DuPont Fluoroproducts

Material of Construction for Pharmaceutical and Biotechnology Processing: Moving into the 21st Century

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Abstract
At the dawn of the new millennium, the Pharmaceutical and Biotechnology Industries are seeking ways to leave behind the currently-used troublesome materials of construction and to accelerate conversion to problem-freeing, leading-edge, improved material.

Throughout this century, the materials of processing equipment construction used in these industries—stainless steel and glass—imposed constant and increasing problems: rouging, pitting, corrosion, metallic-poisoning, aggravated compliance issues, costly and environmentally adverse cleaning protocols, and inadvertent fracture, plus costly biofilm issues. A cursory assessment suggests that the development of increasingly sophisticated pharmaceutical and biochemical manufacturing product and processes are being limited by what can be synthesized and manufactured in glass-lined or, particularly, stainless steel components.

Equipment made with wetted surfaces of fluoropolymers, especially Teflon® PFA HP, represents the most functional 21st Century material of construction for pharmaceutical and biotechnological research and manufacturing. The non-polar, high service temperature, chemically inert, hydrophobic nature of a fluoropolymer surface provides non-interactive, essentially “force field”-like containment for pharmaceutical and biotechnological process fluid streams. These attributes promise reduced production cost and lessened downtime for regulatory compliance procedures, plus synthesis and process design freedoms. Proven service in the chemical processing industry for a half century, and in the microelectronics industry for a quarter century give ready evidence of high purity, non-wetting and non-corrosive performance, and a supply of ample equipment for adoption by the Pharmaceutical and Biotechnology Industries. Moreover, fluoropolymer fabricators with similar years of experience can provide desired specialty items. And new fluoropolymer resin offerings from DuPont and other fluoropolymer resin suppliers further enhance the adaptability of this material to satisfy ongoing Pharmaceutical and Biotechnology Industries’ needs.

Many companies are already moving to fluoropolymer material of construction. Not moving quickly is likely to negatively impact the remaining companies’ sustained competitive advantage going forward.

Introduction, Problem Statement, and Objectives
Approaching the turn of the century, the pharmaceutical and biotechnology industries confront major challenges: increased competition, industry consolidation and globalization, high research and development costs, pervasive government guidelines, and extremely demanding manufacturing and distribution requirements.¹⁻⁷
Faced with such issues, these industries rightfully need to be extremely vigilant in the allocation and expenditure of resources. Contradictory, however, to the careful planning and execution of resource expenditures, the pharmaceutical and biotechnology industries continue to spend untold millions of dollars to compensate for the shortcomings of materials of construction currently used in the production of their products.

The use of an alternative material of construction—namely, fluoropolymers, especially fully fluorinated fluoropolymers such as Teflon® PFA—affords the pharmaceutical and biotechnology industries a means to redirect these funds to more productive initiatives which impact their business well-being—research and development or profitability.

One objective of this paper is to compare the material science of the current materials of construction—stainless steel and glass—with that of the increasingly adopted material of construction—fluoropolymers. A second objective is to compare biochemical and microbiological impact on such materials.

A third objective is to raise the real potential of reduced regulatory compliance costs through the use of unreactive unchanging fluoropolymers as material of construction for pharmaceutical and biotechnology processing equipment. And finally, a fourth objective is to suggest a redirection, with the aid of fluoropolymer materials of construction, of the untold millions of dollars being spent to compensate for the shortcomings of stainless steel and glass materials of construction to other more productive pharmaceutical and biotechnology industry uses.

Material Science Aspects of Stainless Steel, Glass, and Fluoropolymers

Stainless Steel
Stainless steel has historically been adopted for containment of chemical processing because it is resistant to more chemicals than is iron or mild steel. It is an inorganic chemical combination of essentially iron, chromium, and nickel. Products of stainless steel are strong and their initial cost, though higher than iron or mild steel, are often less than other exotic metallurgical materials of construction.

