Joint replacement of the hip and knee remain very satisfactory operations. They are, however, expensive. The actual manufacturing of the implant represents only 30% of the final cost, while sales and marketing represent 40%. Recently, the patents on many well established and successful implants have expired. Companies have started producing and distributing implants that purport to replicate existing implants with good long-term results.

The aims of this paper are to assess the legality, the monitoring and cost saving implications of such generic implants. We also assess how this might affect the traditional orthopaedic implant companies.

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Excellent outcomes continue to be reported for total hip (THA) and total knee arthroplasty (TKA).1,2 According to the tenth Annual Report of the National Joint Registry (NJR) of England, Wales and Northern Ireland, a total of 76 448 primary THAs and 73 340 primary TKAs were performed in 2013.3 The number has been rising over the last 20 years4 and is projected to double in the next decade.5,6 While most remain successful,7,8 the cost remains high. This is particularly important for state funded healthcare systems where the public purse is under scrutiny, but also in private and insurance funded healthcare programmes. While arthroplasty remains a very cost-effective operation,1,9 the American Association of Orthopaedic Surgeons (AAOS) has highlighted the increasing costs and the need to get value for money.10 The cost of implants varies in healthcare systems around the world, but still represents a major component of the cost of the operation.

The constituent parts that make up the final cost of the implant include manufacturing costs, design, research and development and also the cost of support staff including industry representatives. The distribution of costs that make up the total are illustrated in Figure 1 and Table I. Additionally, the costs for the same implant may vary considerably between hospitals. The reasons for this include the lack of transparency in revealing the costs,11-15 cost and volume agreements and exclusivity clauses for some institutions. The actual manufacturing of the implant represents only about 30% of the final cost, while sales and marketing represent 40% (Fig. 1).16-18

Recently the patents on many well established and successful implants have expired. The pharmaceutical industry has a production path for generic drugs once their patents have expired. The use of generic drugs, defined as identical or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use,19 is already well established and delivers significant cost savings. Medicare in the United States saved $33 billion in 2007 through the use of generic rather than branded medication.20 Analysis of the costs of generic drugs following their launch shows a rapid decrease in price as manufacturers compete for the market share, followed by a plateau, a so-called “scalloped decay”.21 This allows for the mass production of significantly cheaper generic drugs to be released to a controlled and regulated market.

The orthopaedic industry has been slow to follow suit. Companies which offer such alternative products into the market have been established. They have started producing and distributing generic replicas based on implants with good long-term results in joint registries and the best Orthopaedic Data Evaluation Panel (ODEP) ratings22 for which patents have expired. While the pharmaceutical industry has strict criteria for the production, quality control and monitoring of drugs, there is currently no such pathway in Europe to allow this to happen for implants used in orthopaedic
surgery. Similarly, the Food and Drugs Administration in the United States also has no experience in licencing or monitoring generic implants. While the 3M hip was introduced to offer a low cost alternative prosthesis, its failure rate of 19% to 21% at five years resulted in its removal from the market and acts as a salutary reminder of the problems associated with the general release of implants without careful assessment.2

The aims of this paper are to assess the legality, the monitoring and potential cost saving implications of such generic implants were they to be released onto the market. We also assess how this might affect the traditional orthopaedic implant companies.

**Current United Kingdom and European Union device regulation**

The regulation of medical devices in the United Kingdom and the European Union (EU) tries to tread the line between allowing innovation and ensuring patient safety. The high rates of failure and adverse reaction to metal debris caused by metal-on-metal (MoM) THAs have highlighted the need for greater monitoring and regulation of the implant market. As a result, the regulatory framework governing medical devices, including implants, is undergoing revision in the European Commission.

