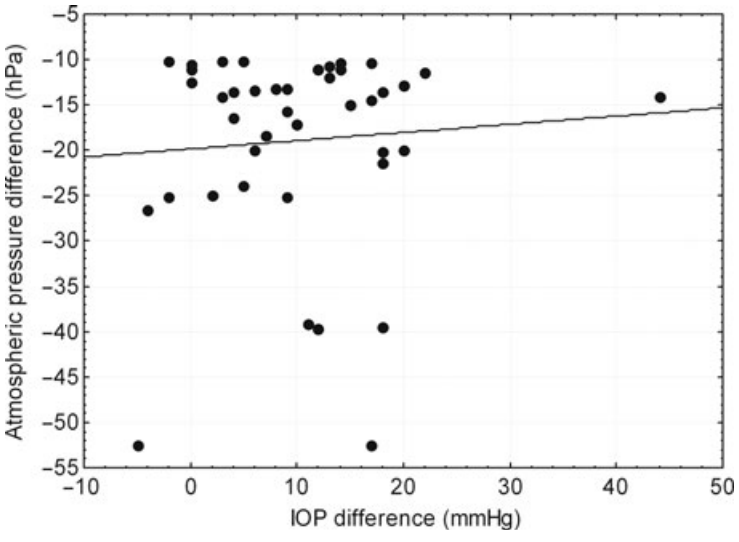

Fig. 1. Correlation between pre- and first-day postoperative IOP difference and pre- and first-day postoperative atmospheric pressure difference in 41 patients, which experienced a drop of the atmospheric pressure of ≥10 hPA.

During flight ascent in high altitudes, the cabin pressure can decrease about 200 mmHg in a few minutes (Dieckert et al. 1986), whereas meteorological alterations of the atmospheric pressure change slower and only in a magnitude of 20–30 mmHg. Nevertheless, in a gas-filled sphere with rigid walls, even a slow decrease in the ambient air pressure would result in an increase in IOP. However, such a model sphere does not reflect the situation in the eye correctly. The fact that even an alteration of 200 mmHg of the surrounding atmospheric pressure in a time frame of 1 hr results in a much lower increase in IOP can most likely be attributed to the existence of compensatory mechanisms, such as increased aqueous humour drain, scleral expansion and choroid compression as described by Lincoff (Lincoff et al. 1989). Accordingly, during flights (Kokame & Ing 1994) or travelling in high altitude (Ferrini et al. 2010), a transient IOP decompensation in gas-filled eyes can be seen, but no influence of the meteorological variation in the atmospheric pressure could be found in this study.

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Challenges facing ophthalmic start-up companies in developing new devices or medicines

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Editor,

The pharmaceutical industry has suffered from a reduction in the number of US Food and Drug Administration (FDA) approved medicines (new molecular entities) from 40.3 per year in 1990 to 1992, to 19.7 in 2007 to 2009 (Reichert 2003; FDA Drug and Biologic Approval Reports 2010). In contrast, in ophthalmology, the number of approved medicines has decreased from an average of 3.7 from 1995 to 2000 to 1.8 from 2004 to 2009 (FDA 2010).

The reasons for the reduction in the number of approved medicines are multi-factorial and may at least include higher regulatory standards required by the FDA and the difficulty in fostering new innovation (Goodman & Gelijns 1996). In addition, less venture capital (VC) money has been available to develop medicines in the past decade and especially in the past several years with the current economic recession (Marks 2010; Buckley 2010; Knowledge@Wharton 2010; BBC 2010).

This reduction in funding to new start-ups by VC groups may be due, at least in part, to lower profitability over the past decade of these types of investments, decreasing from a 10-year 34% average return in 2008 to 14% in 2009 (Buckman 2009). Accordingly, VC firms as well as major pharmaceutical companies appear to have adjusted to this lower return on investment by reducing the overall capital made available to start-ups. Further, many VC firms and major pharmaceutical companies have moved to acquiring medications in later development to decrease investment risk (Marks 2010). These changes in the marketplace have increased the already challenging task for start-ups to adequately finance their new enterprises. The purpose of this study was to evaluate the current challenges facing ophthalmic device and pharmaceutical start-ups in developing a new product.