Depending on the amount of the minor ingredients in the metallurgical formulation, the chemical resistance of stainless steel to certain chemicals can be improved. Such improved chemical resistance comes with a corresponding increase in cost. But even such chemical resistance improvement is not sufficient to overcome chemical attack or the corrosive attack of biofilm components. Stainless steels corrode over time as the minor ingredients are lost and as electrochemical potentials arise which promote the oxidation of iron. In stainless steel weldments, for example, iron is made more readily accessible to oxidation in even the “mildest” of chemical conditions, i.e., hot steam, and the resulting rust (“rouging”) contaminates and compromises the quality of the products being produced in such equipment.

Stainless steel can be further chemically treated to be made less reactive, i.e., passivated, in a time consuming and expensive treatment that must be performed regularly to ensure that the iron in this material doesn’t oxidize—i.e., rust. Passivation is costly, is only temporarily durable, and must be repeated if additional weldments are incorporated into the system. Passivated or not, stainless steel is reactive to many harsh chemicals, particularly chloride and other halides, preventing their beneficial use in pharmaceutical and biotechnologic applications.

The surface irregularities of stainless steel—ranging from 180 grit to 400 grit—can be ameliorated, although with only temporary beneficial effect, to double digit microinches by electropolishing. But, electropolishing is also expensive, non-permanent, and needs to be repeated often to maintain such a surface. Even so, this electro-smoothing only miniaturizes the height of the asperities in the metallurgical surface, but does little to remove the nooks and crannies surrounding the base of the asperities.

Worse still, electropolishing can remove inclusions in the metal creating pits, which, in turn, can harbor microorganisms and biofilm components to perfectly shelter them from even the most vigorous cleaning.

Surface physical chemistry of stainless steel is another significant negative for its use in the Pharmaceutical and Biotechnology industries—it is wettable by aqueous solutions, a characteristic which enhances not only chemical corrosion, but also biofilm adhesion and biofilm resistance to detachment.

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*The cost of corrosion of stainless steel in the Pharmaceutical and Biotechnology Industries in the US in 1998 has been estimated to be $0.31B, obtained at by taking one tenth of the dollar value obtained by proportioning these industries’ total 1998 revenue to that of the US GDP, and multiplying that factor times the % of the GDP estimated by the US Dept of Commerce for corrosion in the general economy, i.e., ~4%.

* A conservative estimate of the cost of passivation of a 1000 foot loop is $10K –$12K, i.e., $10–$12/ft.
only it didn’t break unexpectedly. If only it could endure thermal cycling. If only glass coatings didn’t unpredictably craze and thereby expose the underlying iron substrate to the process fluids. If only it didn’t leach elements used to help it overcome its brittle/crazing shortcomings. If only its surface wasn’t wetted by aqueous media. If only it didn’t tenaciously hold onto biofilms. Feedback indicates that glass surface of most glass-lined vessels in chemical handling industries ends up as a patchwork of perfluoropolymer patches held with tantalum bolts. And, of course, glass is reactive to many harsh chemicals, preventing their beneficial use in pharmaceutical and biotechnologic applications.

**Fluoropolymers**

Because of its outstanding friction reduction, material release, chemical resistance, and thermal stability, fluoropolymers, especially Teflon® perfluoropolymers, have found increasing applications as materials of construction in the pharmaceutical and biotechnology industries. These adoptions showcase its anti-corrosive and non-wetting surface characteristics, enhanced by its reduced surface friction. In combination, these features provide a comparative advantage vis-a-vis biofilm (see below).

Fully fluorinated fluoropolymers, such as Teflon® PFA and Teflon® PTFE are electrochemically, biochemically, enzymatically, and chemically virtually inert. The exceptions chemically are exotic interhalogen compounds, molten metals, etchants such as sodium metal dissolved in naphthalene, and impinging gas plasmas. Such chemical inertness is not the case for partially fluorinated polymers which are subject to varying degrees of reactivity based essentially on their polarity and chemical structure. Figure 3 qualitatively compares the chemical reactivity differences between fully and partially fluorinated fluoropolymers.

Today, the wide availability of components of Teflon® polymers has made them equivalent in installed cost to stainless steel components, and they provide a lower cost of ownership.