Currently in Europe,23,24 medical devices only need to achieve a Conformité Européenne (CE) mark to be available for use by surgeons. A CE mark can be achieved through any one of 76 Notified Bodies.25 These are appointed by competent authorities in each of the EU member states. In the United Kingdom, this is the Medicines & Healthcare Products Regulatory Authority (MHRA). Thus there is potential for variation across Europe and for manufacturers to shop around to achieve a CE mark for their device. There is concern over the rigour of this process following an investigation by the British Medical Journal (BMJ) which reported the variation across Europe and the ability of implant companies to shop around to gain their CE mark.26 Once a CE mark has been achieved, it can legally be used anywhere in the EU. While this mark suggests a “standard of safety”, there is currently no EU law requiring monitoring or post-operative surveillance once a device has been implanted. In response to these concerns, orthopaedic implants have recently been upgraded to a level 3 which requires the submission of designs and clinical data. This can be from a previously released “equivalent” device, as well as a post-marketing surveillance plan. Some replica implants have already gained a CE mark and therefore are permissible for use in EU countries.

Having achieved a CE mark, the regulation of all medicines and medical devices must be assessed by the individual member states, or by the European Medicines Agency (EMEA) in London. In the United Kingdom this is the responsibility of the MHRA.

**The MHRA in the United Kingdom**

While both medicines and medical devices are regulated by the MHRA,23,24 the process of regulation varies between the two.27 Drugs require four separate phases of investigations before reaching the market, with each phase requiring more patients in the trials (Table I).

The regulation of orthopaedic devices is less stringent. Before a device can be sold on the European market, the manufacturer must verify that it conforms to essential

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**Table I. Clinical trial phases for the Conformité Européenne mark**

<table>
<thead>
<tr>
<th>Phases</th>
<th>Who can take part?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 Human pharmacology – looks at whether a trial treatment is safe or has harmful side effects</td>
<td>Normally healthy volunteers but can be patients depending on the study</td>
</tr>
<tr>
<td>Phase 2 Exploratory therapeutics – looks at how well a treatment works</td>
<td>Patients</td>
</tr>
<tr>
<td>Phase 3 Confirmatory therapeutics – tests a new treatment against standard existing treatment</td>
<td>Patients</td>
</tr>
<tr>
<td>Phase 4 Therapeutic use – further testing on the drug after it has been licensed including side effects, safety and long term risks and benefits</td>
<td>Patients</td>
</tr>
</tbody>
</table>

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**Fig. 1**

Pie chart showing the distribution of costs that make up the final cost of orthopaedic implants.
requirements, concerning “the safety, performance and the information on the label and instructions for use”, and the provision of clinical data. More often than not for arthroplasties, these data are “equivalence data”. Thus the new implants need enough similarity in design to existing devices. Further clinical trials are expected only if a new implant has innovative design features or uses new materials.

The relative ease with which new implants can be released to the market and a reliance on “equivalence data” has been questioned and is currently being re-appraised.28,29

The fact that the newer generics are designed to similar specifications as the originals, means that they can use previous clinical trials in their submission to the MHRA.

United States regulation
The reliance on “equivalence data” and equivalent design also underpins regulation in the United States. On 28 May, 1976, the Federal Food Drug and Cosmetic Act was amended to include regulation for medical devices.30 Congress approved an amendment requiring that all medical devices be classified into one of three classes:

- Class I: Devices that do not require premarket approval or clearance but must follow general controls. Dental floss is a class I device.
- Class II: Devices that are cleared using an application process called 510(k). Diagnostic tests, cardiac catheters, hearing aids and amalgam alloys used in dental surgery are examples of class II devices.
- Class III: Devices that are approved by the Premarket Approval (PMA) process, analogous to a New Drug Application. These tend to be devices that are permanently implanted into the human body or may be necessary to sustain life. Devices that do not meet either criterion are generally cleared as class II devices.

Premarket Notification (also called PMN or 510(k)) allows the FDA to determine whether the device is equivalent to a device already in one of the three categories of classification. Any new arthroplasty that reaches the market following a 510(k) application must be “substantially equivalent” to a device on the market before 28 May, 1976 (a “predicate device”). If a device being submitted is significantly similar relative to a pre-1976 device, in terms of design, material, chemical composition, energy source, manufacturing process, or intended use then it is likely to be “cleared” for marketing or “510(k) cleared” devices. This process can be as quick as six months from the initial application. This speedy process was instigated to allow patients access to new potentially life-saving devices.

Importantly, if a device is found to be “substantially equivalent” to a previous device, it is assumed to be safe due to its similarity.

Once marketed, the FDA often request general controls including annual registration, listing of devices, “good manufacturing practice” and labelling but not necessarily clinical studies nor monitoring.