We used Internet search engines http://www.dogpile.com and http://www.google.com to identify ophthalmic pharmaceutical and device start-up companies currently in operation who have not exited. Searches were conducted by two of the authors (BK, LAN). Further, additional websites were checked: http://www.fda.gov and

http://www.centerwatch.com. Companies' websites were used to obtain contact information for the chief executive office/president (CEO) and board of director (BOD) members. An 'exit' was defined as 'a transaction of the product or corporation designed to provide a financial return to investors' (Chitty 2009). The surveys were sent three times each if required within several weeks of each other. In several cases, a fourth (personal) request was sent by the lead author (WCS) to a respondent.

The complete results of the survey can be found online (Table S1). We received 14 responses from CEOs from 48 surveyed companies (29%) and six responses from BOD members (110 sent, multiple BOD members per company) from 40 (some companies did not have a BOD) surveyed companies (6%). The survey represented responses from 16 companies.

In total, eight (50%) companies indicated they were developing a pharmaceutical product, five (31%) a device and three (19%) had both types of products. The major primary focus was AMD (n = 5, 31%), dry eye (n = 3, 19%), retina (n = 2, 13%) and six reported another indication (one incidence each). For BOD members, half (n = 3, 50%) were asked to be on the board by company personnel, while three were placed on the board by a VC firm.

The respondents indicated that the most common level of funding needed to exit was between $0 and 50 million ($n$ = 12, 75%). Many participants estimated that the chances of making the next round of funding were >50% (n = 10, 63%) and the chances of profitably exiting with the next 5 years were >50% (n = 13, 81%). The series of funding needed were spread between Series A-E, with one company ready to create an initial public offering.

Participants indicated overwhelmingly that the greatest perceived threat to their companies was the lack of financial capital (n = 13, 65%). They noted that the greatest difficulty in raising money was both the number of financing rounds required to bring the product to a sellable position and the burden of proof required for the equity markets to demonstrate efficacy and safety (n = 7 each, 35%). Further, respondents observed the greatest challenge in dealing with the regulatory agency was also the burden to prove efficacy and safety (n = 14, 70%). In contrast, the worst part of the relationship with equity partners was the high demand for equity in return for financing (n = 7, 35%). However, six (30%) respondents indicated there was no real problem in working with their investors.

In managing their companies, CEOs observed that the greatest challenge was motivating employees and contractors (n = 4, 29%) and allocating time to demonstrate leadership (n = 3, 21%). In contrast, the BOD members noted their greatest problem in dealing with top level management was their lack of understanding the board governance (n = 2, 33%). Five respondents (25%) stated that being organized as a virtual company also was a drawback for their company.

Most participants indicated the greatest challenges regarding the science of their product were regulatory hurdles and obtaining satisfactory regulatory advice (n = 11, 55%). Apart from obtaining a successful exit, the BOD members and CEOs were motivated most by helping to prevent blindness and belief in their product (n = 9 each, 45%).

This small study provides initial findings that financing and regulatory burdens may represent, in many cases, a difficult hurdle for ophthalmic device and pharmaceutical start-ups seeking to bring new products to market to help prevent blindness in our ophthalmic patients. Further study, with a greater sample size is needed to more fully understand the problems and roadblocks that encumber current ophthalmic device and pharmaceutical start-ups.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. The data for the questions in red is presented per company and not individual response (n = 16).

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Optic nerve head size and cognitive function

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Editor,

The optic disc area with an interindividual variability of about one to seven (Jonas et al. 1988) is associated with the optic nerve fibre number (Jonas et al. 1988), area of neuroretinal rim and optic cup (Bengtsson 1976) and other parameters such as refractive error and body height (Xu et al. 2011). Factors responsible for the optic disc size variability have been unclear so far. It has been discussed that the number of embryologically formed primitive retinal ganglion cell axons influences the size of the optic disc and that the number of embryological retinal ganglion cell axons that eventually regress during fetogenesis influences the size of the future optic cup (Rakic & Riley 1983; Jonas & Naumann 1992). Although the optic nerve as cerebral fascicle is a part of the brain, it has not been assessed yet for an unselected population whether the disc size is associated with cerebral or intellectual functions (Hellström 1999). We therefore examined the potential associations between disc size and level of education and time necessary to perform a standardized automatic visual field test as surrogates of cognitive function.

