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Cultured blood versus donated blood: Long-run perspectives of the economy of blood

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Abstract. Recent advances of fundamental research on the *in vitro* generation of red blood cells (RBCs) from hematopoietic stem cells in the laboratory open new possibilities of the utilization of cultured RBCs in transfusion medicine. We study the economic challenge of the setup and development of the mass industrial production of RBCs in mature transfusion organizations. We argue that: (i) RBC manufacturing could be set up and developed in the short-medium run for the treatment of the small proportion of transfused patients who have a rare blood type or are alloimmunized against blood antigens; (ii) manufactured RBCs could substitute for donated RBCs in the long run if the physical productivity of RBC engineering technology approaches that of bone marrow.

Keywords: Transfusion medicine, red blood cells, manufacture, donation

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1. Introduction

The generation of cultured red blood cells (RBCs) from various sources including hematopoietic stem cells from peripheral blood, bone marrow or umbilical cord, embryonic cells, or induced pluripotent stem cells, is now a well-established laboratory practice. Douay's group, for example, recently produced RBCs from $CD34^+$ cells for autologous transfusion: 10^6 $CD34^+$ cells of an adult donor were collected by apheresis, and subsequently expanded and differentiated to 10^{10} RBCs, which were finally transfused to the donor [1].

The basic challenge confronting this laboratory technology is, presently, its scaling up to viable industrial production. It is in particular, to use the words of Luc Douay, to "design a *cost effective* automated industrial cell culture system capable of maintaining a *self-renewing* progenitor population, which provides an environment for efficient erythroid differentiation and allows sorting/purification and packaging of the end-product RBC in a manner suitable for transfusion" (Giarratana et al. [1]; emphasis added).

This article examines the challenge above from an economic point of view, and considers some of its potential consequences for blood transfusion organizations.

We draw some consequences of a basic condition of economic equilibrium that may be stated, in general terms, as follows: The activities of an industrial branch (say, pharmaceutical industries) have all approximately the same profitability ratios at the long run equilibrium of the branch. That is, capital

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moves from less profitable to more profitable activities until profitability conditions are approximately identical in all the (surviving) activities of the industry. Applied to putative RBCs manufacturing viewed as a pharmaceutical industry, the equilibrium condition implies a simple relation between the supply price of RBC transfusion units and the cost of medium of culture per unit produced (Box 1).

This basic equilibrium condition admits of two practical interpretations, namely a prescriptive interpretation and a predictive interpretation.

In the prescriptive interpretation, the equilibrium condition is used as a norm to assess the economic sustainability of an activity: Equilibrium profitability ratios are approximated by an average of past and/or current profitability ratios of the considered industrial branch, and compared to the profitability ratios of the evaluated activity; activities which achieve profitability ratios at least as large as the average are deemed sustainable. In Section 2 (Stage 1: industry setup), we apply this interpretation of the equilibrium condition to the putative industry of cultured blood, in order to assess the possibility of setting up this industry in sustainable conditions in the near future. We get, in particular, an order of magnitude of €2,200 for the price of manufactured RBC concentrate, that is, about ten times the price of standard transfusion units collected from blood donations. We argue that this high price makes practical sense, economically and medically, for the industrial production of a few hundred RBC concentrates a year, designed specifically for the treatment of the most complex cases of alloimmunization against blood antigens, including notably the so-called cases of transfusional dead-ends [3].

The predictive interpretation of the equilibrium condition is suitable for capturing the main features of a mature industry, that is, of an activity that is well established and is neither expanding nor declining. We use it, accordingly, to investigate the features of the RBCs industry in a remote future, say at horizon 2020 [4] or afterwards, supposing that the industry has established and has reached maturity at that time. We consider two scenarios successively, corresponding to two plausible evolutions of the technology in the long run [5].

In one scenario (Stage 2 of Section 3), the cost of the medium of culture per unit produced has been divided by 4, relative to its value in setup conditions. The equilibrium price of manufactured RBC concentrates has decreased proportionately, at about €550. It remains substantially higher, therefore, than the price of conventional transfusion units. Manufactured RBCs are used in the treatment of alloimmunized patients, corresponding to a market share of at most 3% of all transfused patients.

