The Generics in Transplantation and the Rules on Their Use

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By definition a product identified by its official chemical name rather than an advertised brand name is called a generic. If a drug exert its pharmacological effects at the same site, have the same potency, same dosage form and same bioavailability as a brand name, reference listed drug (RLD), is considered as a generic. However inactive ingredients can differ between brand name and generic. It is through the regulations of the FDA that the generics gained many ground in the drug market, they currently account to more than 42 % of the total prescription in the USA. These regulations include the abbreviated new drug application (ANDA) for the registration process and drug substitution at the pharmacy level without patient or physician consent. This coupled with a keen interest of third party payers and the health authorities to reduce the high transplant health budget (over 2 Billion US $) made it a necessity to introduce the generics into the field of transplantation. Using the above mentioned definition we can theoretically say that all anti-lymphocytes, produced in the same animal species, are generic of each. Moreover, monoclonal antibodies that are directed against the same target and have the same bioavailability are also consider generics to each other. Of all the immunosuppressive drugs that have been introduced into the field of transplantation none has been as dominant as Cyclosporine. Cyclosporine became and still is the backbone for any immunosuppressive protocol. In the year 1992, Consupren, the first, non-FDA approved, generic to Sandimmun was introduced. Although Consupren was not bioequivalent to Neoral, however, long-term results in kidney transplantation have been similar for both drugs. The introduction of Consupren resulted in a near 40 % reduction in the total cost of immunosuppressive therapy. Interestingly the cost of the brand name drug Neoral was also reduced by 20%. The cost reduction allowed the introduction of the new immunosuppressive agents MMF and Rapamycin. Currently there are 5 FDA approved Cyclosporine generics with a 20 % market share in the USA and a mere 0% in Europe. Alternatives formulations to both Rapa and for MMF would be available soon. These forms are not by definition generics and are considered by the FDA to be new brand names act on the same site as Cell Cept and Rapaimmune. Their introduction would be a great welcome and would definitely results in cost saving in transplantation cost. In conclusion, generics efficacy and safety is similar to that of the brand name and their use is cost effective.

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A generic is a product that is identified by its offi-

cial chemical name rather than an advertised brand. If a drug exerts its pharmacological effects at the same site, have the same potency, same dosage form and same bioavailability as a brand name, reference listed drug (RLD), is considered as a generic. Both brand name and generic must be, manufactured under government approved (GMP) and to be demonstrated safe and effective. However, inactive ingredients can differ between brand name and generic. It is through the regulations of the FDA that the generics gained many ground in the drug market especially in the USA. These regulations include:

1. The abbreviated new drug application (ANDA) for the registration process. Thus, the time requirement for registration of a generic is usually much shorter than the time required by the brand name product.
2. Hatch-Waxman act 1984 which states that "if a generic drug manufacturer is able to safely imitate the therapeutic effects of a pioneer drug, whatever release mechanism the manufacturer uses should be irrelevant"
3. Two or more products are considered bioequivalent if no significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action. It follows that nominally different bioavailability between the reference drug and the generic is acceptable (LSM value 80-125%). The 90 % confidence interval of the AUC and C max of the generic must fall within 80 % to 125 % of the reference drug values.
4. No additional clinical tests or examinations by health care provider are needed when a generic is substituted for the brand-name product. FDA found no problems attributed to: Substitution of one approved drug for another (being brand name or generic).
5. Recommendation for administration. This step is for patient compliance only and the FDA would not consider this optional step in determining the dosage form of the product.
6. FDA approval for drug substitution at the pharmacy level without patient or physician consent.