The concerns of MoM devices, and in particular the ASR hip, (DePuy, Warsaw, Indiana) has highlighted the risks of the current 510(k) clearance process and there have been calls for an alternative method of screening and approval31 but, as yet, no changes have been made or suggested.

The replica implants are, however, similar enough to the originals that they would probably not have difficulty in being cleared according to the current 510(k) notification.

Patents
The maximum length of both EU and United States patents is 20 years,32,33 providing fees are paid and there are no successful opposition proceedings. There is the potential to extend some patents for a further five to five and a half years in Europe, but this does not apply to prostheses. We can therefore expect many more opportunities for generic implants to enter the market as patents for well-established implants expire.

Bioequivalence
Bioequivalence is a term in pharmacokinetics used to assess the expected in vivo biological equivalence of two proprietary preparations of a drug. Two products are said to be bioequivalent if they would be expected to be, for all intents and purposes, the same.34

Generic pharmaceuticals are not required to replicate the extensive clinical trials that have already been used in the development of the original, brand-name drug, but they must prove that function in the body is equivalent to the originals. How generic orthopaedic implants might be tested is, as yet, not stated. Comparing the regulation of pharmaceuticals to that of medical devices is difficult.

Sir Kent Woods, Chief Executive of the MHRA, has given three reasons for the differences in regulation of devices and medicines:14

- Devices are innovated differently with relatively small changes to technology and design (perhaps every two years).
- Multiplicity. While there may be low thousands of drugs introduced and in use, there could be hundreds of thousands of devices in the European Union. Regulation of standards would be too difficult.
- Most importantly is the way that implants fail in comparison to drugs. Failure of arthroplasties for example is often reflective of wear and the timescale can be protracted.

Biomechanical equivalence
The new generic implants are similar to the originals by a process of reverse engineering. While their equivalence has been assessed in terms of geometry, this has not been officially supported by an independent advisory body, as no such body exists.

There is no agency, not even the MHRA, that is charged with testing the processes of production and the tolerances of the replicas with reference to the originals.
While it is relatively easy to obtain the CE mark in the EU, the governing body in the United Kingdom feel it safer that new implants go beyond that compliance mark. “Beyond Compliance” is determined by an independent United Kingdom Advisory Group, which was originally set up from the ODEP programme, that uses available data to monitor the early performance of new brands of THA and TKA. Their roles include:

- plans for setting up and designing appropriate post-market clinical follow-up studies;
- methodologies for clinical investigations including numbers, aims, objectives and endpoints;
- choosing centres which might carry out clinical investigations that have the appropriate experience and data collection infrastructure;
- proposed post-market follow-up studies as part of surveillance, clinical outcomes to be met, duration of follow-up, additional tests and timelines etc.

Beyond Compliance was set up to monitor the introduction of entirely new devices and not generic replicas. As such, they have no department that assesses the engineering or biomaterial equivalence.

They also follow the implants through the NJR and report any failures to the relevant clinicians and manufacturers. England is unique in having five sources of post-market surveillance:

- the NJR, collating raw data such as revisions and other complications;
- the ODEP, reviewing submitted clinical data against the guidelines of the National Institute for Health and Clinical Excellence (NICE) for hip implants;
- National Patient Reported Outcome Measures Survey (PROMs), collecting baseline and six month post-operative outcomes;
- joint replacement specific PROM studies which are carried out by the NJR;
- Hospital Episode Statistics (HES), providing admission and treatment data for all NHS patients in England.

ODEP rating of generic implants

The ODEP is an independent, largely self-selected, panel of experts which includes surgeons and procurement experts as a response to the NICE guidelines which suggested that only implants that had a survivorship above a benchmark of 95% at ten years should be used. Those that attain this level in the NJR and/or have good outcomes reported in the literature ten years post-operatively achieve a 10A* rating. Less convincing or smaller numbers receive 10B and those with only three years of data will be 3A or 3B rated and so on (Fig. 2).

All implants that are yet to meet NICE’s three year entry benchmark are listed as ‘pre-entry’, to identify those that are undergoing clinical evaluation. The supposition of those manufacturing the available generic implants was that their replicas would be deemed identical to the originals which all have 10A* rating and hence would also be given a 10A*G (G standing for Generic) rating. This has not been the case thus far.