In the other scenario (Stage 3 of Section 3), the cost of the medium of culture per unit produced has been divided by 20 relative to its value in setup conditions. This happens if bioreactors achieve the same level of productive performance as bone marrow. The equilibrium price of manufactured RBC concentrates has decreased proportionately, at about €110. It is substantially lower than the (present) price of conventional transfusion units. Manufactured RBCs substitute for donated RBCs for some substantial fraction of the whole market.

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2. Scientific, technological and organizational data

Hematopoietic stem cells (HSCs) are immature progenitors whose maturation generates, *in vivo*, the three types of blood cells, namely, RBCs, platelets and the various sorts of granulocytes. The first significant step toward the *in vitro* generation of large numbers of RBCs from HSCs was achieved by Neildez-Nguyen et al. [6] who reported a 200,000-fold expansion of immature erythrocytes from $CD34^+$ hematopoietic stem cells. Giarratana et al. [7] next achieved a two million-fold expansion of *mature* RBCs *in vitro* from the same type of HSCs. Further remarkable advances have since been accomplished,

as reviewed in Peyrard et al. [8]. In terms of quantitative achievements, notably, a 30 million-fold expansion of $CD34^+$ cells by means of suitable combinations of cell growth factors is now accessible in the laboratory. Research has diversified the potential sources of HSCs, which include peripheral blood, bone marrow or umbilical cord blood, and this has been extended recently to human embryonic stem cells [9] and also to induced pluripotent stem cells of human adults [10]. These achievements imply the technical feasibility of the generation of therapeutic quantities of RBCs in the laboratory, from biologically unlimited sources of genetic material.

A recent experiment of the research group of Luc Douay [1] draws the consequences of this state of the art for clinical application in transfusion medicine, by establishing the functionality of *in vitro*-generated RBCs in human transfusion, concerning notably: (i) their capacity to correctly transport oxygen; (ii) and their pattern of survival in blood circulation, which is shown to be similar to the survival pattern of native RBCs. The same study paves the way for industrial application, by designing a medium to culture HSCs (that is, a combination of nutrients and growth factors) compatible with large-scale, automated cell manufacturing.

The change of dimension in the transition from laboratory to manufacturing involves challenges of two types, technological and organizational.

The solutions to the technological challenge considered in recent prospective biotechnological literature consist of suitable developments of bioreactor technologies [4,5]. Bioreactors refer to the general class of engineering devices used notably for cell culture in automated processes of tissue engineering and biochemical engineering principally. A key measure of the technical efficiency of bioreactors in the context of RBC manufacturing is the volume of culture medium that they consume per unit produced. The authors above calculate a theoretical medium requirement of 40 liters per unit of RBC concentrate produced with the standard bioreactors currently in use. They also consider perspectives of improvement of physical yield up to a medium requirement of 2 liters per unit produced, which would make bioreactors' physical productivity comparable to that of bone marrow.

We concentrate on the organizational aspects of the challenge of manufacturing RBCs in economies endowed with *mature* blood transfusion organizations. By the latter we mean the type of transfusion organization that covers most transfusion needs by means of safe blood products collected through voluntary unpaid blood donations. Most countries of the group of high-income countries of the World Health Organization have blood transfusion systems of that kind [11]. They provide sufficient quantities of transfusion units of satisfactory quality, at prices that range usually, as far as RBC transfusion units are concerned, between $100 and $250 in (rounded) current data.

The substitution of blood cultured from HSCs for donated blood would be associated with thorough changes in the practice and mastering of transfusion [8]. Presumably, cultured RBCs would be produced mainly from a limited number of carefully selected cell lines of "true" universal donors, whereas donated RBCs make a gigantic world pool of currently 90 million donations or so per year, representing a large random sample of the whole statistical distribution of blood phenotypes. The substitution of cultured for donated RBCs would drive alloimmunization against RBC antigens in RBC transfusion to a minimum. Leaving aside accidental errors in recipient's typing or donor-recipient matching, and supposing that common (as opposed to rare) blood groups are systematically identified in routine blood typing, residual cases of alloimmunization could result, in such a transfusion system, from one of two rare circumstances. First, the recipient belongs to a rare blood group that is represented in the bank but is not searched in routine blood typing; or the recipient belongs to a rare blood group that is not represented in the bank, possibly because it is not yet known. The first case carries useful information about the patient: her/his rare blood type must be identified and subsequently matched to the appropriate type in the bank. The

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second case carries useful information for the bank: it must be complemented with the missing rare blood type, possibly by using the recipient's HSCs. The transfusion system as a whole, thus, would operate as a powerful algorithm for: (i) exploring the phenotypic diversity of patients; and (ii) reducing the prevalence of alloimmunization.