Currently generic account for more than 42 % of the total prescription in the USA (Table 1). This coupled with a keen interest of third party payers and the health authorities to reduce the high transplant health budget (over 2 Billion US $) made it a necessity to introduce the generics into the field of transplantation. Using the above-mentioned definition, we can theoretically say that all anti-lymphocytes, produced in the same animal species, are generic of each other. Moreover, monoclonal antibodies that are directed against the same target and have the same bioavailability are also considered generics to each other. Of all the immunosuppressive drugs that have been introduced into the field of transplantation, none has been as dominant as Cyclosporine. Cyclosporine became and still is the backbone for any immunosuppressive protocol. In the year 1992, Consupren, the first, non-FDA approved, generic to Sandimmun was introduced. Long-term results of both Neoral and Consupren in kidney transplantation have been similar for both drugs [1-9]. The introduction of Consupren resulted in a near 40 % reduction in the total cost of immunosuppressive therapy. Interestingly the cost of the brand name drug Neoral was also reduced by 20%. The cost reduc-

tion allowed the introduction of the new immunosuppressive agents MMF and Rapamycin. Currently there are 5 FDA approved Cyclosporine generics with a 20 % market share in the USA and a mere 0% in Europe. Alternatives formulations for MMF have been introduced in deregulated market such as India and would be available for other countries soon. Results from healthy volunteers indicate that TM-MMF, a generic of CellCept, indicate that the 2 products are equally bioavailability with a LSM value of 97 % (Table 2) and thus TM-MMF fits the FDA criteria of a generic.

Recently multinational companies have introduced new formulations to both Rapammune and CellCept. These forms are not by definition generics and are considered by the FDA to be new brand names. These agents have the same active ingredients as Cell Cept and Rapammune but their site of dissolution is different. This made their bioavailability to different than the brand names and thus the FDA cannot classify them as generics.

There is no doubt that the generics have established a strong foot hold in the USA market. The rules and regulations of the FDA guarantee quality and safety of these products. The market share of the generics is increasing worldwide. The United Nations (UN) has also joined in the debate over the use of generics. The recent approval by the UN for an application by South Africa allowing it to use generics for the treatment of AIDS patients even though those generics are still patent protected. This ruling made it possible for poor patients to have access for the cost prohibited

Table 1. The estimated distribution and cost of generics and brand name drugs in the USA market for the year 2001.

Drug	% prescription (Market share)	% cost	Total
Pioneer (Brand Name)	58%	92%	110 Billion$
Generics	42 %	8%	10 Billion$
Total	100%	100%	120 Billion$
Projection 2010			
Drug	% prescription (Market share)	% cost	Total
Pioneer (Brand Name)	40%	89%	140 Billion$
Generics	60%	11%	15 Billion$
Total	100%	100%	155 Billion$

Table 2. The comparison between CellCept and TM-MMF in healthy volunteers.

Parameter	CellCept 500mg	TM-MMF 500 mg	Ratio of least Squares
AUC CO-t (ng=hr/ml)	24.35	23.68	97.3
Cmax (ng/ml)	18.91	20.83	102.3
Tmax (hr)	0.626	0.569	

treatment for AIDS. The cost of treatment dropped from 10,000 US $/year/patient to less than a 1000.00 US$. This rule although controversial by its nature opened the door for the production and use of other patent protected products. The UN has also stepped in to insure that the quality of these products is guaranteed, by forming a special inspection team. This team has already approved 10 factories to produce and sell anti AIDS therapy. Many questions still remain to be answered for the timing and mechanism needed for the introduction of generics especially in MESOT countries. Research and development for new agents is very expensive. It is estimated that companies such as Avanties Roche and others have spent over a billion dollars in the year 2001 on research and development. There should be a mechanism that protects the interest of these companies other wise the funds allocated for research and development will dry out and thus the introduction of new product will not be financially feasible. It is possible for the patent protection to be increased to "may be" 15 years rather than the current 10 years. Alternatively the brand name manufacturers could reduce their prices following the first 10 years or they could opt for local production.

In the MESOT countries there is an urgent need to create a similar body of inspectors to the FDA. This body should then establish criteria for quality and safety of the generics in the region.

The use of generics is safe; it is cost effect and can reduce the financial burden on developing nations. It is required by both developed and developing nations. Proper rules, regulations and inspection should be developed to guarantee the quality of generics in MESOT region. And finally generics should not be patent infringing. This way the novelty of innovation and envelopment of new products is insured.

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