**Glass**

This centuries-old, amorphous inorganic material of construction is readily formed into components and coatings. It is chemically resistant to most organic chemicals and many but not all inorganic chemicals. It can be formed into many unsupported components and can be further supported by attachment to steel for larger processing components.

By their careful consideration of its shortcomings, the pharmaceutical and biotechnology industries have exploited this material well considering its positives and negatives from a material science perspective. If only glass were not brittle. If only it didn’t break unexpectedly. If only it could endure thermal cycling. If only glass coatings didn’t unpredictably craze and thereby expose the underlying iron substrate to the process fluids. If only it didn’t leach elements used to help it overcome its brittle/crazing shortcomings. If only its surface wasn’t wetted by aqueous media. If only it didn’t tenaciously hold onto biofilms. Feedback indicates that glass surface of most glass-lined vessels in chemical handling industries ends up as a patchwork of perfluoropolymer patches held with tantalum bolts. And, of course, glass is reactive to many harsh chemicals, preventing their beneficial use in pharmaceutical and biotechnologic applications.

Fully fluorinated fluoropolymers can sustain high temperature service, up to 260 °C for PFA and PTFE. They can be rapidly thermally cycled below their service temperatures. Although fully fluorinated fluoropolymers do not support combustion, they can be burned as long as the oxidizer and temperature source is present.

Most fully fluorinated fluoropolymers are pure as polymerized. Many fluoropolymers, but not all (the exception being partially fluorinated polymers), do not require any additives to withstand the harshest of reagents.
Fully fluorinated fluoropolymer materials of construction are ductile. They are less mechanically strong than partially fluorinated polymers. Systems made from them are widely used. Piping systems up to 2 inch diameter, operating up to 150 psi are available as piping systems without steel piping outer support; piping systems of diameters larger than 2” and for pressures higher than 150 psi, are available with steel outer support. Figure 4 qualitatively depicts the mechanical comparison between fully and partially fluorinated fluoropolymers. Both fully and partially fluorinated fluoropolymers can be abraded by high energy, sharp particle slurries which are directed perpendicular to the fluoropolymer surface, e.g., sandblasting; otherwise, they are likely to be unaffected.

Fully fluorinated fluoropolymers have the lowest surface energy of all solid materials rendering them virtually non-wettable by water and by aqueous solutions. The low surface energy, coupled with chemical inertness and a micro-void-free fully fluorinated surface makes any kind of adhesion very difficult to achieve. The resulting benefit to the pharmaceutical and biotechnology industries is more uptime and ease of cleaning (see “Minimized Biofilm Adversity with Teflon® PFA” below).

The initial cost of fluoropolymer protected systems, heretofore often higher than stainless steel, is now comparable, while their lifetime cost-of-ownership is considerably less—they do not require electropolishing, having a highly definitive, hydrophobic, smooth surface as a natural outcome of their forming technology. They need no “passivation”—ever. Their non-reactivity opens the potential for more efficient, effective, less-costly cleaning systems which can be more environmentally friendly. This inertness also promises the potential of fewer regulatory compliance issues for manufacturing equipment since the perfluoropolymer is non-corrosive and virtually unchangeable under pharmaceutical and biotechnical conditions.

Figure 3. Chemical Resistance of Fluoropolymers

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<thead>
<tr>
<th></th>
<th>HIGHEST</th>
<th>MUCH LOWER</th>
<th>ENOUGH</th>
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<tbody>
<tr>
<td>PFA, PTFE</td>
<td>ETFE</td>
<td>PVDF</td>
<td>149 204 260 degrees C.</td>
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</table>

Minimized Biofilm Adversity with Teflon® PFA

Biofilm Removal Significantly Expedited by Surface of Teflon® PFA

Biofilm removal studies conducted by the University of Minnesota’s Bioprocess Technical Institute and reported by Hyde et. al., confirm the ease of removal of biofilms of E. coli ATCC 8739, Klebsiella pneumonia ATCC 12657, and Salmonella choleraisuis biovar typhimurium ATCC 13311 from Teflon® PFA HP. Recasting the data published by Hyde et. al. (ibid.) shows that 98% to 99% of area covered by the biofilm on injected molded coupons of Teflon® PFA HP was removed by exposure of the biofilm coupons to dilute sodium hypochlorite in a virtually quiescent exposure to the biofilm inactivation protocol with coupons protected from biofilm wash-away fluid flow (Figure 5).