For considerations of cost to be examined shortly, the full substitution of cultured RBCs for donated RBCs is impossible in the short run and remains unlikely in the medium run. The first units of an industrial production of cultured RBCs, if any, should be allocated to the resolution of transfusional dead-end crises, that is, to shortages in RBC concentrates that occasionally affect rare blood types or alloimmunized patients [3]. French clinical experience suggests that an annual production of a few hundred units of cultured RBC concentrates, applied to an annual set of 100 difficult cases of complex alloimmunization, would eliminate most situations of transfusional dead-ends, and thereby save one or two additional lives, on average, each year, relative to current transfusion practices based on the sole donated RBCs [12]. Further expansion of industrial production, above this critical quantitative threshold, would be allocated to the improvement of the donor-recipient match in the set of frequently transfused patients of the Rh, Kell, Duffy, Kidd and MNS blood group systems, in order to reduce the rate of RBC alloimmunization most efficiently [8,10].

3. A model of development of the RBC industry

We formulate a model of development of the RBC industry in three stages, consistent with the data above: industry setup for the resolution of transfusional dead-ends (Stage 1); scaling up to the treatment of all alloimmunized patients (Stage 2); and substitution of manufacture for donation (Stage 3). For each stage, we derive the self-sustaining partial equilibrium of the RBC industry in the (supposed fixed) conditions of technique of the stage. The model is calibrated on French data, but the basic conclusions would hold identically in any mature blood economy.

The basic driving force that moves the industry from one stage to the next is technical progress.

One major source of technical progress is the reduction in the cost of the liter of medium. The latter is the outcome of a complex set of determinants, which combines: (i) the (technical and market) determinants of the prices of the growth factors that enter in the composition of the culture medium; and (ii) medium composition itself, optimized relative to the scientific, technical and cost conditions. This complexity makes predictions of the evolution of the cost of the liter of medium very difficult. We cut short this problem by supposing that the reduction in this cost is achieved in a single shot, at the beginning of manufacture production (of RBCs and, consequently, of culture medium), and that it remains constant thereafter.[1]

Progress in the technical performance of bioreactors is the other major determinant of technical evolution. This progress may be partly autonomous relative to the RBC industry, if only because bioreactor technologies are utilized (and consequently improved) in other bioindustries. It should be viewed, nevertheless, as endogenous also, at least partly, due to research and development (R&D) investments performed at each stage by the RBC industry. We assume, for the sake of numerical illustration, that bioreactors' performances get successively through the three levels of supported cell densities outlined in Abbot [4] and Timmins and Nielsen [5], namely, 5×10^7 cells/ml (in Stage 1), 2×10^8 cells/ml

[1] See Timmins and Nielsen [13] for further observations on the determinants of medium cost.

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For any given stage of development of the RBC industry $i \in \{1, 2, 3\}$, we denote by: p_i the price of RBC concentrate units; $C_i = c \cdot L_i$ the medium cost per unit produced (where L_i is the number of liters of medium consumed per unit produced in stage i, and c is stage independent); q_i the number of units produced.

The sales of the industry at stage i read $S_i = p_i \cdot q_i$. We may realistically neglect intermediary consumptions besides culture medium. The industry's value added of stage i reads then $VA_i = (p_i - C_i)q_i$.

Denoting by $EBITDA_i$ the industry's earnings before interest, tax, amortization and depreciation of stage i, we define the following two standard profitability ratios of the RBC industry in stage i: the gross rate of operating profitability $r_{\rm s}^i = \frac{EBITDA_i}{S_i}$; and the capital income share $r_{\rm va}^i = \frac{EBITDA_i}{VA_i}$.