The population-based Beijing Eye Study included 4439 subjects with a mean age of 56.2 ± 10.6 years (Jonas et al. 2009). All study participants underwent a comprehensive eye examination and an interview with questions on their socioeconomic background and their level of education. The visual field was examined by frequency-doubling threshold perimetry (program C-20-1; Zeiss-Humphrey, Dublin, CA, USA). The disc size was measured on photographs (Wang et al. 2006). Only one eye per subject was taken for statistical analysis.

The study included 4089 (92.1%) subjects for whom the assessable disc photographs and data of education level and perimetric test time were available. In univariate analysis, disc size (mean: 2.61 ± 0.50 mm^2) increased significantly with education level ($p < 0.001$; correlation coefficient $r = 0.14$), shorter perimetric test time ($p < 0.001$; $r = -0.05$), higher age ($p < 0.001$; $r = 0.08$), higher body height ($p = 0.006$; $r = 0.05$), urban versus rural region of habitation ($p < 0.001$) and refractive error ($p = 0.002$; $r = 0.05$) (Table 1). In multivariate analysis, disc area remained to be significantly associated with higher education level ($p < 0.001$) and shorter test duration ($p = 0.004$), in addition to higher age ($p < 0.001$), female gender ($p = 0.004$), higher best-corrected visual acuity ($p = 0.01$) and refractive error ($p < 0.001$) (Table 2). A similar result was obtained if the amount of visual field defects was added and if highly myopic eyes were excluded. In a reverse manner, education level was significantly (multivariate analysis) associated with increasing disc size ($p < 0.001$) and shorter perimetric test duration ($p < 0.001$), in addition to lower age ($p < 0.001$), male gender ($p < 0.001$) and higher best-corrected visual acuity ($p < 0.001$) (Tables 1 and 2). If eyes with an intraocular pressure >21 mm Hg, glaucomatous optic nerve damage, macular or retinal diseases or nuclear cataract were excluded, disc size was still significantly associated with higher level of education ($p < 0.001$) and shorter test duration ($p = 0.002$), after adjustment for age ($p = 0.001$), gender ($p = 0.007$) and refractive error ($p = 0.01$).

Within the Chinese population, optic nerve head size was associated with education level and perimetric test time, after the adjustment for age, gender, refractive error and best-corrected visual acuity. If one considers education level and perimetric test time as surrogates of cognitive or intellectual function, one may speculate that optic disc size was related to cognitive function. One may speculate that the optic nerve as cerebral fascicle and the correlation between the disc size and optic nerve fibre count suggest that the optic nerve and thus the optic nerve head reflects aspects of the brain. This has already been shown by Hellström (Hellström 1999) for patients with adverse event during their prenatal and perinatal life.

Table 1. Level of education and associated parameters in the Beijing Eye Study 2001.

Level of Education	n	%	Optic disc Area (mm^2)	Time needed for perimetric Test (sec)	Age (Years)	Refractive Error (Dioptres)	Gender Men/ Women	Body height (cm)	Visual Acuity (logMAR)
Illiteracy	254	6.2	2.52 ± 0.53	54.6 ± 17.9	62.1 ± 9.8	0.19 ± 3.24	32/222	155.0 ± 7.1	0.19 ± 0.36
'Half-illiteracy'	107	2.6	2.54 ± 0.48	51.4 ± 12.1	59.6 ± 10.4	−0.10 ± 1.77	29/78	157.1 ± 7.1	0.10 ± 0.20
Primary school	614	15.0	2.45 ± 0.48	50.5 ± 40.4	56.5 ± 9.5	0.09 ± 1.84	238/376	159.5 ± 7.8	0.08 ± 0.25
Middle school	1695	41.5	2.61 ± 0.50	47.4 ± 10.5	52.9 ± 9.7	−0.18 ± 1.81	695/1000	161.4 ± 7.5	0.04 ± 0.14
College or more	1419	34.7	2.70 ± 0.49	46.2 ± 8.8	56.4 ± 9.8	−0.85 ± 2.24	808/611	165.3 ± 7.6	0.03 ± 0.14
Total	4089	100	2.61 ± 0.50	48.0 ± 1.5	55.4 ± 10.1	−0.35 ± 2.08	1802/2287	162.0 ± 8.1	0.05 ± 0.18
p-value (anova)			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001