As things stand, at the time of publication, the only replica implants that are certified by Beyond Compliance for post-marketing survey are the copies of the Exeter V40, Stryker metal head and the Contemporary Charnley Elite.
cemented cup equivalents (Stryker, Kalamazoo, Michigan) (these generic implants are manufactured by Orthimo AG, Zug, Switzerland). These are granted the A* rating and the companies in question are hoping that their replicas of the entire Corail stem range (DePuy) and the Trident uncremented cup and XLPE liner (Stryker) with a Crossfire XLPE liner (Stryker) will follow.

Potential savings to the healthcare market

The traditional implant companies have a bottom heavy structure with large numbers of sales representatives and account managers serving the hospitals directly. A total of about 40% of the cost of the implant is spent on sales and marketing whether a representative is present at the operation or not.

The generic companies believe that by eliminating the sales and marketing side of their distribution they can save up to 35% on the cost of an original (Fig. 1). Sales representatives and account managers are deemed to be expendable as most hospitals and surgeons are already familiar with the well-established implants and accompanying equipment. The company plan to offer flexibility in the level of service a hospital wishes to have and thus some hospitals will wish to have representative involvement at a higher implant cost.

At the time of publication, the equivalent Exeter stem and cobalt chrome head and equivalent Charnley Elite component are said to retail for £499 (excluding VAT) (£783). This is a potential saving of between £100 and £355 for the highest and lowest current prices for cemented implants in the NHS (Table II).38

For the equivalent uncremented implant (for stem, acetabular shell, liner and metal head) the price is about £1000 (£1569). This represents a saving of between £266 and £977 per implant if those prices are correct and are sustained.

Procurement and implant pricing

The procurement of hip and knee implants has attracted increasing research and policy interest across the world market.

In the NHS, the National Audit Office has stated that the price of these implants is “not at all uniform and appears to differ significantly between hospitals”.39 This was quantified by the then President of the British Orthopaedic Association (Professor Briggs) in his “Getting It Right First Time (GIRFT) Orthopaedic Clinical Delivery Programme”.40 He visited 120 institutions (incorporating 205 hospitals) and raised awareness of the existence of different prices and the variables contributing to this. He researched NHS Supply Chain data to identify the range of prices paid for the implants and equipment for cemented and uncremented THAs and cemented TKAs. The variation in these prices is shown in Table II.

Davies and Lorgelly41 in their Centre for Competition Policy Working Paper reported that the medical devices market for THAs in the United Kingdom is “highly oligopolistic with a very high seller market power, which in other commercial industries would certainly raise concern”. Oligopolistic describes a market where there are few sellers and they therefore dominate the market.41 Recent mergers between some of the principle implant manufacturers can only have exacerbated this situation.42 In 2013, the Department of Health in the United Kingdom established a National NHS Procurement Efficiency Programme and emphasised the need for improved data, information and transparency about procurement costs for THAs and TKAs. In “Raising Transparency of Pricing for Total Hip and Total Knee Replacements: A National Pilot on Value for Money for the NHS in Orthopaedic Procurement”, Professor Briggs worked with NHS providers, the NJR, NHS Supply Chain and a number of member organisations serving different groups within orthopaedics in order to seek

| Table II. Demonstration in the variation of implant costs across the United Kingdom illustrating the lack of transparency in procurement