A basic assumption of the model, maintained in all three stages, is that *the RBC industry operates in the same conditions of operating profitability and labor remuneration as the industries of the pharmaceutical branch*. Let $r_{\rm s}^*$ and $r_{\rm va}^*$ denote the latter's equilibrium gross rate of operating profitability and capital income share, assumed constant over the three stages for simplicity. We have then, at the partial equilibrium of the RBC industry at stage i:

$$\frac{r_{\rm va}^*}{r_{\rm s}^*} = \frac{p_i}{p_i - C_i}.$$

Rearranging, we get the following markup equilibrium condition of stage i:

$$p_i = \frac{r_{\rm va}^*}{r_{\rm va}^* - r_{\rm s}^*} \cdot C_i.$$

The model is calibrated on French data. In particular, we take $r_{\rm s}^* = 0.14$ and $r_{\rm va}^* = 0.45$, which correspond to their values in the French pharmaceutical industry in 2007 [2]. We get, finally:

$$p_i \simeq 1.4516 \times C_i.$$

Box 1. Derivation of the markup equilibrium relation of the RBC industry.

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(Stage 2) and 1×10^9 cells/ml (Stage 3). This technical parameter summarizes, in other words, the technological (fixed) environment of the stage, and its progress drives the evolution of the RBC industry from one stage to the next, in our simple dynamic modelling exercise.

A key feature of the economic equilibrium of the RBC industry is a markup equilibrium relation between the price of the unit of RBC concentrate and the cost of medium per unit produced. Its detailed derivation is performed in Box 1. For any given stage $i \in \{1, 2, 3\}$ (i.e. setup ($i = 1$), scaling-up ($i = 2$), and full substitution ($i = 3$)), we denote by: p_i the price of RBC concentrate units; C_i the medium cost per unit produced. Supposing that the RBC industry operates in the current conditions of average operating profitability and labor remuneration of the French pharmaceutical industry, we get the following pricing equilibrium relation of the RBC industry:

$$p_i \simeq 1.4516 \times C_i.$$

The difference (or "markup") $p_i - C_i$, of about 45% of the cost of medium, corresponds to the gross remuneration of capital and labor (before tax) per unit produced. The supply price of RBCs units analyzes, consequently, as the sum of three components: medium costs, which account for about 70% of the price; gross wages, which account for about 16.5% of the price; and gross capital costs (i.e. amortization, interest and profits) and tax, which account for the remaining 13.5%.[2]

Finally, the cost of the liter of medium (thereafter denoted by c) currently used by Douay's group in laboratory conditions is €380.[3] Douay considers that this cost would be actually divided by ten in manufacture conditions. We retain $c = €38$ in the calculations below.

Stage 1 (Industry setup). This stage is an economic implementation of the original idea of Douay and Andreu [3]. Manufactured RBCs serve two objectives in Stage 1: the clinical validation[4] of the transfusion of cultured RBCs and the resolution of transfusional dead-ends. We suppose, realistically, that the startup investor is a nonprofit firm.

The technology of the stage is consistent with a consumption of $L_1 = 40$ l of medium per unit [5].[5] With a cost of the liter of medium $c = €38$, we get a medium cost per unit produced of $C_1 = 38 \times 40 = €1{,}520$. The markup equilibrium condition then yields a price of the RBCs unit of $p_1 \simeq 1.4516 \times C_1 \simeq €2206$. This price compares, for example, with the price of collection, transport, processing and storage of units of cord blood stem cells in blood banks for graft purposes (e.g., €1,985 at Cryo-Save in 2012).

We derive an estimate of potential demand from an assessment of the (social) value created by the setup of the industry, that is, from a monetary evaluation of the years of life gained thanks to the latter (see [14] for an application of similar methods of evaluation to the related question of the constitution of optimal bone marrow registries). Let m denote the average number of lives saved per year; Δe denote the gain in life expectancy of surviving individuals, that is, the average number of years of post-transfusion life of these individuals; and let V denote the monetary value of a year of life. We take $m = 1.5$ as an appropriate estimate for m, inferred from clinical experience. The threshold of cost effectiveness of an intervention that averts the loss of one year of healthy life is situated at 3 times the GDP per capita by the World Health Organization [15]. We take the latter as our estimate for V. France's GDP per inhabitant was €30,634 in 2011 [16]. This yields $V = €91{,}092$. Concerning Δe, finally, the empirical literature relative to post-transfusion survival yields estimates of the survival rate 5 years after transfusion of

[2] These shares are computed as follows: $\frac{C_i}{p_i} \simeq \frac{1}{1.4516} \simeq 0.7$; $(1 - r^*_{va}) \cdot (1 - \frac{C_i}{p_i}) \simeq 0.55 \times 0.3 = 0.165$; $r^*_{va} \cdot (1 - \frac{C_i}{p_i}) \simeq 0.45 \times 0.3 = 0.135$; where r^*_{va} denotes the capital income share (see Box 1).

