance proliferation of vascular smooth muscle and the re-endotheliazation process.

Local drug effect

Understanding the biologic effects of a combination device should not be ignored as it is quite a complex task to differentiate the impact of a combination device on the biologic system versus the system on the combination device and, further, the impact of the device, coating, or drug alone *in situ* [1]. Yet, one way to study the effects on the biologic system is to look at the gene expression of a drug used on a device versus the effects of the coating materials or the device substrate alone. It is possible that the polymer and drug act with diverse, synergistic, or additive effects on gene expression that may not be predictable from knowledge of either one independently. The perceived small doses of materials may result in short-term effects locally, but these may be enough to trigger global gene expression effects via biochemical networks. Consider that the complexity of biologic networks in restenosis involves many pathways. Samples taken following 'in-stent restenosis' in patients receiving bare metal stents illustrated how a combination of literature data mining, analysis, and gene expression data could be visualized as a network to identify key genes ADAM17/TNFα converting enzyme and procollagen type 1 α2 gene, which may represent novel anti-restenosis targets [39]. As another example, global gene expression profiling of discs coated with the anti-neoplastic vinblastine and incubated with HUVEC cells showed inhibition of endothelial cell growth with impact on several pathways (ASK-1, JNK, RAS) including the cell cycle (NOA 36) [40]. Further as a third example curcumin, in a resorbable stent material, has been shown to influence MAPK (ERK, JNK) and protein kinase pathways with effects on cell proliferation and differentia-

BOX 1

Drug–drug interactions with combination devices

The presently marketed drug-eluting stents in the US to date use rapamycin or paclitaxel (and in addition in Europe zotarolimus). It has been suggested that individuals receiving multiple stents containing different drugs are unlikely to show interference or drug–drug interactions for rapamycin and paclitaxel as they bind different sites in the tissue. Drugs normally used systemically in cardiovascular disease following stent implantation have also been tested for their ability to displace these two drugs and some of these may also affect binding [16]. It has not been discussed whether drug–drug interactions at the level of metabolism could also occur in the vascular tissue between cardiovascular and other drugs and those used in stents [16]. For example, sirolimus is extensively metabolized by CYP3A4 and CYP3A5 [50], while paclitaxel is metabolized by CYP2C8 [51]. Co-administration of inhibitors for these enzymes may be undesirable [52,53], as coronary arteries express several CYPs [54,55]. The selection of drugs or a drug and biologic used in combination on a single device [31] will also require careful consideration to insure that there are no interactions that will be detrimental. These considerations are applicable to other types of combination devices besides stents.

tion [41]. Finally, flavopiridol (a cyclin-dependant kinase (CDK) inhibitor) eluting stents have been shown to inhibit neointima formation in rat, probably via similar effects on cell proliferation [42] as those described above. To date, we are not aware of any proteomic or metabolomic studies, but these may be important for a complete systems-based understanding of the impact of a combination device *in situ*.

Another local drug effect to understand is drug partitioning. There has been some discussion in the literature on effects of drug movement in the tissue via diffusion and convection, but no discussion on movement of drugs used in devices that is mediated by transporters. This may be likely based on the size or other physicochemical properties of some of the drugs used in combination devices to date (Table 1) that are likely to be substrates for drug transporters. Blood vessels appear to express transporters as well as enzymes at the mRNA level [43] that may be inhibited by polymers [44] that are used in device coatings. The effect of molecular weight and charge has been studied in relation to the diffusion of dextrans (10–282 kDa) across rat carotid arteries where anionic and neutral compounds showed lower rates of diffusion. The extent of deposition of hydrophobic drugs is also greater than hydrophilic drugs for stent-based delivery possibly because they may partition into tissues and are not washed out [17]. As patients are likely to be treated with other drugs before, during, or after receiving a combination device, it may be important to consider potential drug–drug interactions. There has been some discussion of this for coronary stents (Box 1).

Clinical concerns and business drivers

When developing a combination device, it is important to consider the development and clinical time scale. The development cost [45] for a combination device will probably be greater than for a device alone, due to the greater number of regulatory considerations and required tests. The pre-approval and/or post-approval clinical trial time scale may also be increased versus the medical device alone, to account for follow up of long-term effects of the combination device and post marketing surveillance. It is easier to launch a combination device from previously approved components [5]; however, it should be obvious that if either the device or drug are not yet approved by regulatory authorities, the path is longer. In addition to previously described regulatory issues [1], a combination device developer also needs to consider biocompatibility and immunotoxicology of the combination per the ISO-10993 standards that requires biologic response tests [46].

On the business side, development of combination devices should also include the costs of the drug, the device, and the operation. The impact of a combination device may be assessed using pharmacoeconomic methods, such that cost and efficacy of a combination device can be compared with the uncoated device or with a systemic dose of a drug. These studies have been performed predominantly with drug-eluting and bare metal stents [45,47] and yet rarely for other types of devices. The developers should also consider whether it is possible to have exclusivity with a molecule that may be based on the patent position of the active molecule or alternatively it could be a generic drug. The coating formulation and manufacturing methods for a combination device themselves can possibly be patented. The development of a combination device may also aid in extending the patent lifetime for a drug or device and provide a valuable new line extension.

Opportunities and challenges

There are numerous opportunities and challenges for development of profitable combination devices in several areas beyond intravascular stents and their success will very much depend on the selection of the right drug. For example, in the area of developing artificial organs one of the major challenges is avoiding rejection, hence these could also be coated with immunosuppressants, which may remove some of the toxicity (nephrotoxicity) associated with systemic dosing of these molecules [48]. A selection of the molecules that have been pursued so far as potential components of combination devices possesses a wide range of molecular properties as described previously (Table 1). In many cases the molecules would not be considered 'drug-like' (Figure 2) and several are only intravenously dosed when used systemically. Hence in the selection of a potential drug for a device the developer can look beyond the molecules normally considered as 'drug-like' and evaluate those with atypical values for oral bioavailability, absorption, distribution, metabolism, and excretion (ADME) properties, systemic toxicity, and the like, normally desired for lead candidates in a typical orally dosed drug discovery program. Combination devices, therefore, offer possibilities for pharmaceutical companies with drugs or biologics that may be optimal in local delivery scenarios [22]. Understanding the physicochemical properties of the drugs used in combination devices, as well as their eventual location of use, is a key to finding alternatives for the ideal device–drug (and polymer) combination. There is certainly potential for alternatives to the very large molecular weight anti-neoplastic agents already used experimentally in several devices (Table 1, Figure 2) by using lower molecular weight molecules, which are more plentiful in pharmaceutical libraries and may be cheaper and easier to process in a combination device. For example, a smaller tubulin-binding molecule, which occupies the

colchicine-binding site at the interface between α and β tubulin in a similar manner to paclitaxel [49], may be a viable starting point for such alternatives.

We have shown that combination devices are at the interface of many scientific fields, bridging the engineering and life science disciplines. The future implementation of informatics, knowledge-based approaches and computational modeling could all be used to select and optimize the device, coating matrix, drug, and combinations thereof. Considering some of the preceding points raised in this article may result in more examples of *de novo* successful combination device development with an impact on the healthcare business.

Conflicts of interest

MAZH and SE are consultants for medical device and pharmaceutical companies, respectively.

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