The data of Figure 5 show that even surfaces of Teflon® PFA HP greatly roughened intentionally by machining, showed 92% removal in this virtually quiescent process. In quantitative terms, the data of Figure 5 show that the biofilm release from the conventionally injection-molded surface of Teflon® PFA HP exceeded that from the conventionally molded surface of partially fluorinated fluoropolymer PVDF by 10% to 11%, exceeded that for conventionally molded surface of the hydrogenated polymer polypropylene by 31% to 48%, exceeded that from the surface of commercial silicone-treated borosilicate glass by 11% to 26%, exceeded that from the surface of commercial borosilicate glass by 11% to 100%, and exceeded that from the surface of conventional electropolished 316L stainless steel by 74% to 296%.

Figure 4. Comparative Mechanical Properties of Fluoropolymers
The ease of biofilm release from the surface of Teflon® PFA HP virtually translates to ease and speed of cleaning components in pharmaceutical and biotechnology industries which have wetted surfaces of Teflon® PFA HP. The economic benefit for such industries are in increased production “uptime”, and lower manufacturing costs.

Non-Wetting Surface of Teflon® PFA HP is Responsible for Superior Biofilm Release, Wettability of Stainless Steel, and Glass Aid Biofilm Retention

It is not possible for a substance to chemically adhere to a surface if the substance is unable to wet that surface. The critical wetting angle of a fluid on a surface is the traditional method adhesion scientists use to establish wettability of a surface by a given reagent. The higher the critical angle of wetting the lower the wettability of that surface to the wetting fluid.

1. Stainless Steel and Glass vs. Teflon® PFA HP

Hyde et al. determined the water wettability of Teflon® PFA HP fluoropolymer vs 316L stainless steel and borosilicate glass; these data are tabulated in Figure 6 and are shown schematically in Figure 7.

The data of Figure 6 indicate that Teflon® PFA HP is more than 156% less wettable than glass, and more than 137% less wettable than electropolished 316L stainless steel. The depictions of Figure 7 suggest that water molecules roll on the surface of Teflon® PFA HP much like one would picture solid spheres rolling down a tube (this “rolling” can be readily experienced by observing a drop of water “bead up” on a surface of Teflon® PFA HP). The differences in wettability between Teflon® PFA HP, glass, and stainless steel reflect the polarity differences between these materials. Stainless steel and glass are very polar materials whereas Teflon® PFA HP is a non-polar fluoropolymer. This virtual lack of polarity in Teflon® PFA HP resists the polar water molecule.

This essential lack of wetting by water of the surface of Teflon® PFA HP can only result in a significantly slower initiation of biofilm on the surface of Teflon® PFA HP. That result, in turn, will give rise to increased production “uptime” for the pharmaceutical and biotechnology industries manufacturing operations.

<table>
<thead>
<tr>
<th>Per Cent Biofilm Removal</th>
<th>K. Pneumonia</th>
<th>S. Cholera suis</th>
<th>E. coli</th>
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<tbody>
<tr>
<td>Stainless steel</td>
<td>67</td>
<td>25</td>
<td>56</td>
</tr>
<tr>
<td>Poly(propylene)</td>
<td>67</td>
<td>75</td>
<td>75</td>
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<td>Borosilicate glass</td>
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<td>Silicone-coated glass</td>
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<td>78</td>
</tr>
<tr>
<td>Poly(vinylidene fluoride)</td>
<td>89</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Teflon® PFA (machined)</td>
<td>92</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Teflon® PFA (injection molded)</td>
<td>99</td>
<td>99</td>
<td>98</td>
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Source: Hyde, et. al., ibid.