[3] The cost of the culture medium can be very sensitive to experimental design, but is usually very high, in laboratory conditions. Timmins and Nielsen [5,13] report a cost of $8,330 (about €6,400) per unit RBCs in the co-culture setup of Giarratana et al. [7]. The co-culture system is too complex for industrial application. The setup of Giarratana et al. [1] was designed to facilitate manufacture development, at some price in terms of the (laboratory) cost of RBCs: 10^{10} RBCs ($= 0.5 \times 10^{-2}$ RBCs concentrate) were produced using 13 l of medium, which corresponds to a proportional cost of €988,000 ($= 200 \times 13 \times 380$) per RBCs concentrate. Note that the calculation of a proportional cost makes little economic sense in the context of laboratory production (one cannot assume constant returns to scale in such conditions), but for illustration purposes naturally.

[4] Giarratana et al. [1] was only a first step (albeit a successful one) in the direction of clinical validation, since a single individual was transfused, with a quantity of 10^{10} cells that is well below the therapeutic quantum of 2×10^{12} cells. Manufactured RBCs are submitted to the standard regulations of pharmaceutical products, which require the systematic evaluation of treatment on statistically significant samples of patients over periods of at least 5 years before validation (see Abbot [4] for further details).

[5] A consumption of 50 l would be more realistic, actually, in the current sate of the art. The substitution of 50 l for 40 l in the calculations below does not make any substantial difference anyway. The price of the unit RBCs becomes $p_1 \simeq €2758$, allowing for the production of about 250 units, which remains sufficient for the basic purposes of the stage. Gross capital income is essentially unchanged, at about €96,530, allowing for an unchanged startup investment of €3.2 million.

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Table 1
Industry features in setup conditions

Sales: $S_1 = p_1 \cdot q_1$	€683,860
Value added: $VA_1 = (p_1 - C_1) \cdot q_1$	€212,660
Production assets: K_1	€3,191,347
Gross capital income: $EBITDA_1 = r_s^1 \cdot S_1$	€95,740
Gross labor income: $W_2 = (1 - r_s^1) \cdot S_1 - C_1 \cdot q_1$	€116,963

about 50% [17,18]. We may, therefore, realistically let $\Delta e = 5$. We get, finally, $m \cdot \Delta e \cdot V =$ €683,190. This budget supports the production of $q_1 = \frac{m \cdot \Delta e \cdot V}{p_1} \simeq 310$ units. The latter suffices for the resolution of transfusional dead-ends. Out of the 100 cases or so of complex alloimmunization that the French transfusion organization confronts each year, a proportion of only about 10% gets through real dire straits. A supply of 300 units or so of manufactured RBCs is amply sufficient for the management of these about 10 critical cases. Supply in excess of the quantity required for the treatment of critical situations, if any, should be utilized in the management of the other (non-critical) complex cases.

We can now compute the sales $S_1 = p_1 \cdot q_1$, value added $VA_1 = (p_1 - C_1) \cdot q_1$, gross capital income $EBITDA_1 = r_s^1 \cdot S_1$ and gross labor income $W_2 = (1 - r_{va}^1) \cdot VA_1$ of the industry in Stage 1 (by letting $r_s^1 = r_s^* = 0.14$ and $r_{va}^1 = r_{va}^* = 0.45$: see Box 1). The results are collected in Table 1. With long-term interest rates currently set at about 3%, capital income $EBITDA_1 =$ €95,740 is compatible with a (nonprofit) investment of about €3,191,347 $\simeq \frac{EBITDA_1}{0.03} = K_1$, the present value of a perpetual annuity of €95,740 at the annual rate of 3%. K_1 is proportional to q_1, so that an appropriate financing of R&D in Stage 1, which appears essential for the subsequent dynamics of the industry, supposes that q_1 be as large as possible (that is, equal to $\frac{m \cdot \Delta e \cdot V}{p_1}$): maximizing production maximizes the leverage effect of nonprofit investment, in a way that might prove determinant for industry's take off.

These economic data do support, in the main, the scenario imagined by Andreu and Douay for the setup of this industry.