<table>
<thead>
<tr>
<th>Type of prosthesis</th>
<th>Lowest NHS Price</th>
<th>Highest NHS Price</th>
<th>% Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary cemented hip with an acetabulum, femoral stem, and metal femoral head.</td>
<td>£595 ($929)</td>
<td>£854 ($1,333)</td>
<td>44</td>
</tr>
<tr>
<td>The cement restrictor and three mixes of antibiotic loaded cement (including the mixing system).</td>
<td>£123 ($192)</td>
<td>£2470 ($3421)</td>
<td>120</td>
</tr>
<tr>
<td>Primary uncremented hip with an acetabulum, polyethylene liner, femoral stem and metal femoral head.</td>
<td>£1266 ($1977)</td>
<td>£1977 ($3,087)</td>
<td>56</td>
</tr>
<tr>
<td>Primary uncremented hip with an acetabulum, polyethylene liner, femoral stem and ceramic femoral head.</td>
<td>£1457 ($2274)</td>
<td>£2219 ($3324)</td>
<td>52</td>
</tr>
<tr>
<td>Primary uncremented hip with an acetabulum, ceramic liner, femoral stem and ceramic femoral head.</td>
<td>£1636 ($2564)</td>
<td>£2420 ($3778)</td>
<td>48</td>
</tr>
<tr>
<td>Hybrid primary hip with a cemented femoral stem, uncremented cup with a polyethylene liner, and a metal femoral head.</td>
<td>£1,097 ($1712)</td>
<td>£1,399 ($2184)</td>
<td>28</td>
</tr>
<tr>
<td>Hybrid primary hip with a cemented femoral stem, uncremented cup with a polyethylene liner, and a ceramic femoral head.</td>
<td>£1288 ($2020)</td>
<td>£1641 ($2562)</td>
<td>27</td>
</tr>
<tr>
<td>The cement restrictor and two mixes of antibiotic loaded cement (including the mixing system).</td>
<td>£82 ($128)</td>
<td>£180 ($281)</td>
<td>120</td>
</tr>
<tr>
<td>Primary knee arthroplasty</td>
<td>£943 ($1472)</td>
<td>£1,674 ($2613)</td>
<td>78</td>
</tr>
<tr>
<td>One mix of antibiotic loaded cement (with the mixing system).</td>
<td>£41 ($64)</td>
<td>£90 ($140)</td>
<td>120</td>
</tr>
</tbody>
</table>
greater transparency on this subject. He is also working with the Department of Health to investigate how the development of clinical partnerships could lead to better procurement.

In the Review of Operational Productivity in NHS providers Interim Report June 2015, Lord Carter used the data shown in Table II, to calculate the cost savings by switching from uncemented to cemented components with a median or minimum price. He calculated that by implementing this approach nationally the savings could be between £11 million and £17 million each year. This does not, however, take into account surgeon preference, the suitability of cemented implants for some patients, surgical efficiency or longer term outcomes. In a more practical and realistic way, the North Bristol Trust reported dramatic cost savings by streamlining the number of different types of implants to increase buying power, and transformed their THA surgery from a loss of 22% to a profit of 8%. In 2014, the NJR launched an implant price-benchmarking service to the NHS to help procurement teams and healthcare managers understand in greater detail the pricing of THAs and TKAs. The NJR now also provides every trust with a comparison of their current pricing in relation to the national averages.

This lack of transparency of pricing has been a major factor in determining the prices of implants in other countries and health systems.

The traditional model

The threat of this newer model has sparked an interest from the traditional implant companies. In the United States and, more recently, in the United Kingdom, one major implant producer has proposed a distribution system, Syncera, whereby implants are sold without the need for sales account managers. Theatre and hospital staff are trained and empowered to deal with the inventory and management of stock. This limits the number of sales staff required in the operating theatre and stock rooms. So far, the uptake has been limited because of the lack of incentive for surgeons to decrease the costs of implants in the United States. This is partly due to the fee for service model that reimburses for high volume surgery.

OrthodirectUSA (Fort Wayne, Indiana) is an independent company that is buying traditional, well established implants (what they call “Stable Technology”) wholesale and then selling to independent hospitals. There is no need for representatives to be present for simple primary procedures as the surgeon and theatre staff are usually familiar with these implants. Orthodirect USA also aims to facilitate the change in the way that hospitals manage their practice from a reliance on the manufacturers and their representatives. By doing so, they have audited their results to the hospitals that they supply and have decreased the costs of implants by between 60% and 70%. The relationship between industry and surgeons depends greatly upon the healthcare system in which they practice.

The conventional model in some parts of the United States and the EU relies on the presence of representatives in the operating room (scrubbed or unscrubbed), training and stock keeping and the additional fee for service model in the United States. In Scandinavia where the involvement of representatives is minimal, the implant costs remain some of the lowest in the world.