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<th>Comparison of 18 megaOhm Process Water Wetting Contact Angle for 316L Stainless Steel, Borosilicate Glass, Teflon® PFA Fluoropolymer Resin</th>
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<tbody>
<tr>
<td>Stainless Steel*</td>
</tr>
<tr>
<td>------------------</td>
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<tr>
<td>Degrees</td>
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</tbody>
</table>

Source: Hyde, et. al., ibid.

*AFM Rms, Nm 41.74 7.42 24.35
2. PVDF vs. Teflon® PFA HP

The virtual lack of wetting of Teflon® PFA HP is superior not only to that of the inorganic materials of construction such as stainless steel and glass. The surface of Teflon® PFA HP is also less wettable than are the partially fluorinated polymers such as poly (vinylidene fluoride), PVDF, as shown in Figure 8 and schematized in Figure 9.

The data of Figure 8 shows that Teflon® PFA HP is more than 137% less water-wettable than is PVDF. The differences in wettability between PVDF and Teflon® PFA HP reflect the polarity differences between these polymers. PVDF is a very polar fluoropolymer, whereas Teflon® PFA HP is a non-polar fluoropolymer. This lack of polarity resists the polar water molecule. As was pointed out earlier, the lack of attachment of water to surface of Teflon® PFA HP suggests a significantly slower initiation of biofilm on the surface of Teflon® PFA which, in turn, suggests increased production “uptime” for the pharmaceutical and biotechnology industries manufacturing operations. Conversely, the more wettable PVDF surface would be expected to provide comparatively less manufacturing operation “uptime”. Work to confirm this aspect in a dynamic system is planned.

3. Water as Media vs. Nutrient Solution

The wetting data of Hyde, et. al., ibid, show that when nutrients are added to the water, the wettability comparisons are of the same order.

4. Reduced Flow Friction

The hydrophobic nature of the surface of Teflon® PFA HP is further complimented by low friction, stick-slip character for fluid flow in piping systems having such a wetted surface. The benefit of this combination of properties to the pharmaceutical and biotechnological industries is that a smaller pipe diameter in Teflon® PFA will provide the same volume throughput, other things being equal, as a larger diameter high-frictional-flow stainless steel piping. In addition, existing stainless steel piping systems can be retrofitted with perfluoropolymer liners to gain all the benefits discussed above without sacrificing any volume throughput.

Asperity of Surface Teflon® PFA HP is a Non-Factor in its Biofilm Release but a Significant Factor for Stainless Steel Biofilm Retention

The data of Figure 5 combined with that of surface smoothness measurements made of the coupons also confirm that smoothness of the molded surface of Teflon® PFA HP, as measured by precision Atomic Force Microscopy, bears little significance to biofilm release from this surface (Figure 10).

The Ra and Rms data for borosilicate glass and poly(propylene) are significantly lower than those for Teflon® PFA HP, yet the data of Figure 5 show Teflon® PFA to have significantly greater removal of biofilm. The “Z” data of Figure 8 show that the conventional electropolished stainless steel is 38% lower than that for conventionally molded Teflon® PFA, yet the data of Figure 5 shows significantly more biofilm release for rougher perfluoropolymer surface. This same measure data of Figure 8 show the “roughness” of Teflon® PFA HP to be highest with the other materials being substantially lower. Yet the data of Figure 5 confirm the biofilm release from the surface of Teflon® PFA to be significantly higher than from that of the other materials.

The results of surface asperity and biofilm removal from the related data for injected molded vs. machined coupons of Teflon® PFA HP demonstrate that although the surface of the machined coupon was 95% to 115% rougher than the injected molded surface, the biofilm release from the machined surface was only 7% poorer than that from the injected molded surface.
The above findings collectively indicate that asperity measurements on the surface of conventionally molded Teflon® PFA are non-indicators of biofilm adhesion on such a surface.

The Non-corrosive Hydrophobic Inertness of Teflon® PFA HP Promises More Latitude in Regulatory Aspects of Pharmaceutical and Biotechnology Processing

A great deal of the current regulatory constraints designed for product consistency and quality apparently result from the corrosive and changing nature of the current materials of construction. The non-corrosive inertness of Teflon® PFA HP removes such concerns, along with associated roughing, passivation, electropolishing, and glass crazing and breakage.