Stage 2 (Scaling-up to all alloimmunized patients). The startup price p_1 reflects the high use-value of the first units of RBCs produced. Incremental units produced above q_1 will presumably have a lower use-value, if only because they will not save lives anymore. These additional units will be utilized in the management of the simple cases of alloimmunization, for the sake of optimization of the match of pairs of donor-recipient phenotypes, and associate improvement in the quality of transfusion care services. These remarks imply an equilibrium value of $p_2 < p_1$, presumably much lower than the latter. That is, production will not extend above q_1 unless the price decreases substantially. This requires in turn a substantial decrease in production costs, and notably in culture medium costs. We build the equilibrium of Stage 2 on the following assumptions: R&D investments performed during the five years or so of the setup period have pushed the cell density supported by bioreactors up to 2×10^8/ml; and the RBC industry remunerates capital at the pharmaceutical industry's rate of return on physical assets.

At the supposed density, the bioreactor consumes $L_2 = 10$ l of medium per unit [5]. With a price of the liter of medium assumed constant, we get a medium cost of $C_2 =$ €380 per unit produced in Stage 2. The markup equilibrium condition then yields a price of the RBC concentrate as $p_2 \simeq 1.4516 \times C_2 \simeq$ €552. This price compares favorably, for example, with the 2011 French tariff for a unit of autologous RBC concentrate that is cryopreserved and Rh Kell phenotyped (i.e., €552.31). We suppose that the associate equilibrium demand corresponds to the quantity of RBC concentrates required by the management of all alloimmunized patients. That is, we assume that the treatment of alloimmunized patients by manufactured RBCs is financially supported at equilibrium.

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Table 2
Industry features in scaling-up conditions

Sales: $S_2 = p_2 \cdot q_2$	€25,888,800
Value added: $VA_2 = (p_2 - C_2) \cdot q_2$	€8,066,800
Production assets: $K_2 = \frac{EBITDA_2}{r_k^2}$	€7,891,435
Gross capital income before tax: $EBITDA_2 = r_{va}^2 \cdot VA_2$	€3,630,060
Gross labor income: $W_2 = (1 - r_{va}^2) \cdot VA_2$	€4,436,740

We proceed, finally, to an estimation of demand. The French statistics of hemovigilance report 71 cases of alloimmunization unrelated to ABO incompatibility per 100,000 units transfused in 2011 [19, Table 7]. This corresponds to 2217 patients, that is, about 0.39% of the total number of 568,513 patients transfused the corresponding year. Applying to these patients the average number of 5.5 units transfused per patient observed in France in 2011 [19, p. 11], we get a first rounded estimate of current demand of 12,200 units. Nevertheless, the incidence of alloimmunization is known to be presently underestimated. Moreover, an important contribution of the development of an industry of cultured RBCs will consist, precisely, in a better detection of the cases of alloimmunization. We argued in Section 2 that the transfusion system would operate, then, as a powerful search-match algorithm for the detection and resolution of alloimmunization problems. One should expect, therefore, a number of cases situated in the range from 1 to 3% of patients transfused reported in Section 2, possibly after some years of operation of the transfusion system. We select the midpoint of this range, and suppose as above that 5.5 units RBCs are transfused on average to these patients. We end up with a rounded estimate for q_2 of about 46,900 units at the long-run equilibrium of Stage 2. In other words, the industry may start in Stage 2 with an annual output slightly above 12,000 units, and progressively increase the scale of production up to about 47,000 units per year.

The main features of the economic equilibrium of Stage 2 are summarized in Table 2. We derive, in particular, the value K_2 of industry's capital from the gross rate of return on physical assets of the French pharmaceutical industries $r_k^2 = \frac{EBITDA_2}{K_2} \simeq 46\%$ [2].

Stage 3 (Substitution of manufacture for donation). Alloimmunized patients represent a small fraction of at most 3% of all transfused patients. We examine here the conditions that may justify the extension of the utilization of cultured RBCs to all other patients (that is, the remaining 97–99% of transfused patients), and the economic equilibrium that would result from that.

As far as non-alloimmunized patients are concerned, the difference in use value between donated and cultured RBCs reduces in normal (i.e. long-run) circumstances to a difference in exposure to predictable risks of transfusion-transmissible infections (TTI). Predictable TTI risks, as measured by the actual incidence of transfusion-transmitted infections, are currently very low in mature blood donation organizations. Moreover, they should continue to diminish in the future due to foreseeable progress in the techniques and practices of decontamination of transfused units. A first natural assumption for the derivation of the long-run equilibrium of Stage 3 is, therefore, that donated and cultured RBCs are (almost) perfectly substitutable, in terms of their utilization in the transfusion of non-alloimmunized patients. This implies that manufactured RBCs would substitute for donated RBCs at long-run economic equilibrium only if the price of the former is set below the price of the latter.