While this model can work well for the so-called “stable technology”, more involvement of representatives is needed for more complicated equipment, especially revision arthroplasties and this may be reflected in the increased in price of these procedures. This may negate any cost saving gained from the cheaper primary procedures.

The higher number of primary procedures and the greater life expectancy will be associated with an increasing number of revisions in the future and this needs to be considered. As yet, there are no equivalent generic revision implants. The complex primary and revision cases also require more teaching and training, some of which is offered or sponsored by industry.

The implant companies also have a large role to play in education, professional development and many support fellowship programmes around the world, as well as providing grants for meetings, research, innovation and charity work.

The cost of training, innovation and education is factored into the “40% marketing costs” and these would of course be sacrificed.

Discussion

THA is a successful operation which remains cost effective. There is, however, a long history of the introduction of new or “improved” and therefore more expensive implants, most of which turn out to be at best no better than those already available and at worst with significantly poorer outcomes. The most used and best performing cemented (Exeter) and cementless (Corail) femoral stems have been available since the 1970s and 1980s, respectively, with excellent outcomes and survivorship.

The relative ease with which new devices, irrespective of whether they are new designs or generics, can be released and used in the United States and EU on the basis of “equivalent design” is currently being re-appraised.

All new implants should be assessed for the risks of complications and failure. Claims by manufacturers, whether of improvements in design or cost savings should be viewed with scepticism until proven with clinical data. Such claims largely rest on the long-term performance of the implant and not its cost. Recent cost benefit analyses of THA support the contention that the cost of the implant is not a major factor in the calculation of value for money, although in a tariff based NHS fixed cost per case system, the cost of the implant can have a significant impact on the profitability of individual hospitals.

While the introduction of generic replicas of well-proven implants (“stable-technology”) has the potential for large-
scale savings in any healthcare system, whether state or privately funded, an independent assessment and certification of absolute equivalence should provide a degree of confidence to surgeons and patients. Until such implants have been formally tested and shown to behave identically, real equivalence cannot be assured. Generic drugs are metabolised in a few hours or days whereas the performance of an implant can only be assessed over many years. The joint registries and ODEP were set up to prevent the use of underperforming implants. There is evidence that surgeons from certain high use centres have better results than others with the same implant and so the heart of the problem may be in the surgery rather than the implant.

We believe that there should be a formal independent system set up to assess the absolute equivalence of generic implants. The first step is to assess the engineering, metallurgy, production, geometry and maintenance of tolerances of any implant submitted to demonstrate equivalence. There has to follow a long-term surveillance of the performance after implantation to assess it not only in absolute terms but also if its behaviour can truly be considered equivalent. Comparing the original to a generic implant for the purposes of regulation may be difficult as most implant companies do not and are under no obligation to publish their own manufacturing, coating technologies or metallurgy tolerances. However, reverse engineering techniques are available to facilitate this.

While surgeons may take some comfort from using a generic implant that has been demonstrated in engineering terms as being equivalent, it is only by considering these implants as new implants and requiring follow-up to the same standards that this can be assured. It may be possible in the decades to come that in the light of long-term experience these requirements can be modified.

As far as we are aware, no similar regulatory bodies exist in the rest of the EU or the United States. A criticism of the Beyond Compliance and ODEP programmes is that they are highly reliant on NJR data which are potentially flawed due to the underreporting of revisions and failures.

It has recently been made clear that the current pricing of implants is unsustainable and needs better transparency. In order for health economies to save money, there need to be a greater incentive for surgeons to choose the most cost effective implants for their patients. In the United Kingdom, a political move to reveal the national pricing of the market. However, implants that purport to be replicas need independent assessment to prove that they are genuinely as good as the originals. We may need a formal worldwide unbiased bioengineering advisory body to work with ODEP and Beyond Compliance and similar bodies to ensure that all generic implants have the equivalence that they advertise. All implants, generic and otherwise, should then have a period of post-market surveillance before being introduced generally into the market.

Take home message:
While the introduction of generic implants is welcomed and may drive down the costs of orthopaedic prostheses, the monitoring and independent assessment to confirm biomechanical compatibility is essential.

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A. Atrey: Writing and editing the paper.
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O. Gosling: Data and fact gathering.
M. J. L. Porteous: Co-editor.
F. S. Haddad: Co-editor.

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