The hydrophobic nature of Teflon® PFA portends a longer time before the inception of biofilm formation, given systems without designed dead volume and with adequate flow velocity. This suggests that the time between production stoppage for biofilm removal can be lengthened. Combined with more speedy and complete removal of biofilm from the surface of Teflon® PFA, this lengthening between cleanings provides additionally improved production uptime.

Government regulatory agencies are forward-looking in their interest in not impeding improvement in pharmaceutical and biotechnical industries’ effectiveness and efficiency. For processing systems in which wetted surfaces are Teflon® PFA HP, this proactive perspective presages regulatory enhancements which improve these industries productivity and effectiveness, all of which translate to more profitable processing.

Conclusion

Published data from experiments conducted by the University of Minnesota Bioprocess Technical Institute confirms that the non-corrosive hydrophobic surface of Teflon® PFA HP releases biofilm virtually completely in essentially quiescent non-cleaning protocol biofilm inactivation with 50 ppm sodium hypochlorite solution. By comparison, the same biofilms were significantly retained by 316L stainless steel, borosilicate glass, siliconed borosilicate glass, poly(propylene) or poly(vinylidene fluoride). Precision roughness Atomic Force Microscopy measurements on the substrate coupons confirmed that the asperity of the surface of Teflon® PFA HP is a non-factor in biofilm adhesion whereas the asperity of other substrate surfaces enhanced biofilm retention. The combination of surface roughness and biofilm removal data lead intractably to the conclusion that, other things being equal, the chemical polarity of the surface is the key factor enhancing biofilm retention, and that a non-wetting non-polar surface of the perfluoropolymer Teflon® PFA HP maximizes biofilm release. Studies of biofilm onset on, and ease of removal from, the surface of Teflon® PFA HP are planned.

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\begin{array}{|l|c|c|c|}
\hline
& \text{Ra} & \text{Rms} & \text{Z range} \\
\hline
\text{Siliconed borosilicate glass} & 0.84 & 1.56 & 35.14 \\
\text{Borosilicate glass} & 1.11 & 7.42 & 78.41 \\
\text{Poly(propylene)} & 16.19 & 7.42 & 78.41 \\
\text{Teflon® PFA (injection molded)} & 17.17 & 24.35 & 438.85 \\
\text{316L Stainless steel} & 26.64 & 41.74 & 293.09 \\
\text{Poly(vinylidene fluoride)} & 28.48 & 35.09 & 244.24 \\
\text{Teflon® PFA (machined)} & 36.83 & 47.47 & 310.99 \\
\hline
\text{Source:} & \text{Hyde, et. al., ibid; Ra - arithmetic average of deviations of traced line from center line along trace; Rms = corresponding geometric average; Z = largest perpendicular distance measured along the trace line.}
\end{array}
\]
The non-corrosive non-polar hydrophobic surface of Teflon® PFA HP promises potential productivity-enhancing easing of regulatory compliance issues brought about by materials of construction.

Using systems in which the wetted surfaces are perfluoropolymer Teflon® PFA HP eliminates the cost associated with electropolishing, passivation, roughing, protracted cleaning protocols with their adverse environmental ramifications, unexpected down-time from cracked glass-lined equipment, and product quality contamination. Processing equipment with wetted surfaces of Teflon® PFA HP offer significant potential for additional productivity “uptime” with its resulting economic benefit. Instead of paying for the shortcomings of stainless steel and glass materials of construction in pharmaceutical and biotechnology processing equipment, these collective savings, measured in millions of dollars, would then be available for more productive initiatives such as the development of new products or enhanced profitability.

The production and product benefits founded by systems manufactured from Teflon® PFA HP are available to the pharmaceutical and biotechnology industries now, to provide enhanced global competitiveness through lower costs and facilitating continuing advances in process and product development—strengthening our industry for the 21st century.

Literature Cited
15. Fontana, M. G., ibid.


27. Reese, R. C., ibid.


30. Fontana, M.G., ibid.


32. Leaversuch, R. D., ibid.


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