The markup equilibrium condition of the stage reads: $p_3 = 1.4516 \times C_3$. If, therefore, the price of the unit of donated RBCs is the current (rounded) French price of €180, the substitution of cultured for donated RBCs will take place in the long-run only if $C_3 < \frac{1}{1.4516} \times 180 \simeq €124$. With a price of a liter

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Table 3
Industry features in the case of substitution of manufacture for donation

Sales: $S_3 = p_3 \cdot q_3$	€220,000,000
Value added: $VA_3 = (p_3 - C_3) \cdot q_3$	€68,000,000
Production assets: $K_3 = \frac{EBITDA_3}{r_k^3}$	€66,521,740
Gross capital income before tax: $EBITDA_3 = r_{va}^3 \cdot VA_3$	€30,600,000
Gross labor income: $W_3 = (1 - r_{va}^3) \cdot VA_3$	€37,400,000

of culture medium maintained at €38, this implies, in turn, a bioreactor technology consuming less than $\frac{124}{38} \simeq 3.3$ l per unit produced; that is, a level of physical performance close to bone marrow's.

Suppose from there on that Abbot's prediction on the evolution of technology is verified at horizon 2020 or later, that is, bioreactors support a cell density of 1×10^9/ml. The production of one RBC concentrate then consumes $L_3 = 2$ l of medium, at cost $C_3 = €76$. The price of the concentrate is $p_3 = 1.4516 \times C_3 \simeq €110$. Manufacture substitutes for donation. We may assume that substitution is not complete: donated blood will still be collected for plasma, and possibly also for platelets; and reasons of diversification of unpredictable risks in the transfusion of manufactured RBCs support the conservation of some production of RBC components out of donated blood. We may plausibly assume, in particular, that a number of RBC concentrates comparable to the present number of plasma units are still collected through donation, that is, presently about 400,000 units in the French blood donation organization. A plausible order of magnitude for the French production of cultured RBCs, inferred from current data, is then $q_3 = 2$ million units. Calculations identical to those conducted in Stage 2 yield the features of the RBC industry, as summarized in Table 3 (with $r_k^3 = r_k^2 = r_k^* = 0.46$).[6]

4. Conclusion

The perspectives of development of an industry of cultured RBCs are mainly and heavily constrained by the low cost of the transfusion units obtained from blood donation. The current scientific and technological progress in stem cell engineering makes it possible to consider the development of a viable industrial production in the near future, operating on a small scale, for the treatment of alloimmunization in transfusion. The extension of the production and utilization of manufactured RBCs beyond the small

[6]The economic scenario outlined here does not fit in the basic conditions of the blood donation organizations of low- or middle-income countries in two respects at least. The startup supply of Stage 1 is derived from the World Health Organization's formula for the calculation of the value of human life, which is proportional to GDP per capita, and therefore lower in low- and middle-income countries than in high-income ones. And the risks of transfusion transmissible infections (TTI) or blood shortages are much larger in many low- or middle-income countries than in most high income countries. These two differences influence in opposite directions the use value of cultured RBCs in low- and middle-income countries relative to high-income countries (the first one pushing it down, the second one pushing it up). It is unclear, therefore, whether their overall effect does or does not support the development of RBCs manufacture in low- or middle-income countries, relative to high-income ones. The answer could be positive in some countries, negative in others, depending on the particular mix of GDP per capita and safe blood shortage of each. The same kind of remark applies to the high-income countries whose blood donation organization has not reached full maturity yet, such as South Korea for example. Such countries usually manage TTI risks efficiently, but may confront chronic situations of severe blood shortage. The use value of manufactured RBCs is larger in these countries than in the high-income countries whose blood donation organizations have reached maturity. The former countries confront a choice that the latter do not, namely, either investing scarce resources in the development of an industry of manufactured RBCs, or investing them in the development of their blood donation organization. One can imagine circumstances that would make them prefer rationally the first option.

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fraction of patients who are alloimmunized against blood antigens supposes that the physical productivity of the technology progresses considerably, getting close enough to the productive performances of bone marrow.

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Conflict of interest

The author has no competing financial interests in this article.

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